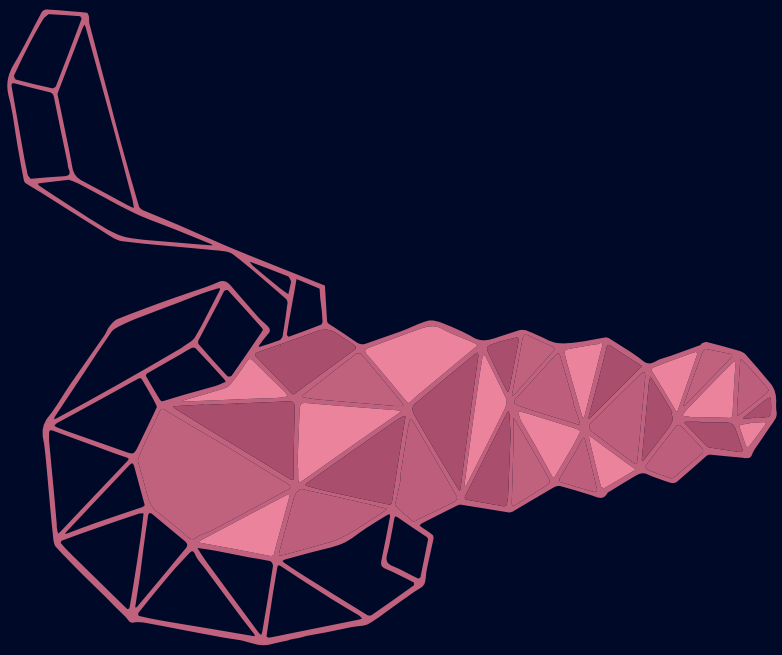

ANOUK LATENSTEIN

EVALUATION AND IMPROVEMENT OF NATIONWIDE PRACTICE IN PANCREATIC AND PERIAMPULLARY CANCER

Evaluation and improvement of nationwide practice in pancreatic and periampullary cancer

Anouk Latenstein

COLOFON

Evaluation and improvement of nationwide practice in pancreatic and periampullary cancer

This thesis was written at the Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands, and in collaboration with the Dutch Pancreatic Cancer Group.

ISBN: 978-94-6416-216-5

Paranimfen:	Charlotte Heidsma en Carmen Latenstein
Cover design and layout:	Edie de Kwaasteniet
Printing:	Ridderprint | www.ridderpint.nl

Part of the research described in this thesis was financially supported by the Dutch Cancer Society (grant no. UVA2013-5842), Mylan Healthcare B.V., Allergan B.V. and Nationaal Fonds tegen Kanker.

The printing of this thesis was financially supported by the Department of Surgery (Amsterdam UMC, Academic Medical Center, University of Amsterdam), the Dutch Pancreatic Cancer Group (DPCG), Living with Hope (LWH), Integraal Kankercentrum Nederland (IKNL), Nationaal Fonds tegen Kanker, Stichting Pancreas, Nederlandse Vereniging voor Gastroenterologie, Citrienfonds NFU, Mylan Healthcare B.V., Stichting Robopump, ChipSoft, Erbe Nederland B.V., Ipsen Farmaceutica B.V., Tramedico B.V., Castor EDC, ABN AMRO, and Servier Nederland Farma.

Evaluation and improvement of nationwide practice in pancreatic and periampullary cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 5 maart 2021, te 13:00 uur

door Anouk Elisabeth Josina Latenstein
geboren te Alkmaar

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INTRODUCTION

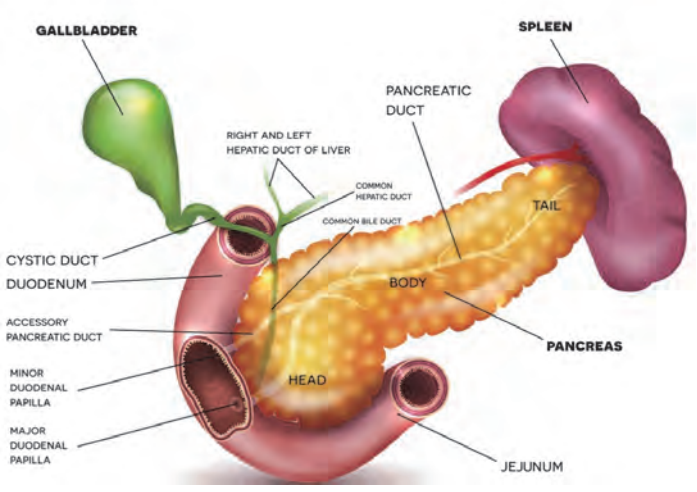
GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

Pancreas and periampullary cancer

The pancreas is located behind the stomach in the retroperitoneal area. The pancreas is anatomically divided into a pancreatic head, body, and tail (Figure 1), and has an exocrine and endocrine function. In the exocrine function, the pancreas secretes digestive enzymes. The digestive enzymes are transported through the pancreatic duct and via the Ampulla and the Papilla of Vater into the duodenum. The common bile duct merges with the pancreatic duct in the ampullary region and facilitates passage of bile from the liver and gallbladder also into the duodenum (Figure 1). In the endocrine function, it produces, among others, the hormones insulin and glucagon for the serum glucose metabolism, which are excreted directly into the blood.

FIGURE 1. Pancreas, duodenum, gallbladder, and spleen.



Cancer can arise from several cell types in the pancreas and periampullary region. Pancreatic cancer, specifically pancreatic ductal adenocarcinoma, is the most common of these cancers and is known for its very poor survival. In the Netherlands, the pancreatic cancer incidence is approximately 15 per 100,000 persons per year.[1] Only 15-20% of patients present with resectable pancreatic cancer, whereas the majority is diagnosed with locally advanced (30-40%) or metastatic disease (40-50%).[1,2] Median

overall survival of pancreatic cancer is 4 months.[1] Periampullary, non-pancreatic, cancers include duodenal cancer, distal cholangiocarcinoma (from the distal part of the bile duct), and ampullary cancer. Overall, these cancers have a better survival compared to pancreatic cancer (one-year survival 60% vs. 21%, respectively) due to a different biological behavior and an earlier detection with increased resection rates.[1,3,4]

Treatment options for pancreatic cancer depend primarily on tumor stage and can roughly be divided into resection (with or without chemotherapy), chemotherapy, and/or supportive care. Resection is the only curative treatment. Even in these patients, median overall survival remains poor with 17 months.[1] Three main types of pancreatic resections are distinguished: a pancreatoduodenectomy (i.e., resection of the head), distal pancreatectomy (i.e., resection of the body and tail), and total pancreatectomy (i.e., resection of the head, body, and tail).

A pancreatoduodenectomy includes resection of the pancreatic head together with the duodenum, distal bile duct, gallbladder, and, occasionally, part of the stomach. Consequently, three anastomoses (i.e., pancreatojejuno-/pancreatogastro-stomy, hepaticojejunostomy, and duodeno-/gastro-jejunostomy) are constructed. A distal pancreatectomy is a resection of the tail and body of the pancreas, and the spleen in case of malignancies. Total pancreatectomy is a relatively rare procedure. A primary total pancreatectomy is performed in case of premalignant disease with a high risk of malignant degeneration (e.g., main-duct intraductal papillary mucinous neoplasm or hereditary chronic pancreatitis), but also for pancreatic cancer or chronic pancreatitis if a partial pancreatectomy does not cover the extent of the disease.[5] It could also be decided intraoperatively to perform a total pancreatectomy, for example if resection margins are not free of cancer cells or to prevent leakage of the pancreatojejunostomy (i.e., postoperative pancreatic fistula). A secondary or completion total pancreatectomy (i.e., second stage after primary partial pancreatectomy) might be performed in patients with a severe pancreatic fistula or after isolated recurrence of cancer or chronic pancreatitis.

Pancreatic resections are challenging due to a close relation with vital structures (e.g., veins, arteries, and other organs) and due to the necessity of constructing anastomoses, mostly with the pancreatic remnant. This is reflected by a major complication rate of 30% and an in-hospital mortality rate of 4% following pancreatoduodenectomy.[6] Some advocate lower complication rates after total pancreatectomy in the absence of postoperative pancreatic fistula. Still, major complication and mortality rates are high with 28% and 9% (in-hospital), respectively.[7–9] If patients' performance status is adequate after resection for pancreatic cancer, they should receive adjuvant chemotherapy such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) or gemcitabine with capecitabine.[10]

Currently, neoadjuvant chemotherapy is increasingly gaining attention. In the Netherlands, it is only available in trial setting.[10] The recent Dutch PREOPANC-1 trial showed no overall survival benefit for neoadjuvant chemoradiotherapy (gemcitabine) combined with adjuvant gemcitabine compared to adjuvant gemcitabine only.[11] The PREOPANC-2 trial is currently ongoing and investigates whether neoadjuvant FOLFIRINOX is beneficial compared to the intervention arm of PREOPANC-1 (i.e., neoadjuvant chemoradiotherapy with adjuvant chemotherapy based on gemcitabine).

For patients with locally advanced pancreatic cancer, treatment and outcomes improved after the introduction of FOLFIRINOX. This regimen resulted in a survival benefit compared to those treated with gemcitabine.[12,13] In addition, resection rates have increased. For patients with chemotherapy treatment only, median overall survival is 11 months, which increases to 25 months after resection.[1,14]

In the Netherlands, 28% of patients with metastatic pancreatic cancer are treated with chemotherapy with a median overall survival of 6 months.[1] The remaining patients receive supportive care only and have a median overall survival of 2 months. The national guideline advises to start FOLFIRINOX as first-line chemotherapy in patients with a good performance status (i.e., WHO performance score 0-1) as this was associated with a survival benefit compared to gemcitabine (median overall survival: 11.1 vs. 6.8 months).[10,15] Gemcitabine with nab-paclitaxel increased survival compared to gemcitabine monotherapy and is therefore advised for patients with a lower performance status (i.e., WHO performance score 2).[16]

Exocrine and endocrine pancreatic insufficiency

The exocrine function of the pancreas involves secretion of amylase, lipase, and protease.[17,18] These enzymes induce digestion of carbohydrates, fatty acids, and proteins, respectively. Lipase is exclusively produced by the pancreas. Consequently, one of the main symptoms of exocrine insufficiency is steatorrhea (i.e., fatty stools). Other symptoms include weight loss, abdominal complaints, or bloating. Exocrine insufficiency is present in 66% of patients with metastatic pancreatic cancer at diagnosis and in 74% of patients six months after a pancreatic resection for cancer.[19,20] Consequences of exocrine insufficiency are malabsorption and malnutrition, including a deficiency of fat-soluble vitamins (i.e., vitamin A, D, E, and K).

The endocrine function of the pancreas mainly comprises of the production of insulin and glucagon by the islets of Langerhans. These hormones are required to maintain glucose levels. Endocrine insufficiency results in diabetes mellitus, often called new-onset diabetes mellitus. In 16-20% of all patients after pancreatoduodenectomy diabetes mellitus develops which is the case in all patients after

total pancreatectomy.[21–23] This requires daily treatment and could cause long-term macrovascular and microvascular complications, both affecting quality of life.[24]

The Dutch Pancreatic Cancer Project

In 2011, the Dutch Pancreatic Cancer Group (DPCG, www.dpcg.nl) was launched as the nationwide multidisciplinary study group for pancreatic and periampullary cancer.[25] The DPCG aims to improve quality of care, and clinical and translational research by nationwide collaboration of pancreatic surgeons, medical oncologists, gastroenterologists, radiologists, radiotherapists, pathologists, nurses, dieticians, researchers, and patient representatives.

One of the national projects initiated by the DPCG was the Dutch Pancreatic Cancer Project (PACAP, www.pacap.nl) in 2013. This multidisciplinary collection of clinical data, tumor tissue, blood samples, and patient-reported outcome measures was established to improve outcomes of pancreatic and periampullary cancer patients and to facilitate research.[26] Clinical data is obtained from the Netherlands Cancer Registry (NCR) and Dutch Pancreatic Cancer Audit (DPCA). The NCR is hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and contains oncological and survival data of all Dutch patients diagnosed with cancer. The data is routinely collected from medical records by trained NCR administrators. The DPCA is a nationwide prospective audit of pancreatic surgery.[6] All patients who undergo pancreatic surgery for any indication are included. The audit is mandatory for all Dutch pancreatic surgery centers and each center is responsible for delivering its own data. Biobanking within PACAP is organized in close collaboration with the Parelsnoer Institute. Pre- and postoperative blood samples are collected and fresh frozen tumor and normal tissue samples are taken from the resection specimen. Interest for quality of life related outcomes is currently increasing. Therefore, all patients diagnosed with pancreatic or periampullary cancer are approached to participate in the PACAP patients reported outcome measures (PROMs). These PROMs exist of a core set of validated questionnaires to measure both generic and disease-specific quality of life.

OUTLINE OF THIS THESIS

The ultimate goal of PACAP is to improve outcomes of patients with pancreatic and periampullary cancer by reducing practice variation and stimulating best practices. This thesis evaluates the nationwide practice in pancreatic and periampullary cancer and outcomes after pancreatic surgery for all indications. In addition, it assesses to what extent care and outcomes improved and how this can be further optimized. In **Part I** of this thesis, nationwide practice and practice variation are outlined, and the PACAP-1 trial protocol shows a strategy to implement best practices to improve pancreatic cancer care. Long-term quality of life and postoperative outcomes in all patients after pancreatic surgery are

described in **Part II**. **Part III** focuses on survival and predictors for survival in patients with pancreatic and periampullary cancer.

Part I Nationwide practice

The first part of this thesis starts with an epidemiological overview of pancreatic ductal adenocarcinoma in the Netherlands. In **Chapter 1,** the trends in incidence, treatment, and survival are evaluated on a population-based level. This chapter illustrates the impact of developments in treatment on survival, which were mainly based on new oncological therapies. These newer treatments were included in the update of the Dutch guideline on pancreatic cancer in 2019.[10] In 2012, it was shown that compliance to three quality indicators (i.e., adjuvant chemotherapy after tumor resection, discussion of the patient within a multidisciplinary team meeting, and a
maximum three-week interval between final multidisciplinary team meeting and start of treatment) of the 2011 national guideline was low.[27] To optimally implement the new 2019 guideline, it is important to assess whether compliance increased naturally over time or if a structured implementation program is required. Therefore, **Chapter 2** describes nationwide compliance to quality indicators of the 2011 guideline in later years (2012-2017).

One of the main aspects that was adjusted in the 2019 guideline is type of chemotherapy for patients with metastatic pancreatic ductal adenocarcinoma. Depending on the performance status, first line treatment with FOLFIRINOX or gemcitabine with nab-paclitaxel is advised. Implementation of these new chemotherapy regimens might differ between hospitals and affect overall survival. In **Chapter 3**, the population-based effect of implementation of these new chemotherapy regimens on clinical practice and overall survival is assessed in patients with metastatic pancreatic ductal adenocarcinoma.

The 2019 guideline also advises on the use of self-expanding metal stent placement rather than plastic stents for preoperative endoscopic biliary drainage for malignant extrahepatic biliary obstruction.[10] This is based on the recommendations in the updated European Society of Gastrointestinal Endoscopy Clinical Guideline of 2017.[28] Compliance to this recommendation might be low due to skepticism about an increased risk of post-endoscopic retrograde cholangiopancreatography pancreatitis and higher upfront costs.[29–31] In **Chapter 4**, the Dutch nationwide practice regarding preoperative endoscopic biliary drainage before pancreatoduodenectomy for patient with pancreatic head and periampullary cancer is outlined and the relation between type of stent and outcomes is investigated.

Based on these mentioned studies with nationwide PACAP data and previous literature, points for improvement in pancreatic cancer care were identified. These so-called best practices were

implemented in daily practice by a nationwide multicenter stepped-wedge cluster randomized controlled trial (PACAP-1) to reduce practice variation and improve outcomes. The protocol of this trial is presented in **Chapter 5**.

Part II Quality of life and clinical outcomes after pancreatic surgery

The step towards centralization of pancreatic surgery in 2011 has been an important improvement. Centralization showed to increase resection rates and decrease in-hospital mortality.[32–34] In 2015, the likelihood to undergo surgery was lower in patients with non-metastatic pancreatic cancer who were diagnosed in a center without pancreatic surgery as opposed to centers performing pancreatic surgery.[35] Hereafter, centralization and regionalization further developed and therefore, in **Chapter 6**, it is investigated whether the resection rate between pancreatic surgery and non-pancreatic surgery centers equalized in patients with pancreatic head and periampullary cancer between 2015 to 2017 and whether this influenced overall survival.

Quality of life and both exocrine and endocrine insufficiency are frequently studied in patients after pancreatic surgery for malignant diseases.[22,23,36] Patients who underwent surgery for benign or premalignant disease have a near normal life expectancy and especially experience the long-term consequences.[37] However, literature focusing on these patients is lacking. Therefore, the long-term quality of life and exocrine and endocrine insufficiency in patients after pancreatic surgery for benign non-pancreatitis or premalignant diseases are assessed in a multicenter study (**Chapter 7**). On the long-term, patients might also suffer from unknown micronutrient deficiencies caused by exocrine insufficiency, resection of critical organs for digestion, or an inadequate dietary intake.[24,38] In **Chapter 8,** a broad spectrum of micronutrients is evaluated in all consecutive patients at least four months after pancreatoduodenectomy in a single center in the Netherlands.

Quality of life might be highly affected in patients after total pancreatectomy as these patients experience the most severe form of exocrine and endocrine insufficiency. The nationwide PANORAMA study (**Chapter 9**) in patients who underwent total pancreatectomy between 2006 and 2016 describes short-term postoperative outcomes and compares long-term quality of life to the normal healthy population. As with the PANORAMA cohort, study periods of series about outcomes after total pancreatectomy are generally long (i.e., ≥6 years) to acquire a proper cohort. This is inherent to the rarity of the procedure but raises the question whether the high complication and mortality rates are representative for current practice. This thesis presents two studies assessing short-term postoperative outcomes after total pancreatectomy in relatively large cohorts and small time periods. In **Chapter 10**, a pan-European snapshot study is performed to assess outcomes after elective total pancreatectomy

between 2018 and 2019. The snapshot design enables an actual insight into current practice by collecting data in a short period of time and therefore creates greater generalizability than longitudinal studies.[39,40] In **Chapter 11**, data of four Western registries (i.e., the United States of America, Germany, the Netherlands, and Sweden) about total pancreatectomy between 2014 and 2018 is combined. In addition to a representative overview of outcomes, intercountry practice variation is identified.

Part III Survival

The biggest challenge to improve in pancreatic cancer care is survival. Survival estimates are traditionally calculated from the time of diagnosis or from the time of surgery. However, in patients who undergo pancreatic resection for pancreatic cancer, predicted survival changes considerably during follow-up.[41,42,43] Conditional survival, defined as the survival probability and calculated in the subgroup of patients who have survived a predefined period, may therefore provide better insight. Based on nationwide data conditional survival probabilities are calculated for patients who underwent resection of pancreatic cancer in **Chapter 12**. Moreover, a nomogram for postoperative use in the outpatient clinic is developed. This nomogram enables to predict personalized conditional survival probabilities based on patient and tumor characteristics with the possibility to adjust for the period already survived after resection.

Survival probabilities are affected by many other influences than duration of follow-up. In previous studies, including mostly other types of cancer than pancreatic cancer, survival was related to quality of life.[44,45] In **Chapter 13**, the PACAP PROMs are combined with NCR data and used to examine which domains of quality of life are predictive of survival in daily clinical practice in patients with pancreatic and periampullary cancer. A second study combining PROMs and NCR data reports on the prevalence of cachexia and dietetic consultations (**Chapter 14**). Moreover, the relation between cachexia and survival is assessed.

SUMMARY OF RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

Chapter	Research question
1	What are the trends in incidence, treatment, and survival for patients with all stages of pancreatic ductal adenocarcinoma in the Netherlands between 1997 and 2016?
2	Did compliance to selected quality indicators of the 2011 Dutch guideline on pancreatic cancer improve in the six years after introduction?
3	How does the implementation of new more effective chemotherapy regimens (FOLFIRINOX and gemcitabine with nab-paclitaxel) for patients with metastatic pancreatic ductal adenocarcinoma affect nationwide clinical practice and overall survival?
4	What is the current nationwide practice of using self-expanding metal stents in preoperative endoscopic biliary drainage for resectable pancreatic head and periampullary cancer and what are the outcomes?
5	Is nationwide implementation of best practices by a multicenter stepped-wedge cluster randomized controlled trial (PACAP-1) effective to improve survival and quality of life for patients with pancreatic cancer?
6	Did the resection rate in patients with non-metastatic pancreatic head and periampullary carcinoma who were diagnosed in pancreatic surgery compared to non-pancreatic surgery centers change between 2009 and 2017 and did this influence survival patterns?
7	What is the long-term quality of life and status of exocrine and endocrine insufficiency in patients after pancreatic surgery for benign non-pancreatitis or premalignant disease?
8	Which micronutrients are deficient in patients during the follow-up after pancreatoduodenectomy?
9	What are the short-term postoperative outcomes and long-term quality of life outcomes in patients after total pancreatectomy?
10	What are the short-term postoperative outcomes after elective total pancreatectomy in a multicenter pan-European snapshot cohort?
11	What are the short-term postoperative outcomes after one-stage total pancreatectomy in patients from four Western registries and do outcomes differ between countries?
12	What is the personalized conditional survival of patients after resection of pancreatic cancer?
13	Is quality of life related to survival in patients with pancreatic and periampullary cancer?
14	To what extent is cachexia present in the real-world setting in patient with pancreatic cancer and how is this associated with dietetic consultation and survival?

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PART I

NATIONWIDE PRACTICE

CHAPTER 1

Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma

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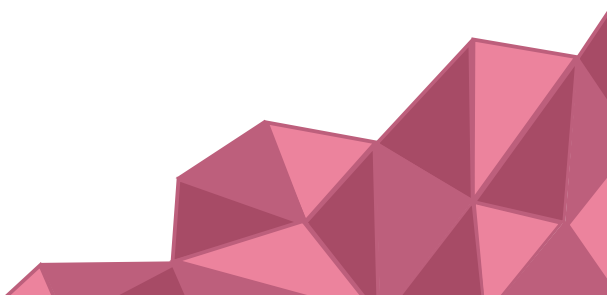
European Journal of Cancer. 2020 Jan;125:83-93.



ABSTRACT

Background: In recent years new treatment options have become available for pancreatic ductal adenocarcinoma (PDAC) including 5-fluorouracil, leucovorin, irinotecan and oxaliplatin. The impact hereof has not been assessed in nationwide cohort studies. This population-based study aimed to investigate nationwide trends in incidence, treatment and survival of PDAC.

Materials and methods: Patients with PDAC (1997-2016) were included from the Netherlands Cancer Registry. Results were categorised by treatment and by period of diagnosis (1997-2000, 2001-2004, 2005-2008, 2009-2012 and 2013-2016). Kaplan-Meier survival analysis was used to calculate overall survival.

Results: In a national cohort of 36,453 patients with PDAC, the incidence increased from 12.1 (1997-2000) to 15.3 (2013-2016) per 100,000 ($p<0.001$), whereas median overall survival increased from 3.1 to 3.8 months ($p<0.001$). Over time, the resection rate doubled (8.3%-16.6%, p-trend<0.001), more patients received adjuvant chemotherapy (3.0%-56.2%, p-trend<0.001) and 3-year overall survival following resection increased (16.9%-25.4%, $p<0.001$). Over time, the proportion of patients with metastatic disease who received palliative chemotherapy increased from 5.3% to 16.1% (p-trend<0.001), whereas 1-year survival improved from 13.3% to 21.2% ($p<0.001$). The proportion of patients who only received supportive care decreased from 84% to 61% (p-trend<0.001).

Conclusion: The incidence of PDAC increased in the past two decades. Resection rates and use of adjuvant or palliative chemotherapy increased with improved survival in these patients. In all patients with PDAC, however, the survival benefit of 3 weeks is negligible because the majority of patients only received supportive care.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with a poor survival. Reported 5-year relative survival rates range around 8.5%, and in 2018 alone, 430,000 patients died from PDAC worldwide.[1] In the last two decades, studies showed an improved survival in patients with PDAC based on new oncological treatments. In 2007, a randomised controlled trial demonstrated that the use of adjuvant gemcitabine improved survival in patients after resection.[2] Randomised trials also demonstrated that the use of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), and gemcitabine plus nab-paclitaxel improved survival in patients with metastatic PDAC, as compared with gemcitabine alone.[3–5] In addition, prospective cohort studies and a systematic review described that FOLFIRINOX improved survival in patients with locally advanced PDAC, though randomised studies are not yet available.[6–9]

It is currently unclear what the impact of these improvements in the treatment of PDAC has been on a nationwide scale.[10] It is known that the strict eligibility criteria in randomised trials hamper extrapolation to the general population. Global trends of PDAC have recently been reviewed, but the most recent nationwide evaluation from Europe dates over a decade ago (i.e. 2008).[11–13]
In 2012, the Dutch Pancreatic Cancer Group was formed with the aim to improve survival of PDAC. Since then, the centralisation and standardisation of PDAC care in the Netherlands has continued, and the implementation of new chemotherapy regimens has been supported. We were interested whether these developments have changed the survival of patients with PDAC on a population-based scale in the Netherlands. The objective of this study, therefore, is to evaluate trends in incidence, treatment and survival for patients with all stages of PDAC in the Netherlands between 1997-2016.

METHODS

Study design

All patients with primary PDAC diagnosed from 1997 to 2016 were included from the Netherlands Cancer Registry (NCR), a population-based database that covers all Dutch hospitals (i.e. a population of 17.3 million). Patients with a newly diagnosed malignancy are identified by two-step signaling consisting of (1) automatic notifications of the national pathological archive and the National Registry of Hospital Discharge Diagnoses and (2) verification of notifications in medical files in hospitals. Patient, tumour and treatment characteristics are routinely collected from medical records by trained NCR administrators. This study was designed in accordance with the STROBE guidelines.[14] The scientific committee of the Dutch Pancreatic Cancer Group approved the study protocol.

Study population

Patients with primary PDAC were included. This diagnosis was based on the International Classification of Disease-Oncology (ICD-O-3) morphology codes according to the WHO classification (Supplementary Material).[15] Patients aged younger than 18 years at diagnosis or patients diagnosed during autopsy were excluded.

Data collection

Socioeconomic status (SES) was based on social deprivation scores per 4-digit postal code (reference data from The Netherlands Institute of Social Research) and categorised into three SES groups (high: 1st-3rd, intermediate 4th-7th, low: 8th-10th deciles). The time of diagnosis was divided into five periods: 1997-2000, 2001-2004, 2005-2008, 2009-2012, and 2013-2016 to facilitate analyses. Primary tumour location was classified as pancreatic head, body, tail or other/non-specified (C25.3, C25.5-9), according to the ICD-O-3 codes. Tumour stage was based on the pathological tumour-node-metastasis (TNM) classification at the time of registration (revised 4th edition of IUCC TNM staging during 1997-1998, 5th edition during 1999-2002, 6th edition during 2003-2009, 7th edition during 2010-2016), supplemented with the clinical TNM classification in case of non-resected tumours or neoadjuvant therapy.[16–19] A one-digit summary stage (Extent of Disease) was recorded in patients without pathological confirmation of cancer.[20] Based on the tumour stage at primary diagnosis and the primary subsequent treatment, patients with PDAC were divided into four groups: (1) patients with localised disease who underwent resection with or without (neo)adjuvant chemo(radio)therapy; (2) patients with localised disease who received chemo(radio)therapy without resection (patients with locally advanced pancreatic cancer and patients unfit for surgery); (3) patients with metastatic disease at diagnosis who received chemotherapy; (4) patients who received supportive care only (and did not receive any tumour directed therapy). Patients treated with chemotherapy but without the possibility to distinguish metastatic or localised diseased (n=43) were excluded. Time to treatment analyses could not be performed because the diagnosis is based on pathology which was often the date of surgery. Furthermore, date of resection was only available since 2015 and start of chemotherapy since 2011. Survival was defined as the time between date of diagnosis and date of death or censored at last follow-up date and was obtained by linkage of the NCR with the Municipal Personal Records Database (updated in February 2019).

Statistical analysis

The incidence of PDAC was described in new cases per 100.000 persons per year stratified by sex, together with the estimated annual percent of change (EAPC). To compare results with old and new literature, the incidence rates were age-standardised to both the European standard population from 1976 (ESP) and the revised ESP from 2013 (RESP).[21,22] The age-standardised incidence is the incidence

that would be observed if the study population had the age structure of the standard population and is essential to compare rates over time or between geographical regions. Imputation was not performed, and missing data were described in the baseline characteristics. Trends over time in treatment were analysed with the Chi-square test for trend. Median overall survival, 3-month survival and 1-, 3- and 5-year survival were calculated using the Kaplan-Meier method and compared using the log rank test. Analyses were based on type of treatment and stratified by period. To demonstrate whether changes in resection and chemotherapy rate were associated with differences in overall survival over time, multivariable Cox regression models, adjusted for potential confounders, were performed without and with these treatment variables. Potential confounders were sex, age, SES, primary tumour location and tumour stage. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All p-values were based on a 2-sided test, and p-values of <0.05 were considered statistically significant. Data were analysed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (cran.r-project.org).

RESULTS

From 1997 to 2016, 36,453 patients were diagnosed with PDAC. The incidence increased from 12.1 to 15.3 per 100,000 persons from 1997 to 2016 (RESP-based, EAPC 1.5%, p<0.001, Figure 1A). The incidence was higher in males and increased significantly for both sexes from 1997 to 2016 (RESP-based, EAPC 1.5%, p<0.001 and EAPC 1.6%, p<0.001, respectively). The ESP-based incidence increased similarly with an EAPC of 1.5% for the overall group (Figure 1B). Median age at diagnosis was 71 years (Table 1). The incidence was highest in patients aged 60-74 year compared with patients aged <60 year or ≥75 year, but increased significantly in all age categories (RESP based, EAPC 1.95 p<0.001, EAPC 0.87 p=0.01 and EAPC p<0.001, respectively, Figure 2A).

All stages pancreatic cancer

Pathological confirmation increased over the years from 58.4% in 1997-2000 to 71.9% in 2013-2016 (p-trend<0.001). Metastatic disease at diagnosis was present in 19,119 patients (52.4%) and increased from 45.2% in 1997-2000 to 57.0% in 2013-2016 (p-trend<0.001). More patients were treated with (neo)adjuvant or palliative chemotherapy (Table 2). Median overall survival was 3.5 months (95%CI 3.5-3.6) for the entire cohort and increased from 3.1 months in 1997-2000 to 3.8 months in 2013-2016 (p<0.001, Table 1). Survival at 3 months after diagnosis increased from 50.9% (95%CI 49.6-52.2) to 56.5% (95%CI 55.5-57.5) (p<0.001, Figure 3D) and 1-year survival from 13.4% (95%CI 12.5-14.3) to 21.0% (95%CI 20.1-21.8, p<0.001). The association between time period of diagnosis and overall survival was significant in multivariable Cox regression, but after including resection and chemotherapy treatment to the Cox model, this association disappeared for all periods except for 2001-2004 (Table 3).

FIGURE 1. Age-standardised incidence rates of patient with pancreatic ductal adenocarcinoma in the Netherlands stratified by sex (1997-2016).

FIGURE 1A. Age-standardised incidence rates based on the Revised European Standard Population.

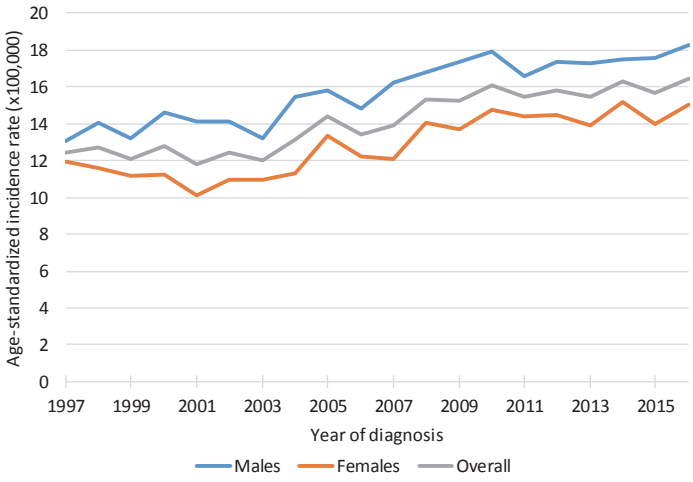


FIGURE 1B. Age-standardized incidence rates based on the European Standard Population.

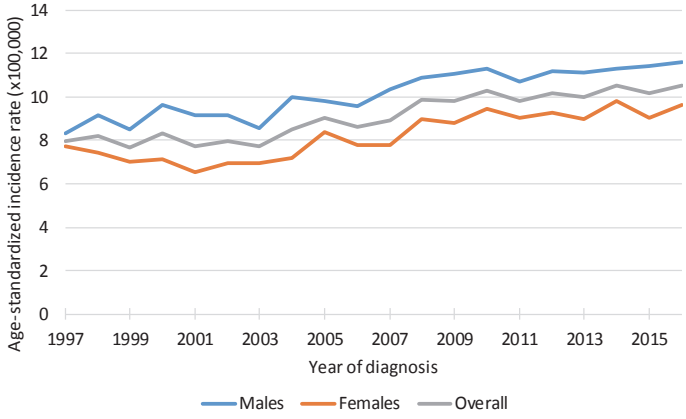


TABLE 1. Patient, tumour and treatment characteristics of 36,453 patients diagnosed with pancreatic ductal adenocarcinoma between 1997-2016 in the Netherlands.

	All patients (n = 36,453)	Patients with localised disease who underwent resection (n = 4,387)	Patients with localised disease who received chemo(radio)therapy (n= 1,604)	Patients with distant metastases who received chemotherapy (n = 4,074)	Patients who only received supportive care (n = 26,388)
Male	18,161 (59.8%)	2,348 (53.5%)	873 (54,4%)	2,288 (56,2%)	12,652 (47.9%)
Age, median (IQR)	71.0 (62.0-78.0)	66.0 (59.0-72.0)	64.0 (56.0-70.0)	63.0 (56.0-69.0)	74.0 (65.0-80.0)
< 60 years	6,658 (18.3%)	1,184 (27.0%)	556 (34.7%)	1,491 (36.6%)	3,427 (13.0%)
60-74 years	16,300 (44.7%)	2,488 (56.7%)	877 (54.7%)	2,267 (55.6%)	10,668 (40.4%)
≥ 75 years	13,495 (37.0%)	715 (16.3%)	171 (10.7%)	316 (7.8%)	12,293 (46.6%)
SES					
Low	10,862 (29.8%)	1,389 (31.7%)	511 (31.9%)	1,323 (32.5%)	7,639 (28.9%)
Medium	14,610 (40.1%)	1,775 (405%)	626 (39.0%)	1,649 (40.5%)	10,560 (40.0%)
High	10,981 (30.1%)	1,223 (27.9%)	467 (29.1%)	1,102 (27.0%)	8,189 (31.0%)
Primary tumour location					
Head of pancreas	23,129 (63.4%)	3,559 (81.1%)	1,097 (6.,4%)	1,810 (44.4%)	16,663 (63.1%)
Body of pancreas	3,589 (9.8%)	166 (3.8%)	258 (16.1%)	666 (16.3%)	2,499 (9.5%)
Tail of pancreas	4,682 (12.8%)	319 (7.3%)	68 (4.2%)	956 (23.5%)	3,339 (12.7%)
Other / non-specified (C25.3, C25.5-9)	5053 (13.9%)	343 (7.8%)	181 (11.3%)	642 (15.8%)	3,887 (14.7%)
Tumour stage*					
Local disease / within pancreas	3,915 (10.7%)	594 (13.5%)	125 (7.8%)	-	3,196 (12.1%)
Extended disease / growth outside pancreas	10,776 (29.6%)	3,579 (81.6%)	1,451 (90.5%)	-	5,746 (21.8%)
Metastatic disease	19,119 (52.4%)	185 (4.2%)	-	4,074 (100%)	14,860 (56.3%)
Unknown	2,643 (7.3%)	29 (0.7%)	28 (1.7%)	-	2,586 (9.8%)
Overall survival in months, median (95% CI)	3.5 (3.5-3.6)	16.9 (16.4-17.4)	10.5 (10.1-11.0)	5.8 (5.7-6.0)	2.3 (2.3-2.3)
Patient treated with chemo(radio)therapy	-	21.9 (20.8-23.1)	-	-	-
Patients not treated with chemo(radio)therapy	-	13.4 (12.8-14.1)	-	-	-

* Tumour stage was based on the pathological TNM classification at the time of registration, supplemented with the clinical TNM or a summary stage (no microscopic verification) in case of non-resected tumours or neoadjuvant therapy.

FIGURE 2. Age-standardised incidence rates of patient with pancreatic ductal adenocarcinoma in the Netherlands stratified by age (1997-2016).

FIGURE 2A. Age-standardised incidence rates based on the Revised European Standard Population.

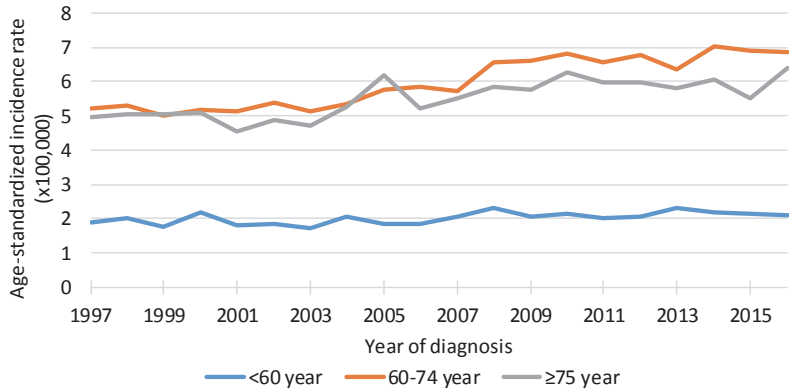
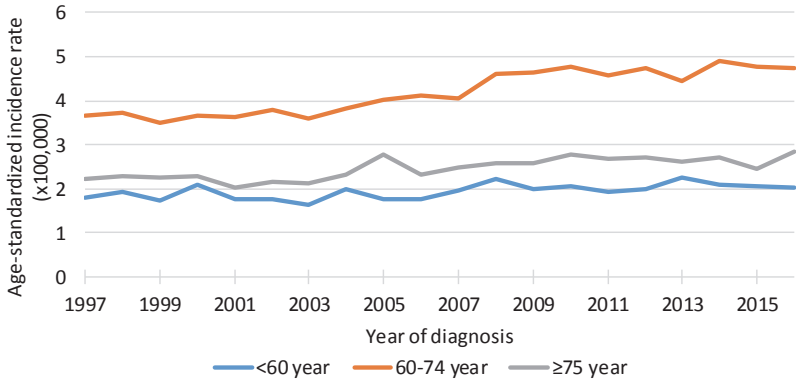


FIGURE 2B. Age-standardised incidence rates based on the European Standard Population.



Patients with localised disease who underwent resection

Resection was performed in 4,387 patients (12.0%), and this percentage doubled from 8.3% in 1997-2000 to 16.6% in 2013-2016 (p-trend<0.001). This increase applied to all age groups (<60 years from 15.2% to 23.8%, 60-74 years from 10.7% to 19.4% and ≥75 years from 2.0% to 9.6%). The use of adjuvant chemotherapy increased from 3.0% in 1997-2000 to 21.1% in 2005-2008 and 56.2% in 2013-2016 (p<0.001, Table 2). In 2013-2016, 8.5% of patients who underwent resection received neoadjuvant chemotherapy. The use of (mainly adjuvant) radiotherapy remained negligible over the years (3.5% of patients).

TABLE 2. Trends in treatment.

	1997-2016 n = 36,453	1997-2000 n = 5,572	2001-2004 n = 5,858	2005-2008 n = 7,179	2009-2012 n = 8,470	2013-2016 n = 9,374	p-value (trend over periods)
Patients with localised disease who underwent resection	4,387 (12.0%)	465 (8.3%)	485 (8.3%)	730 (10.2%)	1,153 (13.6%)	1,554 (16.6%)	<0.001
Neoadjuvant chemotherapy	168 (3.8%)	1 (0.2%)	4 (0.8%)	7 (1.0%)	24 (2.1%)	132 (8.5%)	<0.001
Adjuvant chemotherapy	1,646 (37.5%)	14 (3.0%)	33 (6.8%)	154 (21.1%)	571 (49.5%)	874 (56.2%)	<0.001
Patients with localised disease who received chemo(radio)therapy	1,604 (4.4%)	119 (2.1%)	149 (2.5%)	321 (4.5%)	463 (5.5%)	552 (5.8%)	<0.001
Patients with metastatic disease who received chemotherapy	4,074 (11.2%)	294 (5.3%)	420 (7.2%)	660 (9.2%)	1,188 (14.0%)	1,512 (16.1%)	<0.001
Patients who only received supportive care	26,388 (72.4%)	4,694 (84.2%)	4,804 (82.0%)	5,468 (76.2%)	5,666 (66.9%)	5,756 (61.4%)	<0.001

In all patients who underwent resection, median overall survival was 16.9 months (95% CI 16.4-17.4, Table 1 and Figure 3A). Median overall survival was better with (neo)adjuvant chemotherapy (21.9 months, 95% CI 20.8-23.1) than without (13.4 months, 95% CI 12.8-14.1, p<0.001, Supplemental Figure 1A and 1B). In all patients after resection, 1-year survival increased significantly from 56.1% (95%CI 51.8-60.8) in 1997-2000 to 68.7% (95%CI 66.5-71.1) in 2013-2016 and 5-year survival from 9.1% (95%CI 6.8-12.2) to 16.5% (95%CI 14.3-18.9), respectively.

Patients with localised disease who received chemo(radio)therapy without resection

Of all patients with PDAC, 1,604 patients (4.4%) had localised disease and received chemo(radio)therapy without resection (Table 2). This proportion of patients increased from 2.1% in 1997-2000 to 5.8% in 2013-2016 (p-trend<0.001). Pathological confirmation was present in 1,363 of these patients (85.0%). The use of radiotherapy decreased from 39.5% to 17.7% (p-trend<0.001). Median overall survival was 11 months (95% CI 10-11, Table 1). Three-month and 1-year and 3-year survival were relatively constant over time (Figure 3B).

Patient with metastatic disease who received chemotherapy

In total, 4,074 patients (11.2% of patients with all stages of PDAC, 21.3% of patients with metastatic disease) received chemotherapy for distant metastases (Table 2). In 3,724 treated patients (91.4%), the tumour was pathologically confirmed. The proportion of patients who received chemotherapy for distant metastases increased from 5.3% in 1997-2000 to 16.1% of all patients with PDAC in 2013-2016 (p-trend<0.001) and from 11.7% to 28.3% of patients with metastatic disease (p-trend<0.001), respectively. The use of radiotherapy decreased from 7.8% to 1.1%, p-trend<0.001. Median overall survival was 5.9 months (95% CI 5.7-6.0, Table 1 and Figure 3C) and the 1-year survival increased from 13.3% (95%CI 9.9-17.7) in 1997-2000 to 21.2% (95%CI 19.2-23.3) in 2013-2016 (p<0.001).

Patients who received supportive care only

The majority of patients with PDAC (72.4%) received supportive care only. This percentage decreased significantly (84% in 1997-2000 to 61% in 2013-2016, Table 2, p-trend<0.001). Median overall survival was 2.3 months (70 days, 95%CI 2.3-2.3 months, Table 1) and was less for patients with metastatic disease compared with local or extended disease (1.6 months, 95%CI 1.6-1.7; 4.6 months, 95%CI 4.4-4.8; 4.1 months, 95%CI 4.0-4.3, respectively). In all patients with supportive care only, the 3-month survival decreased significantly from 44.6% (95%CI 43.2-46.1) in 1997-2000 to 36.4% (95%CI 35.2-37.7) in 2013-2016 (Supplemental Figure 1C).

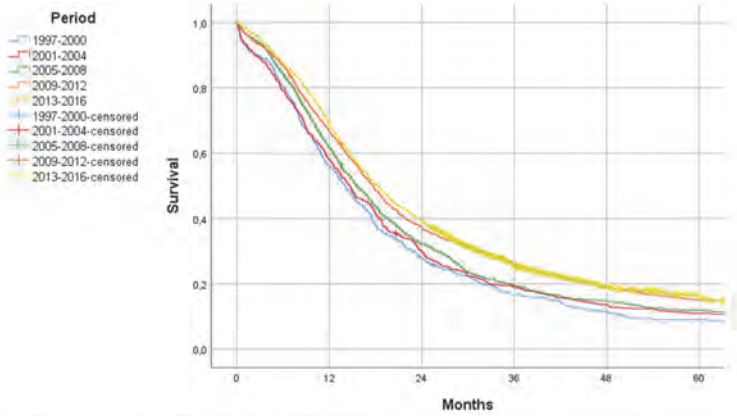
TABLE 3. Univariate and multivariable Cox regressions to assess the effect of resection and chemotherapy on the association between time of diagnosis and mortality in patients with pancreatic ductal adenocarcinoma (1997-2016).

Cox regression	Median overall survival, months	Multivariable analysis without treatment variables HR (95 %CI)	Multivariable analysis including treatment variables HR (95% CI)
Time of diagnosis			
1997-2000	3.1	1.00 (reference)	1.00 (reference)
2001-2004	3.2	**0.94 (0.91-0.98)**	**0.96 (0.93-1.00)**
2005-2008	3.5	**0.92 (0.89-0.96)**	1.00 (0.96-1.03)
2009-2012	3.7	**0.82 (0.79-0.85)**	0.99 (0.95-1.02)
2013-2016	3.8	**0.75 (0.72-0.77)**	0.98 (0.95-1.02)
Sex			
Male	3.5	1.00 (reference)	1.00 (reference)
Female	3.6	**0.98 (0.96-1.00)**	**0.96 (0.94-0.98)**
Age			
< 60 years	5.2	1.00 (reference)	1.00 (reference)
60-74 years	3.9	**1.24 (1.21-1.28)**	**1.11 (1.08-1.14)**
≥ 75 years	2.5	**1.91 (1.86-1.97)**	**1.32 (1.27-1.36)**
SES			
Low	3.8	1.00 (reference)	1.00 (reference)
Medium	3.5	**1.03 (1.01-1.06)**	**1.01 (0.99-1.04)**
High	3.3	**1.08 (1.06-1.11)**	**1.05 (1.02-1.08)**
Primary tumour location			
Head of pancreas	4.3	1.00 (reference)	1.00 (reference)
Body of pancreas	3.2	**1.08 (1.04-1.12)**	**1.06 (1.02-1.10)**
Tail of pancreas	2.1	**1.19 (1.15-1.23)**	**1.24 (1.20-1.28)**
Other	2.4	**1.23 (1.19-1.27)**	**1.21 (1.17-1.25)**
Tumour stage*			
Local disease / within pancreas	5.7	1.00 (reference)	1.00 (reference)
Extended disease / growth outside pancreas	7.6	**1.09 (1.05-1.13)**	**1.35 (1.30-1.40)**
Metastases	2.2	**2.69 (2.59-2.79)**	**2.53 (2.44-2.63)**
Unknown	2.7	**1.59 (1.51-1.67)**	**1.40 (1.33-1.47)**
Resection		Not included	
Yes	16.9		1.00 (reference)
No	2.9		**2.54 (2.45-2.64)**
Any chemotherapy treatment		Not included	
Yes	9.1		1.00 (reference)
No	2.6		**2.21 (2.14-2.27)**

HR, hazard ratio; SES, socioeconomic status; CI, confidence interval; TNM, tumour-node-metastasis. Bold numbers indicate statistical significance. * Tumour stage was based on the pathological TNM classification at the time of registration, supplemented with the clinical TNM in case of non-resected tumours or neoadjuvant therapy.

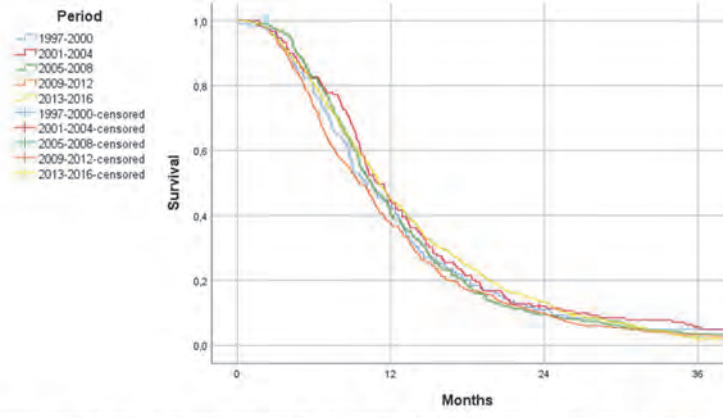
FIGURE 3. Kaplan Meier curve and survival at 3 months, 1, 3, 5 years among patients with pancreatic ductal adenocarcinoma per period of diagnosis (1997-2016).

FIGURE 3A. Survival of patients with localised disease who underwent tumour resection.



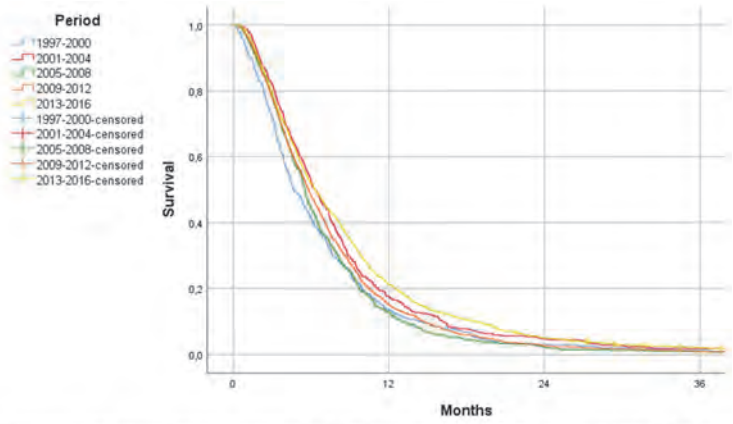
A	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)	5 year (95%CI)
1997-2000	14.0 (12.5-15.4)	89.5% (86.7-92.3%)	56.1% (51.8-60.8%)	16.9% (13.8-20.7%)	9.1% (6.8-12.2%)
2001-2004	14.6 (12.9-16.3)	88.9% (86.1-91.7%)	57.9% (53.7-62.5%)	19.1% (15.9-22.9%)	11.0% (8.5-14.2%)
2005-2008	15.5 (14.2-16.9)	93.6% (91.8-95.4%)	61.9% (58.5-65.5%)	19.5% (16.8-22.6%)	12.0% (9.8-14.6%)
2009-2012	17.6 (16.7-18.6)	93.1% (91.7-94.6%)	66.7% (64.0-69.5%)	26.3% (23.8-28.9%)	15.1% (13.2-17.3%)
2013-2016	18.1 (17.1-19.1)	95.0% (94.0-96.1%)	68.7% (66.5-71.1%)	25.4% (23.3-27.8%)	16.5% (14.3-18.9%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

FIGURE 3B. Survival of patients with localised disease who received chemo (radio)therapy without resection.



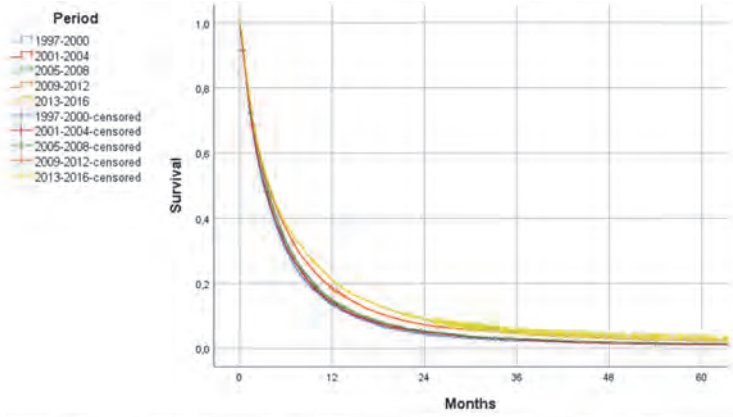
B	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)
1997-2000	10.1 (8.1-12.1)	95.8% (92.3-99.5%)	42.8% (34.8-52.7%)	5.0% (2.3-1.1%)
2001-2004	11.0 (9.6-12.4)	96.6% (93.8-99.6%)	44.3% (37.0-53.0%)	5.7% (2.9-11.0%)
2005-2008	10.5 (9.5-11.5)	97.2% (95.4-99.0%)	40.5% (35.5-46.2%)	3.4% (1.9-6.1%)
2009-2012	9.5 (8.7-10.4)	94.4% (92.3-96.5%)	37.4% (33.2-42.0%)	3.0% (1.8-5.1%)
2013-2016	11.0 (10.3-11.7)	94.6% (92.7-96.5%)	45.1% (41.1-49.4%)	2.1% (1.1-4.1%)
p-value	0.106	0.315	0.040	0.072

FIGURE 3C. Survival of patients with synchronous distant metastases who received chemotherapy.



C	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)
1997-2000	4.6 (4.0-5.3)	72.1% (67.6-77.4%)	13.3% (9.9-17.7%)	1.4% (0.5-3.6%)
2001-2004	6.3 (5.7-7.0)	81.9% (78.3-85.7%)	17.6% (14.3-21.7%)	1.9% (1.0-3.8%)
2005-2008	5.5 (5.2-5.8)	77.9% (74.8-81.1%)	12.7% (10.4-11.5%)	1.1% (0.5-2.2%)
2009-2012	5.8 (5.5-6.1)	78.1% (75.8-80.5%)	15.1% (13.2-17.2%)	1.0% (0.6-1.8%)
2013-2016	6.3 (5.9-6.7)	79.5% (77.5-81.6%)	21.2% (19.2-23.3%)	2.2% (1.5-3.1%)
p-value	<0.001	0.013	<0.001	<0.001

FIGURE 3D. Survival of all patient.



D	mOS (months)	3 month (95%CI)	1 year (95%CI)	3 year (95%CI)	5 year (95%CI)
1997-2000	3.1 (2.9-3.2)	50.9% (49.6-52.2%)	13.4% (12.5-14.3%)	2.4% (2.0-2.8%)	1.3% (1.1-1.7%)
2001-2004	3.2 (3.1-3.4)	52.1% (50.8-53.4%)	14.1% (13.2-15.0%)	2.8% (2.4-3.2%)	1.2% (0.98-1.6%)
2005-2008	3.5 (3.3-3.6)	54.3% (53.2-55.5%)	14.7% (13.9-15.6%)	3.0% (2.6-3.4%)	1.6% (1.3-1.9%)
2009-2012	3.7 (3.6-3.9)	55.7% (54.6-56.8%)	18.5% (17.7-19.4%)	4.6% (4.2-5.1%)	2.5% (2.2-2.8%)
2013-2016	3.8 (3.7-4.0)	56.5% (55.5-57.5%)	21.0% (20.1-21.8%)	5.4% (4.9-5.9%)	3.4% (3.0-3.9%)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

CI, confidence interval.

DISCUSSION

This Dutch population-based study found an increasing incidence of PDAC in the period 1997-2016, and 23% more patients being treated with resection and/or systemic treatment. The resection rate doubled (8.3% to 16.6%), more patients received adjuvant chemotherapy (3.0% to 56.2%), and 3-year overall survival following resection increased (16.9% to 25.4%). The proportion of patients with metastatic disease who received palliative chemotherapy increased (5.3% to 16.1%), whereas 1-year survival improved (13.3% to 21.2%). Most strikingly, however, throughout the entire study period, the majority of patients received supportive care only. This could explain the negligible improvement in overall survival of only 3 weeks (0.7 months) to 3.8 months for the entire population.

It appears that improvements in oncological treatments of any kind are the most likely explanations for the increased overall survival. However, the overall survival advantage for all patients is disappointing compared with for example colorectal cancer.[23] It is clear that improvements are needed, for instance through early detection of PDAC and better or individualised treatments.[24] Survival increased in patients with localised disease who underwent resection in the most recent years (2009-2016). Resection rates doubled, and this is likely explained by centralisation with improved referral patterns, improved surgical techniques and – in recent years – extending indications for surgery (e.g. locally advanced disease with response to chemotherapy).[25] Moreover, postoperative complications and mortality after pancreatic resection decreased, which increased the number of patients eligible for adjuvant treatment.[26–28] This increase was probably also strongly related to several adjuvant chemotherapy studies, such as the ESPAC-1 trial in 2004 and the CONKO-001 trial in 2007.[2,29] The use of neoadjuvant chemo(radio)therapy mainly increased since 2013 with the start of the Dutch PREOPANC-1 trial on neoadjuvant chemoradiotherapy in patients with (borderline) resectable pancreatic cancer (NL3525, EudraCT number 2012-003181-40).[30] Survival in patients with localised disease who undergo a resection may further improve because of new (neo)adjuvant chemotherapy regimens, as recently was proven for adjuvant therapy with modified FOLFIRINOX.[31] In patients who underwent a resection, the use of radiotherapy was negligible during the study period. The role of radiotherapy remains under debate, and literature is inconclusive.[32]

In patients with metastatic disease who received chemotherapy, survival rates increased, especially from 2005-2008 to 2009-2012 (1-year survival 12.7% and 21.2%, respectively), probably explained by the uptake of new combinations of chemotherapeutic agents FOLFIRINOX and gemcitabine plus nab-paclitaxel.[3–5] The percentage of patients who only received supportive care decreased, as did their survival. More patients were treated with chemotherapy and relatively more elderly underwent surgery

and thus especially patients with a relatively poor prognosis received supportive care only and subsequently overall survival decreased.[33]

Locally advanced pancreatic cancer was initially not registered in the NCR, and in this study, these patients were categorised as patients with localised disease without metastases. Depending on their treatment they were included in the group of patients who underwent resection or patients with localised disease who received chemo(radio)therapy without resection. This last group was small, but increased over the years, probably related to more attention for patients with locally advanced disease after the introduction of FOLFIRINOX.[34] In addition, after FOLFIRINOX treatment emerged, resection rates in patients with locally advanced disease increased.[7,8]

Survival differed between tumour locations. Patients with tumours of the pancreatic body or tail had worse survival compared with patients with pancreatic head tumours. This was also seen in other series.[35,36] Diagnostic delay of patients with body and tail tumours, because of lack of early symptoms such as jaundice, may play some role, but it seems that body and tail tumours mostly have a more aggressive tumour biology.[37–39]

In general, the incidence of PDAC varies across countries.[11,12,40] The incidence is highest in North America and Western Europe and continues to increase.[11,12,41,42] This increase could be related to the increased exposure to risk factors, such as obesity, alcohol or diabetes and because of increased availability of high-quality cross-sectional imaging.[11,12,40] Better diagnostic modalities could explain the increased proportion of patients with metastatic disease at diagnosis (i.e. stage migration). Older age was given a greater weighting in the RESP, and therefore, the incidence was higher if calculated with the RESP than with the ESP, which represents the age shift that is occurring in Europe. An analysis of incidence of PDAC across Europe described an age-standardised incidence, based on the ESP, between 12 (UK/Ireland and southern Europe) to 15 (northern and eastern Europe) per 100.000 persons per year between 2000-2007.[43] The incidence in our population was lower in this period with 8-9 per 100.000 person annually.

The findings of this study should be seen in light of several limitations. First, the division of the patients into four subgroups based on clinical findings of metastases and treatment. A classification in the commonly seen subgroups of resectable, locally advanced, and metastatic disease was not possible. Second, the actual incidence of PDAC might have been higher than reported in the NCR.[44] However, this probably did not influence the trend over the years because the notification sources of the NCR remained stable and similar patterns of mortality rates in Statistics Netherlands were found.[45] Third, information on tumour stage was lacking in several patients diagnosed in earlier time periods. Stage

migration because of improved imaging equipment may have influenced grouping of patients but not patterns in the entire population. The main strength of this study is the analysis of population-based nationwide data with a very high national coverage. The results are therefore more representative than studies with selective cohorts, for example randomised controlled trials or from single, high volume centres.

In conclusion, the incidence of PDAC increased over the last two decades, while overall survival only improved marginally despite an increase of patients receiving treatment (16% to 39%). Survival increased in the subgroup of patients who underwent pancreatic resection (3-year survival: 16.9% to 25.4%) and in patients with metastatic disease who received chemotherapy (1-year survival: 13.3% to 21.2%). However, because the survival of pancreatic cancer only improved with 3 weeks for the entire population and still the majority of patients only received supportive care, there is a clear and urgent need for further improvement in diagnostics and treatment of PDAC.

ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection. The Dutch Pancreatic Cancer Project, including the Netherlands Cancer Registry, received funding from the Dutch Cancer Society (KWF Kankerbestrijding; grant no. UVA2013-5842).

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SUPPLEMENTARY MATERIAL

Supplementary material is available online.

CHAPTER 2

Nationwide compliance with a multidisciplinary guideline on pancreatic cancer during 6-year follow-up

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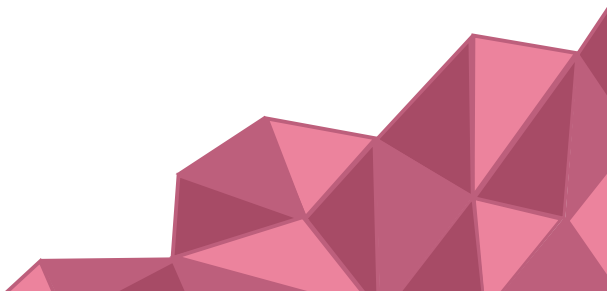
Pancreatology. 2020 Dec;20(8):1723-1731.



ABSTRACT

Background: Compliance with national guidelines on pancreatic cancer management could improve patient outcomes. Early compliance with the Dutch guideline was poor. The aim was to assess compliance with this guideline during six years after publication.

Materials and methods: Nationwide guideline compliance was investigated for three subsequent time periods (2012-2013 vs. 2014-2015 vs. 2016-2017) in patients with pancreatic cancer using five quality indicators in the Netherlands Cancer Registry: 1) discussion in multidisciplinary team meeting (MDT), 2) maximum 3-week interval from final MDT to start of treatment, 3) preoperative biliary drainage when bilirubin >250 µmol/L, 4) use of adjuvant chemotherapy, and 5) chemotherapy for inoperable disease (non-metastatic and metastatic).

Results: In total, 14 491 patients were included of whom 2 290 (15.8%) underwent resection and 4 561 (31.5%) received chemotherapy. Most quality indicators did not change over time: overall, 88.8% of patients treated with curative intent were discussed in a MDT, 42.7% were treated with curative intent within the 3-week interval, 62.7% with a resectable head tumor and bilirubin >250 µmol/L underwent preoperative biliary drainage, 57.2% received chemotherapy after resection, and 36.6% with metastatic disease received chemotherapy. Only use of chemotherapy for non-metastatic, non-resected disease improved over time (23.4% vs. 25.6% vs. 29.7%).

Conclusion: Nationwide compliance to five quality indicators for the guideline on pancreatic cancer management showed little to no improvement during six years after publication. Besides critical review of the current quality indicators, these outcomes may suggest that a nationwide implementation program is required to increase compliance to guideline recommendations.

INTRODUCTION

Despite advances in the management of pancreatic ductal adenocarcinoma (here: pancreatic cancer) in recent years, patient outcomes are still poor.[1,2] National guidelines may improve diagnosis and treatment of pancreatic cancer resulting in improved survival and quality of life.[3] Previous systematic reviews, however, have demonstrated that implementation of guidelines in clinical practice is often difficult and that the implementation varies greatly between the various recommendations.[4,5] In the Netherlands, impact of guidelines for general practitioners mostly on clinical care was observed in 17 of 19 studies with largely varying effect sizes across the different recommendations, while effects on patient outcomes, observed in 6 of 9 studies, were small.[5] Similar effects may be seen after implementation of guidelines for specialist care such as in pancreatic cancer.

In 2011, a new national multidisciplinary guideline on diagnosis and treatment of pancreatic cancer was introduced in the Netherlands.[6] At that time, three quality indicators were identified: patients discussed in a multidisciplinary team (MDT) meeting, treated within a maximum 3-week interval between final MDT meeting and start of treatment, and use of adjuvant chemotherapy. One year later, in 2012, compliance to these three quality indicators was investigated using the Netherlands Cancer Registry (NCR). At that moment, guideline compliance was considered poor; 64% of patients with a suspected pancreatic or periampullary cancer were discussed in an MDT meeting, 39% of patients met the maximum 3-week interval between final MDT meeting and start of treatment, and 54% of patients received adjuvant chemotherapy after resection of pancreatic cancer.[7]

For this study, two additional indicators were selected by the Dutch Pancreatic Cancer Group[8]: preoperative biliary drainage in patients with a bilirubin >250 µmol/L and chemotherapy for inoperable (non-metastatic and metastatic) pancreatic cancer. International guidelines recommend preoperative biliairy drainage in case of severe (symptomatic) jaundice to reduce symptoms and postoperative complications.[9,10] Chemotherapy for inoperable cancer is recommended for patients with adequate performance as it can improve survival and quality of life, and may even convert locally advanced to resectable disease in 10-25% of patients.[11-15]

An update of the national Dutch guideline was recently published in 2019[16] and it is unclear whether a structured implementation program should accompany this new guideline or whether with time guideline compliance will improve naturally. It is therefore of interest to know whether the compliance after the 2011 guideline has increased over the years after introduction. Suboptimal compliance would provide a strong incentive to develop implementation strategies for guidelines to improve outcomes of pancreatic cancer patients nationwide. Therefore, the aim of this study was to assess compliance to the

2011 Dutch guideline on diagnosis and treatment of pancreatic cancer in the years 2012-2013 vs. 2014-2015 vs. 2016-2017.

METHODS

Study design

This was a retrospective nationwide study using clinical data from the population-based NCR between 2012-2017. The NCR covers the total Dutch population of approximately 17 million inhabitants. This study was designed in accordance with the STROBE guidelines[17] and the protocol was approved by the scientific committee of the Dutch Pancreatic Cancer Group.[8]

Study population

Patients registered in the NCR and diagnosed with pancreatic ductal adenocarcinoma (International Classification of Disease – Oncology (ICD-O-3) C25 excluding C25.4 and morphology code 8000, 8010, 8012, 8020, 8140, 8141, 8260, 8310, 8440, 8453, 8480, 8481, 8490, 8500 and 8560) were included. Patients <18 years at diagnosis or who were diagnosed abroad or at autopsy were excluded.

Data collection and definitions

Data were routinely collected from medical records by trained NCR data managers. Treatment with curative intent was defined as neoadjuvant chemotherapy, resection, or surgical exploration with curative intent without resection. Tumor-directed treatment was defined as resection or chemo(radio)therapy. Patients who received at least one course of palliative or (neo)adjuvant chemotherapy were categorized as the chemotherapy receiving group. Highest bilirubin before tumor-directed treatment or preoperative biliary drainage was registered. Preoperative biliary drainage was performed either with stent or percutaneously, before exploration or resection. Tumor stage was classified according to TNM 7 for the years 2012-2016 and to TNM 8 for 2017. Pathological tumor stage was used primarily if available and was complemented by clinical tumor stage. The total cohort was divided into three time periods based on date of diagnosis: period 1 (2012-2013), period 2 (2014-2015), and period 3 (2016-2017). Additionally, patients who either initiated tumor-directed treatment or underwent exploration were assigned to non-academic or academic hospital based on center of treatment, and the remaining patients (receiving best supportive care) based on center of clinical diagnosis.

Outcome measures

The primary outcome measure was the rate of compliance to five quality indicators in the three periods: 1) discussion in a MDT for pancreatic cancer who were treated with curative intent (MDT data available

in 2012 partially for 8/9 regions for May 1st until December 31st (59.2% of all patients in 2012), and in 2014-2017 completely. Numerator indicator 1: patients with pancreatic cancer who were treated with curative intent and who were discussed in a MDT. Denominator indicator 1: all patients with pancreatic cancer who were treated with curative intent.); 2) maximum transit time until start of treatment with curative intent (available 2014-2017; 2A: maximum 3-week interval between final MDT meeting and start of treatment[7]; 2B: maximum 6-week interval between first contact and start of treatment (based on national 'SONCOS' guidelines for oncological care[18]); 3) preoperative biliary drainage for pancreatic head cancer and bilirubin >250 µmol/L (available 2015-2017, normal total bilirubin values are <17 µmol/L); 4) adjuvant chemotherapy after resection of pancreatic cancer (available 2012-2017); and 5) palliative chemotherapy for inoperable pancreatic cancer (available 2012-2017; 5A: metastatic disease, non-resected; 5B: non-metastatic disease, non-resected; excluding patients who died within 30 days after diagnosis). Our previous analysis showed that compliance was different for patients <75 and ≥75 years old and for different hospital types. Therefore, secondary outcome measures were rates of compliance to the quality indicators for patients <75 and ≥75 years, and for non-academic and academic hospitals.

Statistical analysis

Descriptive statistics were used for analysis of baseline, tumor, and treatment characteristics. They were reported as proportions for binary or categorical variables, and as mean with standard deviation (SD) or as median with interquartile range (IQR) for continuous variables as appropriate. Primary and secondary analyses were performed with Chi-squared test for categorical variables, and unpaired t-test or Mann-Whitney U test for continuous variable as appropriate. Trends over time were analyzed with Chi-square test for trend. Missing data have been described and not imputed. A two-sided $p<0.05$ was considered statistically significant. All calculations were performed with SPSS.

RESULTS

In total, 14 491 patients with pancreatic ductal adenocarcinoma were included with a mean age of 70.4 years. The number of diagnosed patients increased gradually over the study period (from 4 425 in 2012-2013 to 4 822 in 2014-2015 to 5 244 in 2016-2017). The majority of patients had a tumor in the pancreatic head (n=8 244, 56.9%) and tumor stage IV (n=8 169, 56.4%). Overall, 2 290 patients (15.8%) underwent pancreatic resection of whom 82 (3.6%) received neoadjuvant chemotherapy, 1 206 (52.7) adjuvant chemotherapy, and 98 (4.3) neoadjuvant and adjuvant chemotherapy, and median overall survival was 17.2 months (IQR 10.4-29.7). Among all patients, median overall survival was 3.9 months (IQR 1.4-10.3). Patient, tumor, and treatment characteristics are shown in Table 1.

TABLE 1. Patient, tumor, and treatment characteristics of Dutch patients with pancreatic cancer diagnosed between 2012-2017.

	All patients N = 14 491	**Patient selection**
Age, mean years (SD)	70.4 (10.8)	All patients
Missing, N (%)	0 (0.0)	
Male, N (%)	7 356 (50.8)	All patients
Missing, N (%)	0 (0.0)	
Tumor location, N (%)		All patients
Pancreas head	8 244 (56.9)	
Pancreas body	1 846 (12.7)	
Pancreas tail	2 378 (16.4)	
Pancreas head-body or body-tail	1 148 (7.9)	
Pancreas, not otherwise specified	778 (5.4)	
Other*	97 (0.7)	
Missing, N (%)	0 (0.0)	
Pathologically confirmed, N (%)	10 119 (69.8)	All patients
Missing, N (%)	1 (0.0)	
Preoperative biliary drainage, N (%)	494/1 173 (42.1)	Pancreatic head tumor before exploration or resection (2015-2017)
Missing, N (%)	0 (0.0)	
Total bilirubin, median µmol/L (IQR)	144 (38-255)	Resected pancreatic head tumors
With biliary drainage	191 (109-283)	
Missing, N (%)	13/494 (2.6)	
Without biliary drainage	48 (10-186)	
Missing, N (%)	917/1 287 (71.3)	
Chemotherapy received, N (%)		All patients
No	9 930 (68.5)	
Yes, no resection	3 174 (21.9)	
Yes, preoperatively only	82 (0.6)	
Yes, postoperatively only	1 207 (8.3)	
Yes, pre- and postoperatively	98 (0.7)	
Missing, N (%)	0 (0.0)	
Explorative surgery without resection, N (%)	787 (5.4)	All patients
Missing, N (%)	0 (0.0)	
Resection, N (%)	2 290 (15.8)	All patients
Missing, N (%)	0 (0.0)	
Resection margin, N (%)	N = 2290	Resections
R0	1 392 (60.8)	
R1	778 (34.8)	
R2	28 (1.2)	
Missing, N (%)	92 (4.0)	
Tumor stage, N (%)		All patients
IA	315 (2.2)	
IB	837 (5.8)	
IIA	999 (6.9)	
IIB	1 860 (12.8)	
III	1 945 (13.4)	
IV	8 169 (56.4)	
*Missing, N (%)**	366 (2.5)	

SD = standard deviation. IQR = interquartile range. * Pancreatic duct, pancreatic islet cells, other not specified.

Over one third of patients diagnosed with pancreatic cancer were ≥75 years: 36.5% vs. 35.9% vs. 38.3% (p-trend=0.062). The distribution of patients across type of hospital of first diagnosis did not change over time (non-academic centers: 90.8% vs. 92.4% vs. 91.1%, p-trend=0.735). Small differences between the time periods were found for the proportion of patients diagnosed with a pancreatic head tumor (59.5% (n=2 632) vs. 55.8% (n=2 690) vs. 55.7% (n=2 922), p-trend=0.012), tumor stage (stage III: 12.1% (n=525) vs. 13.1% (n=618) vs. 15.7% (802); stage IV: 56.7% (n=2 451) vs. 57.5% (n=2 701) vs. 59.1% (n=3 017), p-trend=0.012). The proportion of patients who underwent resection decreased (16.6% (n=735) vs. 16.5% (n=795) vs. 14.5% (n=760), p-trend=0.004).

Indicator 1: patients treated with curative intent discussed in MDT meeting

The proportion of patients who were discussed in an MDT did not change over time (87.3% vs. 87.9% vs 90.3%, p-trend=0.066, Table 2). No difference was found between the <75 and ≥75 year age groups (88.6% vs. 89.4, p=0.695). For both age groups, no time trends were found (Figure 1A and 1B). Discussion MDT rates were similar for non-academic and academic hospitals (88.8% vs. 90.4%, p=0.222). Over time, the proportion of discussed patients increased for non-academic hospitals (Figure 2A), yet remained similar for academic hospitals (Figure 2B).

Indicator 2A: maximum transit time from MDT to curative intent treatment of 3 weeks

The proportion of patients who were treated within the maximum transit time did not change over time (unknown vs. 44.8% vs. 40.5%, p=0.064, Table 2). Patients <75 years more often were treated within the maximum transit time than ≥75 (44.1% vs. 38.0%, p=0.032). Over time for patients <75 years, the proportion of patients who were treated within the maximum transit time decreased (unknown vs. 46.7% vs. 41.3%, p=0.046, Figure 1A). For patients ≥75 years, no time trend was found (Figure 1B). Patients from non-academic hospitals were treated within the maximum transit time more often than from academic hospitals (51.5% vs. 32.7%, p<0.001). Over time, the proportion of patients treated within the maximum transit time decreased for non-academic hospitals (Figure 2A), yet remained similar for academic hospitals (Figure 2B).

Indicator 2B: maximum transit time from first contact to curative intent treatment 6 weeks

The proportion of patients who were treated within the maximum transit time did not change over time (unknown vs. 72.8% vs. 75.3%, p=0.209, Table 2). No difference was found between <75 and ≥75 age groups (75.0% vs. 71.1%, p=0.119). For both age groups, no time trends were found (Figure 1A and 1B). Patients from non-academic hospitals were slightly more often treated within the maximum transit time than from academic hospitals (75.7% vs. 71.8%, p=0.057). For both hospital types, no time trends were found (Figure 2A and 2B).

FIGURE 1. Compliance to five quality indicators of the nationwide guideline for pancreatic cancer over three time periods for patients (A) <75 and (B) ≥75 years old.

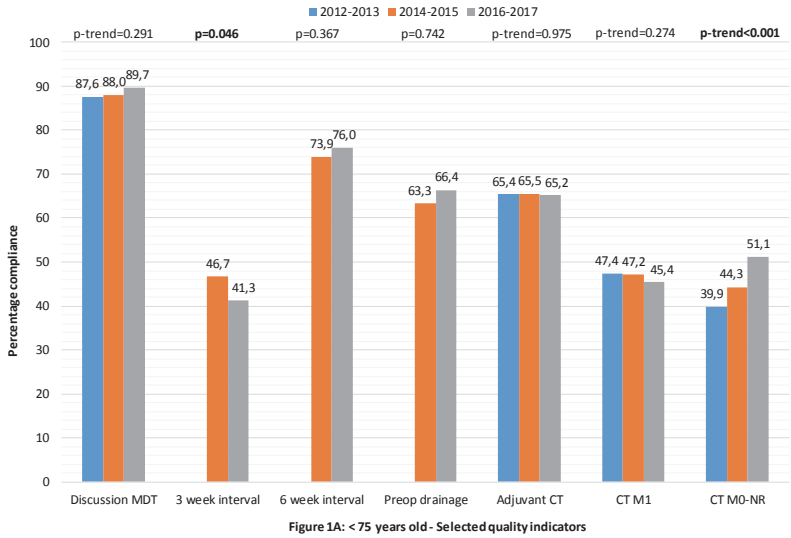


Figure 1A: < 75 years old - Selected quality indicators

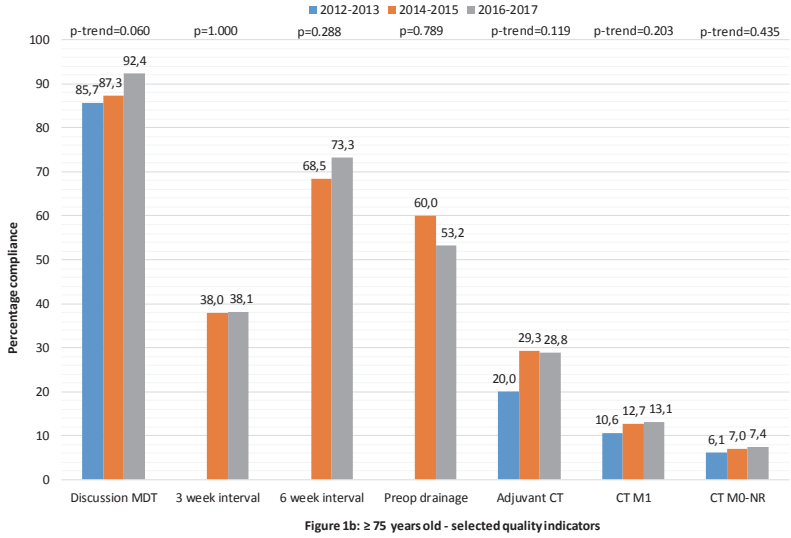


Figure 1b: ≥ 75 years old - selected quality indicators

MDT = multidisciplinary team. Preop = preoperative. CT = chemotherapy. M1 = metastatic disease. M0-NR = non-metastatic, non-resected disease. Bold p-values indicate statistical significance.
Indicator 1: discussion in a MDT meeting for pancreatic cancer treated with curative intent.
Indicator 2: maximum transit time until start of treatment with curative intent (2A: maximum 3-week interval between final MDT meeting and start of treatment; 2B: maximum 6-week interval between first contact and start of treatment).
Indicator 3: preoperative biliary drainage for pancreatic head cancer with bilirubin >250 µmol/L.
Indicator 4: adjuvant chemotherapy after resection of pancreatic cancer.
Indicator 5: chemotherapy for inoperable pancreatic cancer (5A: metastatic disease, non-resected; 5B: non-metastatic disease, non-resected).

FIGURE 2. Compliance to five quality indicators of the nationwide guideline for pancreatic cancer over three time periods for patients from (A) non-academic and (B) academic hospitals.

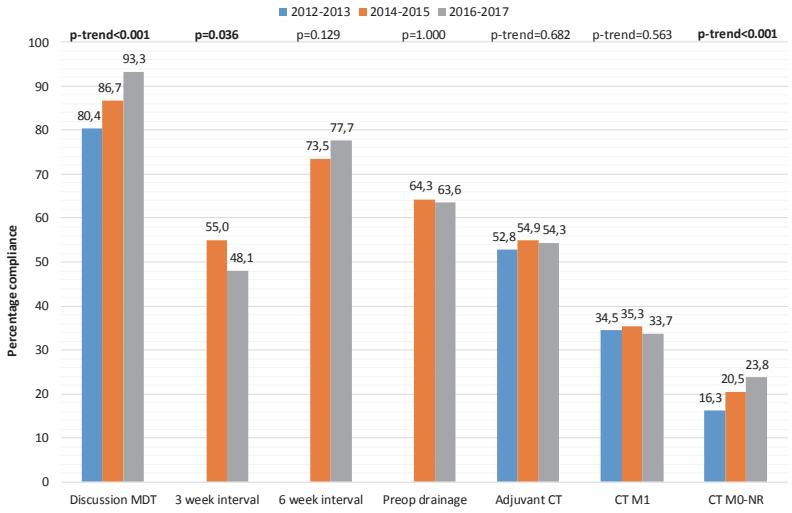


FIGURE 2A: NON-ACADEMIC hospital - Selected quality indicators

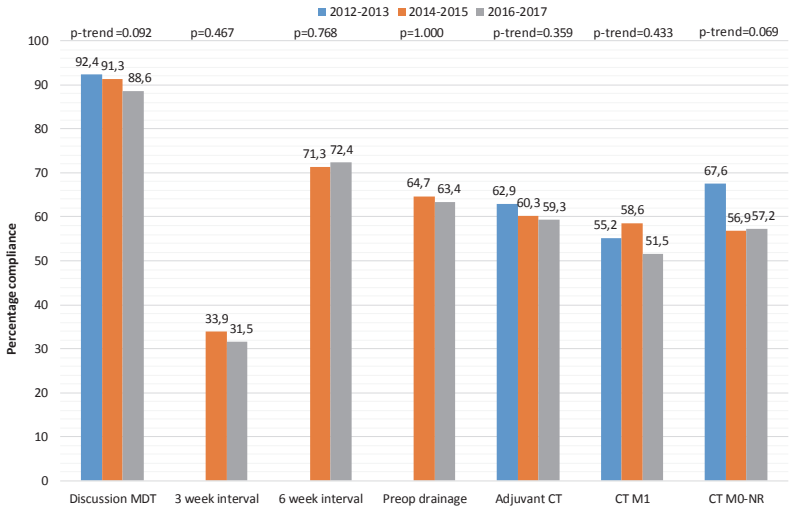


FIGURE 2B: ACADEMIC hospital - Selected quality indicators

MDT = multidisciplinary team. Preop = preoperative. CT = chemotherapy. M1 = metastatic disease. M0-NR = non-metastatic, non-resected disease. Bold p-values indicate statistical significance.
Indicator 1: discussion in a MDT meeting for pancreatic cancer treated with curative intent.
Indicator 2: maximum transit time until start of treatment with curative intent (2A: maximum 3-week interval between final MDT meeting and start of treatment; 2B: maximum 6-week interval between first contact and start of treatment).
Indicator 3: preoperative biliary drainage for pancreatic head cancer with bilirubin >250 µmol/L.
Indicator 4: adjuvant chemotherapy after resection of pancreatic cancer.
Indicator 5: chemotherapy for inoperable pancreatic cancer (5A: metastatic disease, non-resected; 5B: non-metastatic disease, non-resected).

Indicator 3: preoperative biliary drainage when bilirubin >250 µmol/L

The rate of preoperative biliary drainage remained similar over time (unknown vs. 62.5% vs. 62.8%, p=1.000, Table 2). No statistical difference was found in drainage rates between the <75 and ≥75 year age groups (65.4% vs. 55.2%, p=0.144). For both age groups, no time trends were found (Figure 1A and 1B). Drainage rates were similar between non-academic and academic hospitals (both 63.8%, p=1.000). For both hospital types, no time trends were found (Figure 2A and 2B). For patients without drainage, highest median bilirubin before treatment was 326.5 µmol/L (IQR 287.3-372.3) and median time from final MDT meeting to start of treatment with curative intent was 22.0 days (IQR 14.0-34.0).

Indicator 4: adjuvant chemotherapy

The use of adjuvant chemotherapy did not change over time (57.5% vs. 57.3% vs. 56.7%, p-trend=0.781, Table 2). Patients <75 years more often received adjuvant chemotherapy than those ≥75 years (65.4% vs. 26.5%, p<0.001). For both age groups, no time trends were found (Figure 1A and 1B). Patients who underwent resection in non-academic hospitals less often received chemotherapy than those who underwent resection in academic hospitals (54.0% vs. 60.9%, p=0.001). For both hospital types, no time trends were found (Figure 2A and 2B).

Indicator 5A: chemotherapy in metastatic disease

Use of chemotherapy in metastatic disease did not change over time (36.7% vs. 37.7% vs. 35.4%, p-trend=0.360, Table 2). Patients <75 years old more often received chemotherapy than those ≥75 years (46.6% vs. 12.2%, p<0.001). For both age groups, no time trends were found (Figure 1A and 1B). Patients from non-academic hospitals less often received chemotherapy than those from academic hospitals (34.5% vs. 55.0%, p<0.001). For both hospital types, no time trends were found (Figure 2A and 2B).

Indicator 5B: chemotherapy in non-metastatic, non-resected disease

Use of chemotherapy increased over time (23.4% vs. 25.6% vs. 29.7%, p-trend=0.001, Table 2). Patients <75 years old more often received chemotherapy than those ≥75 years (45.5% vs. 6.9%, p<0.001). Over time, more patients <75 years with non-metastatic, non-resected disease received chemotherapy (39.9% vs. 44.3% vs. 51.1%, p-trend<0.001, Figure 1A). For patients ≥75 years, no time trend was found (Figure 1B). Patients from non-academic hospitals less often received chemotherapy than those from academic hospitals (20.4% vs. 60.0%, p<0.001). Over time, the proportion of patients who received chemotherapy from non-academic hospitals increased (Figure 2A), yet remained similar for academic hospitals (Figure 2B).

TABLE 2. Compliance to five quality indicators of the nationwide guideline for pancreatic cancer during a six year period.

	All 2012-2017 n=14 491	Period 1 2012-2013 n=4 425	Period 2 2014-2015 n=4 822	Period 3 2016-2017 n=5 244	P-value	P-trend
Discussion in MDT meeting^, N (%)						
Patients treated with curative intent	2 104/2 369 (88.8)	288/330 (87.3)	922/1 049 (87.9)	894/990 (90.3)	0.136	0.066
Maximum transit time#, N (%)		NA				NA
MDT-treatment (3 week interval)	775/1 816 (42.7)		413/922 (44.8)	362/894 (40.5)	0.064	
First contact-treatment (6 week interval)	1 410/1 903 (74.1)		668/918 (72.8)	742/985 (75.3)	0.209	
Preoperative biliary drainage$, N (%)		NA				NA
Bilirubin >250 µmol/L	158*252 (62.7)		50/80 (62.5)	108/172 (62.8)	1.000	
Adjuvant chemotherapy*, N (%)	903/2 109 (57.2)	411/715 (57.5)	416/726 (57.3)	379/668 (56.7)	0.961	0.781
Metastatic disease, non-resected						
Non-metastatic disease, non-resected	2 237/6 116 (36.6)	657/1 789 (36.7)	773/2 050 (37.7)	807/2 277 (35.4)	0.300	0.360
Non-metastatic disease, non-resected	872/3 298 (26.4)	235/1 004 (23.4)	277/1 082 (25.6)	360/1 212 (29.7)	**0.003**	**0.001**

Curative intent = neoadjuvant chemotherapy, exploration, or resection. MDT = multidisciplinary team. Bold P-value indicates statistical significance. ^ MDT data: partially available in 2012; not available in 2013. # For patients treated with curative intent = neoadjuvant chemotherapy, exploration, or resection. Not available: 2012-2013. # 3 week interval: median 25 days (IQR 15-36), 223/2039 (10.9%) missing. 6 week interval: median 28 days (IQR 16-43), 136/2039 (6.7%) missing. $ For patients with a pancreatic head tumor, and resection or exploration. Excluding preoperative chemotherapy. Not available: 2012-2014. * Excluding preoperative chemotherapy. ~ Excluding patients who died within 30 days after diagnosis.

DISCUSSION

Nationwide compliance to five selected quality indicators showed little to no increase during six years after release of the national multidisciplinary guideline on pancreatic cancer in 2011. Overall, 89% of patients treated with curative intent were discussed in a MDT meeting, 43% were treated with curative intent within the recommended maximum transit time from final MDT meeting, 63% with bilirubin >250 µmol/L underwent preoperative biliary drainage, 57% received adjuvant chemotherapy, and 37% with metastatic disease received palliative chemotherapy. The proportion of patients with non-metastatic, non-resected disease who received chemotherapy was the sole indicator that increased over time, yet was still only 30% in 2016-2017.

It seems unlikely that compliance to all these quality indicators will reach 80-100%. However, the absolute compliance rates indicate that there is room for improvement. Notably, the nationwide Dutch Pancreatic Cancer Group was established in 2011 and has since increased focus on quality aspects of pancreatic cancer care.[8, 19-23] This paradox could be explained by the fact that many researchers and physicians involved with the Dutch Pancreatic Cancer Group work in higher volume or academic hospitals. The Dutch guideline on pancreatic cancer is nationwide and covers all hospital types. After the guideline introduction in 2011, various meetings with presentations were organized to increase guideline adherence. Therefore, compared to the previous analysis by our study group one year after guideline release,[7] it was expected that compliance rates to the selected guideline quality indicators would have improved over the years, especially since pancreatic cancer guideline compliance has been associated with improved survival.[3,24] The compliance rates seen in this study suggest that guideline release with only meetings is not sufficient and extra attention should be given to guideline implementation with the aim to improve patient outcomes, potentially involving all centers within the various regional pancreatic surgery referral networks. Regional care pathways could also be used to improve guideline adherence.

Previous studies in a number of other countries have also demonstrated that guideline compliance is generally also suboptimal. In Germany, where adjuvant chemotherapy for pancreatic cancer is recommended for all patients, only 69% of eligible patients received adjuvant treatment. Guideline compliance by adjuvant chemotherapy administration resulted in improved survival.[24] In the USA, compliance to the National Comprehensive Cancer Network (NCCN) guideline for pancreatic cancer regarding (palliative) surgery, and (neo)adjuvant or palliative chemo(radio)therapy was as low as 35% in large Californian hospitals. Compliance to these guideline recommendations was independently associated with better survival.[3] Failure of compliance to guidelines for intraductal papillary mucinous neoplasm (IPMN) in the USA was seen in 58% of patients (e.g., for acknowledgement of IPMN, to

undergo endoscopic ultrasound, to undergo resection, to undergo proper surveillance). On the other hand, it was shown that careful implementation of the Enhanced Recovery After Surgery (ERAS) protocol was feasible and safe after pancreatectomy. This resulted in similar or better patient outcomes regarding length of stay, morbidity, mortality, and readmissions.[25,26] Therefore, to ultimately improve patient outcomes, structured implementation may lead to improved guideline compliance. Currently, this is of particular importance in the Netherlands because the national guideline was updated recently in 2019. This is an opportunity to address this issue.

What is the optimal compliance to quality indicators? Apart from doctors' and patients' preference, and logistical problems, there may be lack of awareness of the guideline recommendations. For the chemotherapy quality indicators, 'compliance' is mostly dependent on the proportion of suitable patients receiving treatment, such as patients with adequate performance status and who wish to be treated. It is difficult to exclude certain groups of patients since eligibility criteria differ between chemotherapy regimens and eligibility for adjuvant therapy is influenced by recovery from surgical complications. However, the 57% rate of adjuvant chemotherapy and 26-37% of chemotherapy for inoperable disease on a nationwide level may be improved. For example, one fourth of patients develop major postoperative complications.[27] This suggests that adjuvant chemotherapy may probably be administered to more than 57% of patients, especially when taken into account that most patients recover from postoperative complications. Type of hospital and center volume are likely also of influence. Our results showed that patients treated in academic hospitals more often received adjuvant chemotherapy. Moreover, a recent studies found that adjuvant treatment rates varied among the pancreatic surgery centers (range 32%-88%) and that a higher volume of pancreatoduodenectomy was a predictor for receiving adjuvant treatment.[27-29] In a Californian, state-wide, population-based study, similar to our study design, chemotherapy for inoperable disease was given to 42% of patients.[30] Although performance status was not available from the NCR, likely more patients with inoperable disease than 26-37% were fit enough to receive chemotherapy, especially after excluding patients who died within 30 days after diagnosis. However, in a national expert meeting in the Netherlands, in preparation for a nationwide randomized trial most medical oncologists concluded that probably around 40% of patients with metastatic disease should receive palliative chemotherapy compared to around 60% of patients with locally advanced disease. The 'optimal' compliance to the chemotherapy indicator for metastatic disease may therefore almost be reached (37% vs. 40%), whereas for non-metastatic, non-resected disease may leave room for improvement (26% vs. 60%). Interestingly, over time, the proportion of patients with non-metastatic, non-resected disease who received chemotherapy increased from 40% to 51% for the <75 age group, whereas remained similar (6-7%) for the ≥75 group. Studies that suggest beneficial effects of chemotherapy, especially FOLFIRINOX, in patients with locally

advanced pancreatic cancer included mostly patients <75 years.[14] Physicians may therefore be conservative in treating patients ≥75 years. In addition, in the Netherlands 52% of patients with non-metastatic, non-resected disease were ≥75 years old and likely not fit enough for either surgery or chemotherapy.[31]

The 3-week maximum interval between final MDT meeting and start of treatment with curative intent did not return in the 2019 national guideline on pancreatic cancer and was replaced by a 6-week maximum interval between first contact and start of treatment.[18] The latter was therefore investigated additionally in this study and may be chosen as the prefered compliance indicator in future studies. The proportion of patients discussed within the maximum transit time did not increase, despite centralization of pancreatic cancer care in the past years. Even though centralization may be improved even further, perhaps certain patient and hospital factors may be of more influence than logistical factors. Patients <75 years and from non-academic hospitals were more often treated within the maximum transit time. Possibly, this could be a capacity issue, or these patients were less complex (e.g. less comorbidites, less biliary drainage complications), as lower performance status and post-drainage complications can lead to longer transit times. These details were not available in the NCR. Interestingly, 11% of patients who were treated with curative intent were not even discussed in a MDT meeting prior to treatment. This remains unexplained and was not influenced by the patients' age or type of hospital. This finding also clearly complicates the definition of maximum time between MDT and start of treatment.

In patients without neoadjuvant treatment with bilirubin ≤250 µmol/L, early surgery is prefered over biliary drainage.[10, 32] On the contrary, in Dutch practice and in this study, a bilirubin cutoff value of >250 µmol/L was used for preference of primary biliary drainage over early surgery. Even though hyperbilirubinemia is associated with higher risk of postoperative complications, perhaps reports of worse postoperative outcomes after biliary drainage contribute to the absence of increase of this quality indicator in patients with bilirubin >250 µmol/L.[33] In addition, a proportion of the patients may have had a bilirubin ≤250 µmol/L at the time of the final MDT, while it increased to >250 µmol/L at the time of surgery. Together, this probably led to the finding that 37% of these patients did not receive preoperative drainage and underwent surgery in a median of 22 days after final MDT meeting. It would be interesting to understand what drives physicians' treatment decision-making in these patients and future studies should clarify this. Perhaps, physicians tend to treat patients with good performance status with early surgery regardless of their bilirubin value. This quality indicator is therefore difficult to interpret. In the current era of neoadjuvant treatment we expect that the use of preoperative biliary drainage will increase.[34,35] Because patients with neoadjuvant treatment are now excluded from this

quality indicator, in future studies this indicator should be adjusted into an indicator that is more suitable for evaluation of patients treated with neoadjuvant treatment.

Guideline compliance varied across hospital types (i.e. non-academic vs. academic) which could be partly explained by patient selection (e.g. younger patients treated in academic hospitals, referral in case of specific treatment preference). Compliance to several quality indicators changed over time for non-academic hospitals, while it remained similar for academic hospitals. Academic hospitals may be fast adapters, as these clinicians are more often involved in randomized studies and guideline design. In non-academic hospitals there may have been more room for change following guideline publication. Still, in all hospital types, including academic hospitals, improvement seems desired.

The main limitation of this study is that some details on possible reasons for non-compliance to the quality indicators are not registered such as performance status or indications for biliary drainage. Furthermore, a previous internal survey showed that data on MDT meetings were less available in a few smaller general hospitals. Although the completeness of registration in elderly patients with pancreatic cancer in the NCR was questioned previously,[36] in recent years some improvement of available notification sources in hospitals has occurred. To optimize data quality in this study, a strict selection of patients was used, as well as a stratification by age and hospital type. Unfortunately, a proper selection of patients with locally advanced disease within the group of patients with non-resected non-metastasized disease was not possible (indicator 5B). However, it remains interesting that compliance to the guideline hardly improved over a 6-year period, especially after the development of nationwide auditing and feedback through the Dutch Pancreatic Cancer Group and nationwide projects.[8,19,21] Perhaps these quality indicators do not reflect 'quality' adequately. Still, optimizing compliance if possible remains important. Nationwide improvement of guideline compliance is addressed within the ongoing PACAP-1 trial (ClinicalTrials.gov: NCT03513705).[37] This nationwide trial was initiated in 2018 and aims to determine to what extent an enhanced implementation of best practices in pancreatic cancer care (all stages) leads to a prolonged survival and improvement of quality of life as compared to current practice. Key best practices include optimization of treatment with chemotherapy, treatment of exocrine pancreatic insufficiency, and biliary drainage with metal stents. In addition, the trial aims to improve logistics within and between centers, which could ultimately lead to an increased proportion of patients being discussed in MDT meetings with shorter transit times.

In conclusion, this nationwide study demonstrated that compliance to five selected quality indicators on pancreatic cancer care hardly improved during a period of six years after release of a multidisciplinary guideline. These outcomes highlight the importance of a critical review of the current quality indicators

and of a structured implementation program to create awareness and enhance compliance to guideline recommendations, with the ultimate goal to improve outcomes of patients with pancreatic cancer.

ACKNOWLEDGEMENTS

The Dutch Pancreatic Cancer Project, including the Netherlands Cancer Registry, received funding from the Dutch Cancer Society (KWF Kankerbestrijding; grant no. UVA2013-5842). The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection.

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CHAPTER 3

Implementation of contemporary chemotherapy for patients with metastatic pancreatic ductal adenocarcinoma: a population-based analysis

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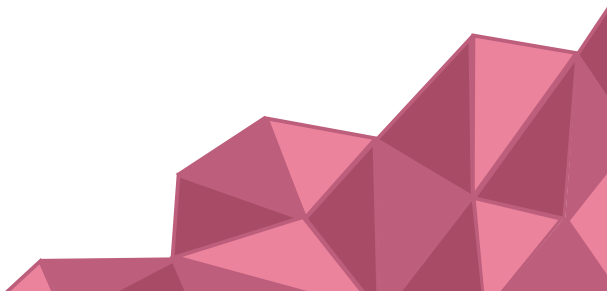
Acta Oncologica. 2020 Jun;59(6):705-712.



ABSTRACT

Background: Positive results of randomized trials led to the introduction of FOLFIRINOX in 2012 and gemcitabine with nab-paclitaxel in 2015 for patients with metastatic pancreatic ductal adenocarcinoma. It is unknown to which extent these new chemotherapeutic regimens have been implemented in clinical practice and what the impact has been on overall survival.

Materials and methods: Patients diagnosed with metastatic pancreatic ductal adenocarcinoma between 2007-2016 were included from the population-based Netherlands Cancer Registry. Multilevel logistic regression and Cox regression analyses, adjusting for patient, tumor, and hospital characteristics, were used to analyze variation of chemotherapy use.

Results: In total, 8726 patients were included. The use of chemotherapy increased from 31% in 2007-2011 to 37% in 2012-2016 (P<0.001). Variation in the use of any chemotherapy between centers decreased (adjusted range 2007-2011: 12-67%, 2012-2016: 20-54%) whereas overall survival increased from 5.6 months to 6.4 months (P<0.001) for patients treated with chemotherapy. Use of FOLFIRINOX and gemcitabine with nab-paclitaxel varied widely in 2015-2016, but both showed a more favorable overall survival compared to gemcitabine monotherapy (median 8.0 vs. 7.0 vs. 3.8 months, respectively). In the period 2015-2016, FOLFIRINOX was used in 60%, gemcitabine with nab-paclitaxel in 9.7% and gemcitabine monotherapy in 25% of patients receiving chemotherapy.

Conclusion: Nationwide variation in the use of chemotherapy decreased after the implementation of FOLFIRINOX and gemcitabine with nab-paclitaxel. Still a considerable proportion of patients receives gemcitabine monotherapy. Overall survival did improve, but not clinically relevant. These results emphasize the need for a structured implementation of new chemotherapeutic regimens.

INTRODUCTION

Most patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed with metastatic disease.[1–3] These patients are treated with palliative chemotherapy combined with supportive care or supportive care alone, depending on their performance status and preference. In 1997, gemcitabine was found to improve survival compared to 5-fluorouracil (5.7 vs. 4.4 months median overall survival).[4] Over the years, several combination chemotherapy regimens have been investigated without any gain of survival.[5,6] More recently, FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) was associated with a survival benefit compared to gemcitabine (11.1 vs. 6.8 months median overall survival) in patients with a good performance status.[7] The phase III MPACT trial revealed a superior survival with gemcitabine with nab-paclitaxel as compared to gemcitabine alone (8.7 vs. 6.6 months median overall survival).[8] It is unclear how these findings of trials with often strict eligibility criteria translate to nationwide clinical practice.

Most population-based studies on metastatic PDAC were performed in the gemcitabine era.[1,9,10] A recent study in Canada showed that use of FOLFIRINOX in patients with metastatic PDAC increased from 41% in 2012 to 56% in 2014 although treatment regimens varied considerably across geographic regions.[11] In the Netherlands FOLFIRINOX and gemcitabine with nab-paclitaxel were introduced in 2012 and 2015 respectively.[7,8,11,12] The identification of nationwide trends over the years and variation across hospitals is relevant as different treatment strategies might influence patients' outcomes.[7,8] Patients could receive other chemotherapy regimens leading to a difference in survival. Nationwide variation between hospitals may exist over time, due to geographical or hospital volume differences, but also due to differences in patient characteristics and clinical practice in prescribing palliative chemotherapy.[13–15] For example, physicians with less experience with triplet chemotherapy in the treatment of PDAC, may have been reluctant to prescribe FOLFIRINOX treatment.

Therefore, the aim of this study is to assess whether the implementation of new more effective chemotherapy regimens (FOLFIRINOX and gemcitabine with nab-paclitaxel) for patients with metastatic PDAC has affected nationwide clinical practice and overall survival.

METHODS

Data collection

For this nationwide study, data from the Netherlands Cancer Registry (NCR) were used, covering the total population of approximately 17 million inhabitants. Patients with a newly diagnosed malignancy were identified by automatic notifications of the national pathological archive (PALGA) and the National Hospital Discharge Register. Information on patient, tumor and treatment characteristics, and visited

hospitals (for diagnosis and for treatment), were routinely collected from medical records by trained NCR administrators. This study was designed in accordance with the STROBE guidelines and the study protocol was approved by the scientific committee of the Dutch Pancreatic Cancer Group.[16]

Study population

Patients diagnosed in the period 2007-2016 with PDAC (International Classification of Disease – Oncology (ICD-O-3) morphology code 8000, 8010, 8012, 8020, 8140, 8141, 8260, 8310, 8440, 8453, 8480, 8481, 8490, 8500 and 8560) and distant metastasis at time of diagnosis were extracted from the NCR database. Patients younger than 18 years at diagnosis, patients who underwent pancreatic resection, patients who received neoadjuvant chemotherapy prior to surgical exploration or patients who died within 30 days after diagnosis were excluded.

For patients with metastatic PDAC, use of FOLFIRINOX was recommended in 2012 and gemcitabine with nab-paclitaxel in 2015, after positive judgement of a national commission (Commissie BOM). Therefore, the period of diagnosis was divided into a period before (2007-2011) and after (2012-2016) the implementation of the new regimens. Patients were assigned as receiving chemotherapy treatment if they started any chemotherapy regimen. Socioeconomic status (SES) was based on social deprivation scores per 4-digit postal code (reference data from The Netherlands Institute of Social Research) and categorized into three SES groups (high: 1st-3rd, intermediate 4th-7th, low: 8th-10th deciles). Primary tumor location was classified as pancreatic head (C25.0), body (C25.1), tail (C25.2), or other (C25.3, 7-9), according to the ICD-O-3. Metastatic organ site(s) was categorized as liver only, peritoneum only, lung only, extra-regional lymph nodes only, other site only, 2 sites (any combination), ≥3 sites (any combination) and unknown. Nationwide data on comorbid conditions, performance status (WHO; Karnofsky scores were converted to WHO according to the following values: 90-100 to WHO 0, 80-90 to WHO 1, 60-70 to WHO 2, 40-50 to WHO 3, 20-30 to WHO 4) and type of first-line chemotherapy were available for diagnoses in 2015 and 2016 only.[17] Survival data were obtained by annual linkage with the Municipal Personal Records Database, which contains vital status of all Dutch inhabitants. Survival time was defined as the time between the date of diagnosis and date of death or censoring (1 February 2018).

Hospital classifications

Patients were assigned to their hospital of diagnosis, which was defined as the hospital of first visit or clinical diagnosis of PDAC. In 2016, patients were diagnosed in 78 hospitals in the Netherlands, merged hospitals were counted as one for the entire study period. Classifications of hospitals were: (1) type of hospital, divided in university and non-university hospitals; (2) volume of diagnoses of metastatic PDAC per hospital per year, evenly divided into three groups (tertiles: 1-12, 13-19, 20-39); (3) volume of

patients receiving chemotherapy per hospital per year (the number of patients with metastatic PDAC with chemotherapy per hospital per year was applied to all patients diagnosed with metastatic PDAC in that hospital) (tertiles: 0-3, 4-6, 7-31); or (4) diagnosed in a center for pancreatic surgery (no/yes, only available for 2012-2016). Nationwide variation for type of chemotherapy could only be assessed for 2015-2016, because type of chemotherapy was not registered before. In the analysis about type of chemotherapy per hospital in 2015-2016, type of chemotherapy was linked to the hospital of treatment.

Statistical analysis

Time trends in the use of chemotherapy and referral for chemotherapy (chemotherapy treatment in other hospital than hospital of diagnosis) were analyzed with the Chi-square for trend. Multilevel logistic regression models were built to analyze variation of chemotherapy treatment between hospitals, since patients were arranged in a natural hierarchy (clustered within hospitals).[18] For each hospital of diagnosis (separately for 2007-2011 and 2012-2016), a mean probability of receiving chemotherapy was calculated, adjusted for differences in patient and tumor characteristics. Change in hospital variation between both time periods was investigated using intraclass correlation coefficients (ICC) for the proportion of variance explained by hospital level. Sensitivity analyses were performed for patients (1) under 75 years only, (2) alive 60 days after diagnosis, (3) with pathologically verified PDAC, and (4) diagnosed in 2015-2016 additionally adjusted for number of comorbid conditions and WHO performance status. To investigate mechanisms underlying the variation of receiving chemotherapy between hospitals, the hospital classifications were added one by one to the multivariable multilevel models.

Overall survival was analyzed by means of Kaplan-Meier curves and compared with log-rank tests. Multivariable Cox regression analyses were performed to assess the effect of (1) the period of diagnosis (for all patients and for patients receiving chemotherapy), (2) probabilities of receiving chemotherapy per hospital grouped in tertiles (2007-2011 and 2012-2016 separately) and (3) the different chemotherapy regimens (patients with chemotherapy in 2015-2016) on survival. Results were presented as hazard ratios (HR) with a 95% confidence interval (CI). All multivariable regression analyses were adjusted for sex, age, SES, pathological confirmation, primary tumor location and number and location of distant metastases. The third regression assessing the different chemotherapy regimens was also adjusted for performance status and number of comorbidities. All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Data was analyzed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, N.Y., USA) and Stata version 14.2 (StataCorp, TX, USA) for multilevel analyses of hospital variation, performed by LvdG to maintain anonymity of hospitals.

FIGURE 1. Use of chemotherapy in and survival of all patients with metastatic pancreatic ductal adenocarcinoma in 2007-2016.

FIGURE 1A. Use of chemotherapy in patients with metastatic pancreatic ductal adenocarcinoma and the percentage of patients that were referred for chemotherapy treatment in 2007-2011 and 2012-2016 in the Netherlands (N=8726).

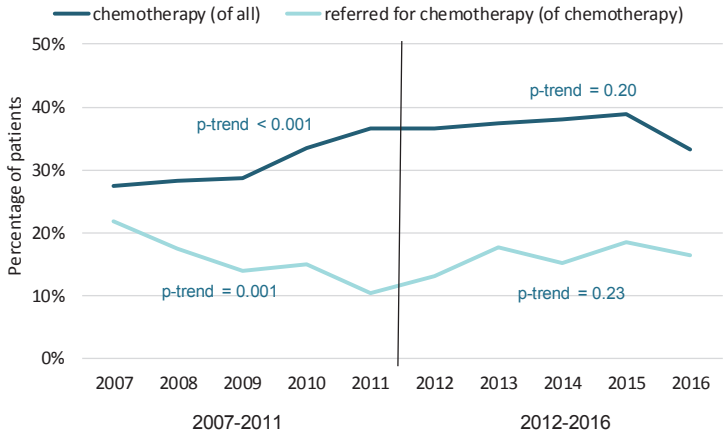
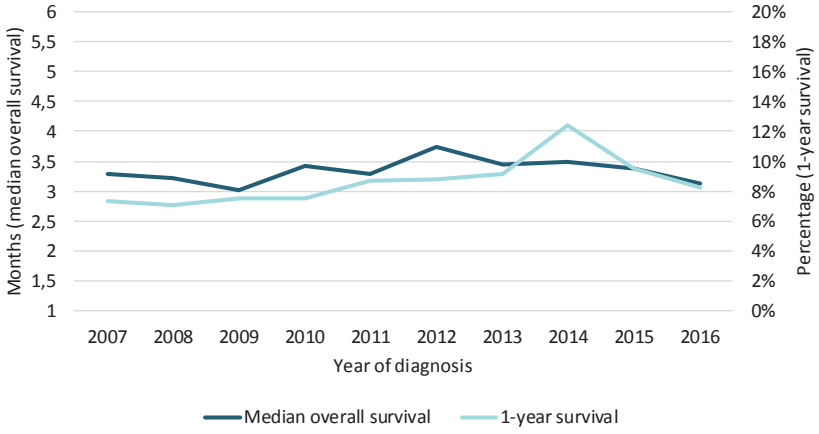


FIGURE 1B. Median overall survival and 1-year survival of all patients with metastatic pancreatic ductal adenocarcinoma in 2007-2016.



RESULTS

Patient population

In total, 8726 patients diagnosed with metastatic PDAC were included. The median age was 68 years (range 21-99) and one-third of patients was treated with chemotherapy (34%). Table 1 provides an overview of the baseline characteristics. Use of palliative chemotherapy increased significantly from 31% in 2007-2011 to 37% in 2012-2016 (P<0.001, Figure 1A). During 2012-2016, the use of chemotherapy stabilized (p-trend=0.20). The percentage of patients that was referred to another hospital for chemotherapy treatment decreased from 22% to 10% from 2007-2011 (p-trend=0.001) and fluctuated between 13% and 18% in 2012-2016 (p-trend=0.23). Median age of patients receiving chemotherapy was 63 and 64 years in the consecutive time periods.

Nationwide variation in administration of chemotherapy

In the study period, an increasing number of hospitals provided chemotherapy to patients diagnosed with metastatic PDAC: 60 (IQR 58-67) hospitals per year in the period 2007-2011 and 71 (IQR 70-72) hospitals in the period 2012-2016 (P=0.009). The median number of patients receiving chemotherapy per treating hospital was 13 and 21 patients per five-year period, respectively.

Between individual hospitals of diagnosis, a large variation in chemotherapy prescription for patients with metastatic pancreatic cancer was found (observed range in 2007-2011: 6.3-87%, 2012-2016: 14-62%). Multilevel analyses, adjusted for patient and tumor characteristics, showed that this variation decreased over time (adjusted probabilities ranges: 12-67% and 20-54%, and ICC: 14% and 6%, respectively, Supplementary Figure 1). Sensitivity analyses showed similar ranges between hospitals (Supplementary Table 1). In hospitals with high volumes of chemotherapy and in hospitals with high volumes of diagnoses, the likelihood of receiving chemotherapy was significantly higher (respectively, compared to medium and low volumes in both time periods and compared to low volumes in 2007-2011 only, Table 2). Being diagnosed in a university hospital or a center for pancreatic surgery was not associated with the likelihood of receiving chemotherapy.

TABLE 1. Baseline characteristics of 8726 patients with metastatic pancreatic ductal adenocarcinoma in the Netherlands diagnosed between 2007-2016.

	All patients 2007-2016, *N*=8726 (%)	Period 1 (2007-2011) *N*=3941 (%)	Proportion of chemotherapy (row %)	*P*-value	Period 2 (2012-2016) *N*=4785 (%)	Proportion of chemotherapy (row %)	*P*-value
Gender							
Male	4496 (52%)	2033 (52)	33%	**0.002**	2463 (51)	39%	**<0.001**
Female	4230 (48)	1908 (48)	29%		2322 (49)	34%	
Age (years)				**<0.001**			**<0.001**
<50	413 (5%)	207 (5)	52%		206 (4)	67%	
50-59	1427 (16%)	683 (17)	46%		744 (16)	57%	
60-69	2857 (33%)	1294 (33)	41%		1563 (33)	47%	
70-79	2832 (32%)	1229 (31)	21%		1603 (36)	27%	
≥80	1197 (14%)	528 (13)	4%		669 (14)	4%	
Socioeconomic status				**0.017**			**0.016**
High	2619 (30)	1207 (31)	32%		1412 (30)	39%	
Medium	3490 (40)	1552 (39)	33%		1938 (41)	37%	
Low	2617 (30)	1182 (30)	28%		1435 (30)	34%	
Pathologically confirmed				**<0.001**			**<0.001**
Yes	6430 (74%)	2814 (71)	39%		3616 (76)	45%	
No	2296 (26)	1127 (29)	13%		1169 (24)	12%	
Primary tumor location				**<0.001**			**<0.001**
Head of pancreas	4121 (47%)	1971 (50)	28%		2150 (45)	33%	
Body of pancreas	1317 (15%)	552 (14)	36%		765 (16)	43%	
Tail of pancreas	1874 (21%)	784 (20)	38%		1090 (23)	40%	
Other	1414 (16%)	634 (16)	30%		780 (16)	37%	
Metastatic site				**<0.001**			0.114
Liver	4384 (50%)	2098 (53)	32%		2286 (48)	36%	
Lung	401 (5%)	187 (5)	21%		214 (5)	33%	
Peritoneum	746 (9%)	306 (8)	26%		440 (9)	39%	
Extra regional lymph nodes	317 (4%)	143 (4)	29%		174 (4)	41%	
Other	195 (2%)	88 (2)	18%		107 (20	26%	
2 metastatic sites*	1920 (22%)	812 (21)	33%		1108 (23)	38%	
3 or more metastatic sites*	730 (8%)	275 (7)	37%		455 (10)	36%	
Unknown	33 (<1%)	32 (1)	22%		1 (<1)	-	

Bold numbers indicate statistical significance. *Any combination of metastatic sites.

TABLE 2. Proportion of patients receiving chemotherapy and multivariable multilevel logistic regression to investigate hospital-related predictors for chemotherapy use in patients diagnosed with metastatic pancreatic ductal adenocarcinoma in the Netherlands in 2007-2016, for 2 periods of diagnosis separately.

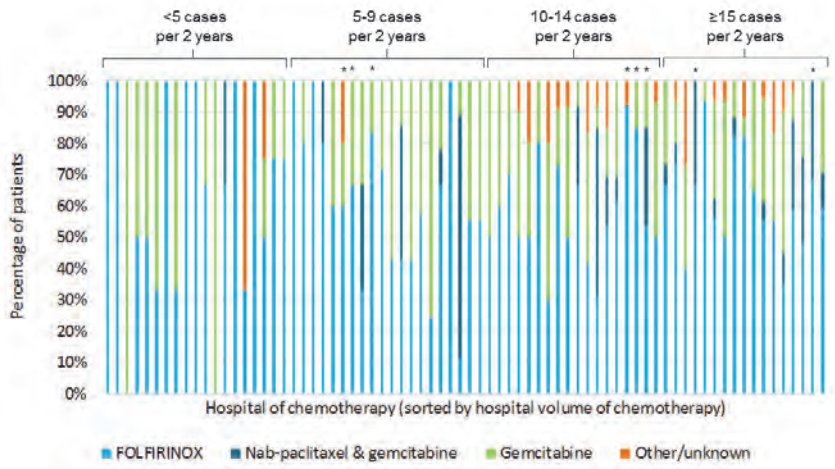
	Period 2007-2011				Period 2012-2016			
Hospital measures*	**% of patients with chemotherapy**	***P*-value**	**OR (95% CI)**	***P*-value**	**% of patients with chemotherapy**	***P*-value**	**OR (95% CI)**	***P*-value**
Classification 1								
Type of hospital		0.858				0.236		
University	31.5		1.00 (reference)		33.7		1.00 (reference)	
Non-university	31.1		1.66 (0.93-2.99)	0.088	37.0		1.48 (0.98-2.24)	0.065
Classification 2								
Hospital volume of diagnoses		0.057				0.467		
High	32.2		1.00 (reference)		37.0		1.00 (reference)	
Medium	33.0		0.86 (0.66-1.12)	0.260	35.5		0.89 (0.72-1.12)	0.322
Low	29.1		**0.66 (0.49-0.89)**	**0.006**	37.6		0.96 (0.77-1.21)	0.761
Classification 3								
Hospital volume of chemotherapy		<0.001				<0.001		
High	47.9		1.00 (reference)		44.5		1.00 (reference)	
Medium	38.0		**0.62 (0.47-0.80)**	**<0.001**	38.0		**0.76 (0.64-0.91)**	**0.003**
Low	19.9		**0.24 (0.19-0.31)**	**<0.001**	25.3		**0.37 (0.30-0.46)**	**<0.001**
Classification 4			Not applicable					
Pancreatic center (surgery)						0.104		0.052
No					37.5		1.00 (reference)	
Yes					34.9		0.77 (0.59-1.00)	

Bold numbers indicate statistical significance. P: percentage of patients receiving chemotherapy, OR: odds ratio, CI: confidence interval. * Individual hospital classifications were adjusted for sex, age, SES, pathological confirmation, location of primary tumor, number and location of distant metastases, and hospital of diagnosis by using multilevel regression analysis.

Overall survival

Patients who received chemotherapy had a median overall survival of 6.0 months (95%CI 5.8-6.2) compared to 2.5 months (95%CI 2.4-2.6) in patients without chemotherapy use (*P*<0.001). In all patients, median overall survival slightly improved between 2007-2011 and 2012-2016 (3.3 vs. 3.4 months, *P*<0.001) with a 1-year survival of 7.6% vs. 9.6% respectively (Table 3, Figure 1B). After adjustment for patient and tumor characteristics, patients in 2012-2016 had a significantly higher overall survival compared with patients in 2007-2011 in multivariable Cox regression (adjusted HR 0.91, 95%CI 0.87-0.95, *P*<0.001). Besides increased chemotherapy use, patients treated with chemotherapy in 2012-2016 also had slightly better median overall survival (6.4 months vs. 5.6 months, *P*<0.001) and 1-year overall survival (20% vs. 15%) than in 2007-2011 (adjusted HR 0.82, 95%CI 0.76-0.89). Median overall survival did not increase sequentially per year (6.5-6.2-6.4-6.3-6.7 months in 2012-2013-2014-2015-2016).

FIGURE 2. Proportions of type of chemotherapy per hospital of treatment for patients diagnosed with metastatic pancreatic ductal adenocarcinoma in 2015-2016, N=74/78 hospitals prescribed chemotherapy.



The number of patients receiving chemotherapy per 2 years was grouped and represented in the figure. The asterisk represents a university hospital.

TABLE 3. Univariable and multivariable Cox regression analyses of overall survival for all patients with metastatic pancreatic ductal adenocarcinoma in the Netherlands in 2007-2016 (n=8726), overall and for 2 periods of diagnosis separately.

	N=	Crude1-year OS (%)	Univariable HR (95% CI)	Multivariable HR (95% CI)*	*P*-value
All patients					
Period					
2007-2011	3941	7.6	1.00 (reference)	1.00 (reference)	
2012-2016	4785	9.6	**0.92 (0.88-0.96)**	**0.91 (0.87-0.95)**	**<0.001**
Period 2007-2011					
Chemotherapy treatment probability**					
High (36%-67%)	1275	9.4	1.00 (reference)	1.00 (reference)	
Medium (25%-35%)	1344	7.9	**1.13 (1.04-1.22)**	**1.12 (1.03-1.20)**	**<0.001**
Low (12%-25%)	1322	5.7	**1.22 (1.13-1.32)**	**1.21 (1.12-1.31)**	**0.006**
Period 2012-2016					
Chemotherapy treatment probability**					
High (40%-54%)	1543	11.4	1.00 (reference)	1.00 (reference)	
Medium (35%-39%)	1571	9.4	**1.09 (1.01-1.17)**	1.05 (0.98-1.13)	**0.202**
Low (20%-34%)	1671	8.2	**1.19 (1.11-1.28)**	**1.13 (1.05-1.21)**	**0.001**

Bold numbers indicate statistical significance. * Adjusted for sex, age, SES, pathological confirmation, location of primary tumor, number and location of distant metastases. ** Within periods of diagnosis patients were evenly divided into three groups according to the adjusted probabilities of receiving chemotherapy (per hospital per period) based on the hospital of diagnosis.

In 2007-2011, patients diagnosed in hospitals with low and intermediate probabilities of receiving chemotherapy had a significant lower overall survival compared to patients in hospitals with high probabilities (adjusted HR 1.21, 95%CI 1.12-1.31 and 1.12, 95%CI 1.03-1.20, respectively, Table 3). In 2012-2016, a significant worse survival was only found in patients diagnosed in hospitals with a low probability of receiving chemotherapy treatment compared to a high probability (adjusted HR 1.13, 95%CI 1.05-1.21, Table 3).

Nationwide variation in type of chemotherapy

In 2015-2016, 36% of all patients (723 patients) received chemotherapy of whom most patients received the newly introduced regimens: 436 patients FOLFIRINOX (60%) and 70 patients gemcitabine plus nab-paclitaxel (9.7%, Supplementary Table 2). The remaining patients received gemcitabine only (182 patients, 25%), and other or unknown chemotherapy regimens (35 patients, 4.8%). FOLFIRINOX was given in nearly all hospitals (72/74 hospitals of treatment in 2015-2016), while less than one-third of hospitals administered gemcitabine plus nab-paclitaxel (22/74, Figure 2). Gemcitabine monotherapy was administered to a relatively low proportion of patients in university hospitals. In general, patients treated with FOLFIRINOX were younger (median 61 vs. 66-70 years) and had a better performance score

compared to patients treated with other regimens (WHO 0-1 in 70% vs. 44-69%). Compared to patients treated with gemcitabine, patients receiving FOLFIRINOX and gemcitabine plus nab-paclitaxel had a significantly higher median OS (3.8 months vs. 8.0 months vs. 7.0 months respectively). In multivariable Cox regression the corresponding adjusted HR were 0.46 (95%CI 0.37-0.57, *P*<0.001) and 0.46 (95%CI 0.34-0.63, *P*<0.001), respectively, compared to gemcitabine only.

DISCUSSION

This population-based analysis of patients with metastatic PDAC showed that over the course of a decade the nationwide use of chemotherapy increased and the nationwide variation in the use of chemotherapy decreased. Since the introduction of FOLFIRINOX and gemcitabine with nab-paclitaxel the overall survival of all patients with metastatic disease increased slightly, yet significantly (from 0.1 to 0.8 months) although only one third of patients received chemotherapy. FOLFIRINOX was widely implemented in 2015-2016, but its use varied between hospitals. A considerable proportion of patients still received gemcitabine monotherapy. Nevertheless, differences in survival due to variation in use of chemotherapy between hospitals seem to have decreased over the study period.

During the last decade, on average 34% of patients with metastatic PDAC received chemotherapy in the Netherlands compared to 17%-58% reported from other countries.[9,10,15,19–22] Between 2007-2011 and 2012-2016, an increase was observed in the use of chemotherapy. The volume of patients receiving chemotherapy per hospital increased, more hospitals prescribed chemotherapy and consequently the number of referrals to tertiary centers decreased. Moreover, variation between hospitals in the probability of receiving chemotherapy for metastatic PDAC per hospital decreased in 2012-2016. Hospitals with a higher volume of patients receiving chemotherapy had an increased likelihood of receiving chemotherapy in both 2007-2011 and 2012-2016. Hospital volume of diagnosis did affect the likelihood of receiving chemotherapy in 2007-2011, but this effect disappeared in 2012-2016. Type of hospital or pancreatic surgery centers did not affect the likelihood of receiving chemotherapy in both periods. There are several possible explanations for the increased use of chemotherapy (regardless of the type of chemotherapy) and the decrease in variation between hospitals: 1) the introduction of FOLFIRINOX and gemcitabine with nab-paclitaxel with reported higher survival benefits; 2) the rise of inter-hospital multidisciplinary meetings; and 3) the implementation of the national guideline on PDAC in 2011.[7,8,23]

On a population level, results of the new chemotherapy regimens on overall survival are somewhat disappointing. As expected, in patients receiving chemotherapy the survival increase was higher compared to patients who did not receive chemotherapy, but still only 0.8 months (24 days). The overall

survival of patients treated with FOLFIRINOX was lower than in the randomized controlled trial (8.0 months in our study vs. 11.1 months in the trial of Conroy et al.).[7] This was also the case for gemcitabine with nab-paclitaxel (7.0 in our study vs. 8.7 months in the trial of Goldstein et al.).[8] The limited effect on survival on population level probably originates from differences in patient selection compared to clinical trials. Another study including patients with advanced pancreatic cancer from a single institution showed that survival could achieve benefits as shown in randomized clinical trials, but that this differed between treatment regimens.[24] Moreover, the study demonstrated protocol adherence to be one of the explanations for differences between real-world outcomes and results in randomized controlled trials. Both the effects of patient selection and protocol adherence emphasize the importance of population-based studies to show real-life effects of new treatments.[25]

Remarkably, gemcitabine was still often prescribed (25%). The median overall survival of patients receiving this regimen was considerably low (3.8 months) compared to the new chemotherapy regimens (FOLFIRINOX and gemcitabine plus nab-paclitaxel 8.0 and 7.0 months, respectively) and to patients without chemotherapy use (2.5 months). This could be related to worse performance status in these patients. A population-based study from the United States found a rapid decline of the use of gemcitabine monotherapy after 2009.[13] Gemcitabine can be considered currently in patients not eligible for FOLFIRINOX or gemcitabine with nab-paclitaxel. In daily practice these are patients with multiple comorbidities, a WHO performance status of ≥2, or patients older than 75 years, because those patients were not included in the previous mentioned trial.[7] In our cohort, gemcitabine was not only prescribed in this selected population, but it was also given to patients younger than 70 years old, with a WHO performance score of 0, and without comorbidities. Probably the relatively severe toxicity of these new regimens, and the inexperience with the chemotherapy combinations restrain the medical oncologist in prescribing these drugs.[26]

Based on the results, speculations for future perspectives could be made. Better outcomes on population level and a decrease of variation might be achieved by further implementation of the new chemotherapy regimens. Enhanced implementation of new treatments should be performed on a national scale by a structured approach. It could be considered to centralize (palliative) care of PDAC, because in 2012-2016 there still was a difference in the probability of receiving chemotherapy between centers (however less pronounced compared to 2007-2011). Also, type of chemotherapy prescribed was highly variable between hospitals. In pancreatic surgery, centralization increased resection rates and reduced mortality.[27,28] In palliative care there is limited data on the benefit of centralization, or at least centralized assessment, but it has been demonstrated that volume matters regarding the use of chemotherapy.[15]

This study has some limitations. First, the incidence of PDAC is underestimated in the NCR. The missing patient group consists especially of elderly patients without pathological confirmation of cancer, patients with no cancer treatment and patients with a very poor survival.[29] To reduce the influence of possible incompleteness, only patients alive at 30 days after diagnosis were included. Sensitivity analyses addressing these limitations (selecting younger patients, pathologically confirmed PDAC or patients alive at 60 days after diagnosis) showed similar patterns. Second, treatment allocation bias could have occurred. To reduce this bias, patients who died within 30 days after diagnosis were excluded. Third, important case-mix factors like comorbid conditions and performance status were not available in the total study period. However, a similar pattern was found in sensitivity analysis including these factors. Fourth, details about chemotherapy regimens were only available for the 2015-2016 period. Possible trends in the use of FOLFIRINOX and nab-paclitaxel with gemcitabine could not be confirmed.

In conclusion, nationwide variation in the use of chemotherapy in patients with metastatic PDAC decreased after the implementation of FOLFIRINOX and gemcitabine with nab-paclitaxel in 2012-2016. Nevertheless, a considerable proportion of patients still received gemcitabine with a disappointing survival benefit. This study clearly shows that the implementation of more effective chemotherapeutic regimens in patients with metastatic PDAC is difficult and does not translate directly to a clinically relevant improvement in overall survival. These results emphasize the need for a structured implementation of new and more effective chemotherapeutic regimens in order to increase the use of these regimens and further decrease prescription variations.

ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FIGURE 1. Mean adjusted probability of receiving chemotherapy per hospital of diagnosis in 2007-2011 and 2012-2016 respectively for patients diagnosed with metastatic pancreatic ductal adenocarcinoma.

Hospitals of diagnosis are sorted by probability of receiving chemotherapy: red indicates university hospitals and blue indicates non-university hospitals.

SUPPLEMENTARY TABLE 1. Sensitivity analyses of variation in the use of chemotherapy in various subgroups.

	Period	Number of patients (*N*)	Number per hospital (min-max)	Overall (P)	Observed proportion per hospital (min-max)	Adjusted probability per hospital (min-max)
Basic models	2007-2011	3941	11-122	31%	6-87%	12-67%
	2012-2016	4785	9-146	37%	14-62%	20-54%
Selection patients under 75 years of age	2007-2011	2873	5-105	39%	6-100%	18-76%
	2012-2016	3414	6-105	47%	14-74%	28-64%
Selection patients alive 60 days after diagnosis	2007-2011	2842	7-102	39%	8-92%	16-73%
	2012-2016	3473	6-106	46%	18-73%	27-63%
Selection patients with pathological confirmation of cancer	2007-2011	2814	6-109	38%	8-92%	16-70%
	2012-2016	3616	6-125	46%	18-78%	29-62%
Selection period 2015-2016, additional adjustment with number of comorbid conditions and WHO performance status	2015-2016	2015	4-67	36%	8-64%	14-54%

Adjusted for patient and tumor factors.

SUPPLEMENTARY TABLE 2. Baseline characteristics of 723 patients with palliative chemotherapy in 2015-2016.

	Patients with chemotherapy, n (%) 2015-2016, *N*=723 (%)	FOLFIRINOX, n (%) *N* = 436	Gemcitabine plus nab-paclitaxel, n (%) *N* = 70	Gemcitabine, n (%) *N* = 182	Other, n (%) *N* = 35	p-value over types of chemotherapy
Gender						
Male	403 (56%)	245 (56%)	35 (51%)	99 (55%)	24 (59%)	0.817
Female	320 (44%)	189 (44%)	34 (49%)	80 (45%)	17 (41%)	
Age (years)						
Median (IQR)	64 (58-70)	61 (55-67)	68 (61-72)	70 (64-74)	66 (57-72)	**<0.001**
<50	47 (6.5%)	39 (9%)	2 (2.9%)	1 (0.6%)	5 (12%)	**<0.001**
50-59	179 (25%)	148 (33%)	11 (16%)	17 (9.5%)	6 (15%)	
60-69	295 (40%)	181 (42%)	30 (43%)	68 (38%)	16 (39%)	
70-79	194 (27%)	68 (16%)	25 (36%)	88 (49%)	13 (32%)	
≥80	8 (1.1%)	1 (0.2%)	1 (1.5%)	5 (2.8%)	1 (2.4%)	

Number of comorbidities						**<0.001**
None	211 (29%)	150 (35%)	14 (20%)	36 (20.1%)	11 (27%)	
1 condition	235 (33%)	156 (36%)	21 (30%)	46 (25.7%)	12 (29%)	
≥ 2 conditions	224 (31%)	94 (22%)	29 (42%)	88 (49.2%)	13 (32%)	
Unknown	53 (7.3%)	34 (7.8%)	5 (7.3%)	9 (5.0%)	5 (12%)	
Performance status (WHO)						**<0.001**
0	205 (28%)	160 (37%)	16 (23%)	23 (13%)	6 (15%)	
1	241 (33%)	142 (33%)	32 (46%)	55 (31%)	12 (29%)	
2-3-4	81 (11%)	24 (6%)	14 (20%)	40 (22%)	3 (7%)	
Unknown	196 (27%)	108 (25%)	7 (10%)	61 (34%)	20 (49%)	
Socioeconomic status						0.052
High	211 (29%)	144 (33%)	11 (16%)	45 (25%)	11 (27%)	
Medium	309 (43%)	180 (42%)	31 (45%)	80 (45%)	18 (44%)	
Low	203 (28%)	110 (25%)	27 (39%)	54 (30%)	12 (29%)	
Pathological confirmation	672 (93%)	409 (94%)	67 (97%)	159 (89%)	37 (90%)	**0.046**
Primary tumor location						0.721
Head of pancreas	298 (41%)	178 (41%)	26 (38%)	72 (41%)	21 (51%)	
Body of pancreas	138 (19%)	84 (19%)	14 (20%)	32 (18%)	8 (20%)	
Tail of pancreas	168 (23%)	107 (25%)	15 (22%)	38 (21%)	8 (20%)	
Other	119 (16%)	66 (15%)	14 (20%)	36 (20%)	4 (10%)	
Metastatic site						0.259
Liver	306 (42%)	186 (43%)	30 (43%)	73 (41%)	17 (41.5%)	
Lung	31 (4.3%)	13 (3.0%)	6 (8.7%)	9 (5.0%)	3 (7.3%)	
Peritoneum	67 (9.3%)	38 (8.8%)	10 (14%)	17 (9.5%)	2 (4.9%)	
Extra regional lymph nodes	31 (4.3%)	19 (4.4%)	5 (7.3%)	7 (3.9%)	-	
Other	12 (1.7%)	7 (1.6%)	-	3 (1.7%)	2 (4.9%)	
2 metastatic sites*	190 (26%)	120 (28%)	12 (17%)	49 (27%)	9 (22%)	
3 or more metastatic sites*	86 (11%)	51 (12%)	6 (8.7%)	21 (12%)	8 (20%)	
Unknown	-	-	-	-	-	
Median overall survival, months (95%CI)	6.5 (5.9-7.0)	8.0 (7.3-8.8)	7.0 (5.0-8.9)	3.8 (3.1-4.6)	6.4 (4.6-8.2)	**<0.001**
One-year survival	21%	26%	26%	6.6%	29%	**<0.001**

Bold numbers indicate statistical significance. *Any combination of metastatic sites.

CHAPTER 4

Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer

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HPB (Oxford). 2020 Jul 16:S1365-182X(20)31056-X.

ABSTRACT

Background: Guidelines advise self-expanding metal stents (SEMS) over plastic stents in preoperative endoscopic biliary drainage (EBD) for malignant extrahepatic biliary obstruction. This study aims to assess nationwide practice and outcomes.

Methods: Patients with pancreatic head and periampullary cancer who underwent EBD before pancreatoduodenectomy were included from the Dutch Pancreatic Cancer Audit (2017-2018). Multivariable logistic and linear regression models were performed.

Results: In total, 575/1056 patients (62.0%) underwent preoperative EBD: 246 SEMS (42.8%) and 329 plastic stents (57.2%). EBD-related complications were comparable between the groups (44/246 (17.9%) vs. 64/329 (19.5%), p=0.607), including pancreatitis (22/246 (8.9%) vs. 25/329 (7.6%), p=0.387). EBD-related cholangitis was reduced after SEMS placement (10/246 (4.1%) vs. 32/329 (9.7%), p=0.043), which was confirmed in multivariable analysis (OR 0.36 95% CI 0.15-0.87, p=0.023). Major postoperative complications did not differ (58/246 (23.6%) vs. 90/329 (27.4%), p=0.316), whereas postoperative pancreatic fistula (24/246 (9.8%) vs. 61/329 (18.5%), p=0.004; OR 0.50 95% CI 0.27-0.94, p=0.031) and hospital stay (14.0 days vs. 17.4 days, p=0.005; B -2.86 95% CI -5.16--0.57, p =0.014) were less after SEMS placement.

Conclusion: This study found that preoperative EBD frequently involved plastic stents. SEMS seemed associated with lower risks of cholangitis and less postoperative pancreatic fistula, but without an increased pancreatitis risk.

INTRODUCTION

Patients with resectable pancreatic head and periampullary cancer may require preoperative endoscopic biliary drainage (EBD) due to extrahepatic bile duct obstruction. Early surgery is, however, preferred, as this is associated with fewer perioperative complications compared to preoperative EBD.[1] Indications for EBD include cholangitis, severe jaundice, long waiting times for surgery, and the use of neoadjuvant therapy, which is a rapidly emerging indication for longer-term EBD.[2–4]

Historically, EBD is performed by placement of a plastic stent which has to be replaced every three months to prevent stent occlusion. In the recently updated European Society of Gastrointestinal Endoscopy Clinical Guideline, self-expanding metal stent (SEMS) placement is recommended in case of preoperative EBD of malignant extrahepatic biliary obstruction.[2] A potential downside of SEMS placement could be the increased risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.[5] Plastic stents are still frequently used, however, possibly because of lower upfront costs. Nationwide studies assessing clinical practices and outcomes of EBD with SEMS or plastic stents in pancreatic head and periampullary cancer are lacking.

The aim of this study was to assess the use of SEMS on a nationwide scale in daily clinical practice in patients with pancreatic head and periampullary cancer undergoing preoperative EBD and to determine the relation between type of stent and EBD-related complications and postoperative outcomes.

METHODS

Patients and design

This nationwide, retrospective cohort study included all patients with a pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampulla of Vater adenocarcinoma who underwent pancreatoduodenectomy (PD) between January 2017 and December 2018 after EBD in the Netherlands. In general, biliary drainage was considered indicated in patients with clinical suspicion of cholangitis (characterized by fever, abdominal pain and/or jaundice), severe jaundice (bilirubin concentration ≥250 µmol/L), or mild jaundice (>25 µmol/L) before commencing neoadjuvant chemotherapy. EBD was also indicated for bilirubin <250 µmol/L if the waiting time for surgery exceeded 3 weeks and it was anticipated that the bilirubin might be above ≥250 µmol/L at time of surgery. In the Netherlands, endoscopy is always performed by a gastroenterologist and local protocols are followed for procedures concerning EBD and stent placement. Endoscopic ultrasound for obtaining pathological material is performed prior to ERCP and stent placement. Type of stent depends on the expertise and preference of the gastroenterologist. Prevention of post-ERCP pancreatitis exists of rectal nonsteroidal anti-inflammatory drug administration and in case of manipulation of the

pancreatic duct, a 5 Fr plastic stent is placed in the pancreatic duct. Patients with percutaneous biliary drainage were excluded. Patients were identified from the Dutch Pancreatic Cancer Audit (DPCA), a nationwide, mandatory, prospective audit of pancreatic surgery. Data were registered by the surgeons of each center. Since 2017, several variables containing information about preoperative EBD and stents were added to the DPCA. All 17 pancreatic centers in the Netherlands performing pancreatic surgery participate in this audit. Annually, each center is required to perform at least 20 PDs. Data are registered anonymously and evaluated retrospectively. This study is reported in accordance with the STROBE guidelines.[6]

Data collection

Patient, tumor, and treatment characteristics were collected. Center of stent placement was not registered, but center of surgery (pancreatic center) was. Therefore, pancreatic centers represent stent placements from the center itself and from regional centers referring to the pancreatic center. Dates of the final multidisciplinary team (MDT) meeting in pancreatic centers and of drainage were available as well as type of stent and EBD-related complications. No other data about stent replacement were available. Postoperative outcomes were postoperative complications, in-hospital mortality, length of hospital stay, and readmissions within 30 days after discharge.

Definitions

Data from patients with pancreatic head and periampullary cancer were pooled in this study. Pancreatic centers were divided according to volume in <40 or ≥40 PDs annually. Site of origin was categorized into pancreas, distal bile duct, ampulla of Vater, or duodenum or other. Type of stent was SEMS versus plastic stent. SEMS were categorized into fully covered SEMS and uncovered SEMS. Neoadjuvant therapy was chemo(radio)therapy, mostly given within a randomized trial. Preoperative pathological confirmation was obtained by duodenoscopy with biopsy, ERCP with brush, or endoscopic ultrasound guided puncture of the primary tumor. PD included pylorus-preserving PD, pylorus-resecting PD, and classical Whipple. EBD-related complications included pancreatitis, cholangitis, stent occlusion, perforation of the bile duct or duodenum, and hemorrhage. These complications were registered accordingly to judgement of the local physicians. It was documented whether reinterventions (radiological or endoscopic) were performed for any EBD-related complication. All postoperative complications during hospital admission or up to 30 days after resection were also registered. Major postoperative complications were defined as a Clavien-Dindo score ≥3.[7] Pancreatic surgery specific complications (i.e. postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, and chyle leak) were defined by the International Study Group on Pancreatic Surgery (ISGPS) and scored in three groups of severity.[8–11] Bile leakage was scored accordingly as was defined by the International

Study Group of Liver Surgery.[12] Grade B and C graded complications were considered clinically relevant. Reintervention for a postoperative complication was categorized as an endoscopic, radiological, or surgical intervention. Exact details about the type of reintervention were not registered.

Statistical analysis

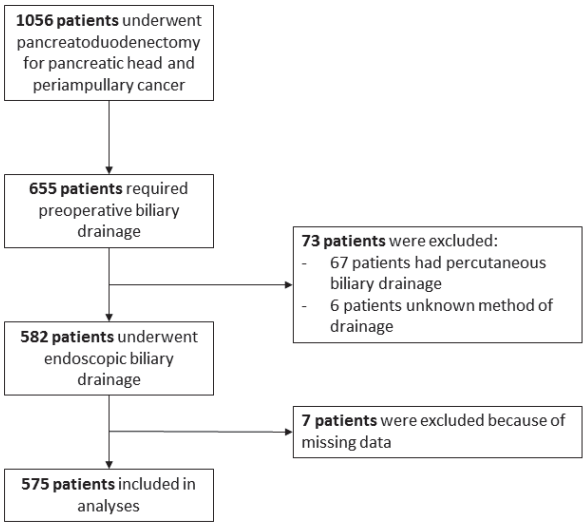
Missing data (range 0-24%) were imputed by multiple imputation with predictive mean matching in which 25 dummy sets were created. Age, sex, hospital of treatment, date of drainage and date of MDT meeting were not imputed, because only a selected number of variables could be imputed. Patients with missing data in age, sex and hospital of treatment were excluded for further analyses. Baseline characteristics were presented using descriptive statistics. Normally distributed continuous data were compared using a Students t-test and presented as means with standard errors (SE). Non-normally distributed continuous data were compared using the Mann Whitney U test and presented as medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages and compared using the Chi-square test or with the Fisher's exact test if the expected count was less than 5. To determine the association between type of stent and EBD-related complications or postoperative outcomes that differed statistically significantly between the plastic stent and SEMS group, multivariable logistic or linear regression models were performed, adjusted for patient characteristics, differences in baseline data and other potential risk factors per specific outcome. Postoperative outcomes were also adjusted for hospital volume. The patient characteristics were age, sex, body mass index (BMI), and American Society of Anesthesiologists (ASA) score. Potential risk factors were found for postoperative pancreatic fistula, specifically BMI, pancreatic texture, and pancreatic duct diameter.[13] The results were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI) in logistic regression or as the regression coefficient (B) with corresponding 95% CI in linear regression. All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, N.Y., USA) and R version 3.4.3 (cran.r-project.org).

RESULTS

In total, 1056 patients underwent PD for pancreatic head and periampullary cancer in 2017 and 2018 (Figure 1). In 655 patients (62.0%) preoperative biliary drainage was performed, of whom 73 patients were excluded because the method of drainage was unknown or occurred percutaneously due to ERCP failure or technical impossibilities to perform EBD (e.g. after gastric bypass). Of the remaining 582 patients, 7 patients were excluded because of missing data in age, sex, and hospital of treatment. The final cohort undergoing EBD existed of 575 patients (54.4%). Missing data were randomly distributed

between the pancreatic centers. Baseline characteristics after multiple imputation are demonstrated in Table 1. All 17 pancreatic centers performed ≥20 PDs annually, of which 8 centers performed ≥40 PDs annually.

FIGURE 1. Flow chart of endoscopic biliary drainage in patients who underwent pancreatoduodenectomy for pancreatic head and periampullary cancer in 2017 and 2018 in the Netherlands.



Type of stent

SEMS were placed in 246 of 575 patients (42.8%) and plastic stents in 329 patients (57.2%). The use of SEMS varied from 0 to 77.1% between pancreatic centers (Supplemental Figure 1, p<0.001). Of all SEMS, 196 were covered (79.7%) and 50 were uncovered (20.3%). Timing of stent placement relative to the date of the MDT meeting was analyzed in 493 patients (non-imputed data). The majority of patients (n=343, 69.6%) had EBD before being discussed in the MDT meeting of a pancreatic center. From these 343 patients, 215 (62.7%) received plastic stents compared to 64 out of 150 patients (42.7%) after the MDT meeting in a pancreatic center (p<0.001).

TABLE 1. Baseline characteristics.

Variable	All patients (n = 575), n (%)	SEMS* (n =246), n (%)	Plastic stents (n =329), n (%)	Pooled p-value
Age, mean (SE)	68 (0.4)	68 (0.6)	67 (0.6)	0.117
Male	315 (54.8)	136 (55.3)	179 (54.4)	0.784
BMI*, mean (SE)	25.3 (0.2)	24.9 (0.3)	25.6 (0.3)	0.074
ASA score*				**0.001**
I and II	419 (72.9)	162 (65.9)	257 (78.1)	
III and IV	156 (27.1)	84 (34.1)	72 (21.9)	
Comorbidity				0.098
Liver cirrhosis	10 (1.7)	7 (2.8)	3 (0.9)	
Pancreatitis	24 (4.2)	7 (2.8)	17 (5.2)	
Site of origin				**0.008**
Pancreas	310 (53.9)	155 (63.0)	156 (47.4)	
Distal bile duct	152 (26.4)	57 (23.2)	96 (29.2)	
Ampulla of Vater	99 (17.2)	30 (12.2)	68 (20.7)	
Duodenum or other	14 (2.4)	5 (2.0)	9 (2.7)	
Diameter pancreatic duct, mean (SE)	4.6 (0.1)	4.8 (0.2)	4.4 (0.2)	0.095
Preoperative cytological or histological examination				0.328
Endoscopy with biopsy	201 (35.0)	95 (38.6)	106 (32.2)	
ERCP* and brush	289 (50.3)	115 (46.7)	174 (53.2)	
Other	13 (2.3)	4 (1.6)	10 (3.0)	
Type stent				NA
Covered		196 (79.7)		
Uncovered		50 (20.3)		
Neoadjuvant therapy	48 (8.3)	31 (12.6)	17 (5.2)	**0.011**
Hospital volume				**<0.001**
<40 PDs annually	201 (35.0)	55 (22.4)	146 (44.4)	
≥40 PDs annually	374 (65.0)	191 (77.6)	183 (55.6)	
Time to surgery#, days, median (IQR)	32.0 (22.0-48.0)	27.0 (21.0-41.0)	37.5 (25.0-53.0)	**<0.001**
Pancreatic texture during surgery				**0.001**
Normal/soft	331 (57.6)	121 (49.2)	209 (63.5)	
Fibrotic/hard	244 (42.4)	125 (50.8)	119 (36.2)	

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation. * SEMS: self-expandable metal stents, BMI: body mass index, ASA score: American Society of Anesthesiologists score, NA: not applicable, ERCP: endoscopic retrograde cholangio- and pancreatography, PD: pancreatoduodenectomie # Only in patients without neoadjuvant chemotherapy and based on non-imputed data: 414 patients in overall group, 240 patients in plastic stent group, and 174 in SEMS group.

Patients with SEMS had higher ASA scores, more often a fibrotic/hard pancreatic texture during surgical exploration, were more often treated with neoadjuvant therapy and the site of origin was more often the pancreas compared to patients with plastic stents (Table 1). Of all patients with neoadjuvant therapy, 31 patients (64.6%) received a SEMS. Time to surgery after stent placement was significantly shorter for patients with SEMS compared to patients with plastic stents after excluding patients with neoadjuvant therapy (non-imputed data: 27.0 (21.0-41.0) vs. 37.5 (25.0-53.0) days, p<0.001).

Endoscopic biliary drainage-related complications

The rate of any complication after EBD was comparable in both stent groups (44 patients (17.9%) vs. 64 patients (19.5%) for SEMS and plastic stents respectively, p=0.607). EBD-related cholangitis occurred less often in patients with SEMS compared to plastic stents (10 patients (4.1%) vs. 32 patients (9.7%), p=0.043, Table 2). Post-ERCP pancreatitis occurred in 22 patients (8.9%) with SEMS and 25 patients (7.6%) with plastic stents (p=0.387). Reintervention (endoscopic or radiological) was required in 22 patients (8.9%) of the SEMS group and 32 patients (9.7%) of the plastic stent group (p=0.584). In multivariable logistic regression, adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), site of origin, and neoadjuvant therapy, SEMS were associated with a lower OR of cholangitis (OR 0.36 95% CI 0.15-0.87, p=0.023, Figure 2A) compared to plastic stents. The rate of any complication after EBD, pancreatitis, cholangitis, perforation, hemorrhage, occlusion, and reintervention for complications did not differ between the covered and uncovered SEMS (See Supplementary Table 1).

TABLE 2. Complications related to endoscopic biliary drainage.

Variable	All patients (n = 575), n (%)	SEMS* (n =246), n (%)	Plastic stents (n =329), n (%)	Pooled p-value
Any complication	107 (18.6)	44 (17.9)	64 (19.5)	0.607
Pancreatitis	47 (8.2)	22 (8.9)	25 (7.6)	0.387
Cholangitis	43 (7.5)	10 (4.1)	32 (9.7)	**0.043**
Perforation	16 (2.8)	3 (1.2)	13 (4.0)	0.120
Hemorrhage	23 (4.0)	8 (3.3)	15 (4.6)	0.365
Occlusion	38 (6.6)	11 (4.5)	27 (8.2)	0.173
Reintervention	54 (9.4)	22 (8.9)	32 (9.7)	0.584

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation. * SEMS: self-expandable metal stents.

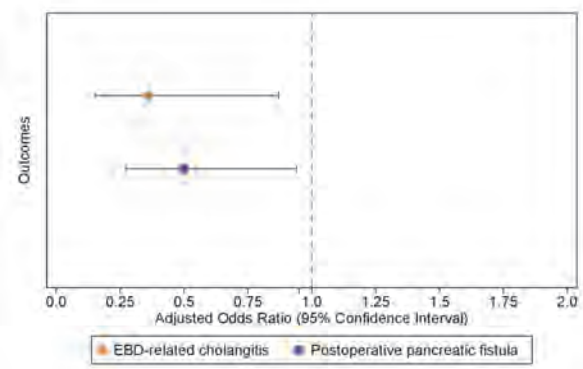
Postoperative outcomes after pancreatoduodenectomy

Patients with SEMS and plastic stents had similar rates of major postoperative complications (58 patients (23.6%) vs. 90 patients (27.4%), p=0.316, Table 3). Major postoperative complications occurred in all 43 patients who had EBD-related cholangitis (100%) and in 181 patients who did not have EBD-related cholangitis (34.0%, p<0.001). The proportion of patients with postoperative pancreatic fistula grade B-C (i.e. clinically relevant fistula) was lower in patients with a SEMS compared to plastic stents (24 patients (9.8%) vs. 61 patients (18.5%) respectively, p=0.004). After adjustment for patient characteristics, hospital volume, neoadjuvant therapy, site of origin, pancreatic duct diameter, and pancreatic texture, the use of SEMS was still associated with a significantly lower risk on postoperative pancreatic fistula (OR 0.50 95% CI 0.27-0.94, p=0.031, Figure 2A).[13] Patients with SEMS had a shorter mean length of hospital stay than patients with plastic stents (14.0 days (SE 0.6) vs. 17.4 days (SE 1.0)

respectively, p=0.005). In multivariable linear regression, adjusted for patient characteristics, hospital volume, site of origin, neoadjuvant therapy, pancreatic texture, and major postoperative complications, length of hospital stay was almost three days shorter in patients who received a SEMS (B -2.86 95% CI -5.16--0.57, p =0.014) compared to patients with a plastic stent (Figure 2B).

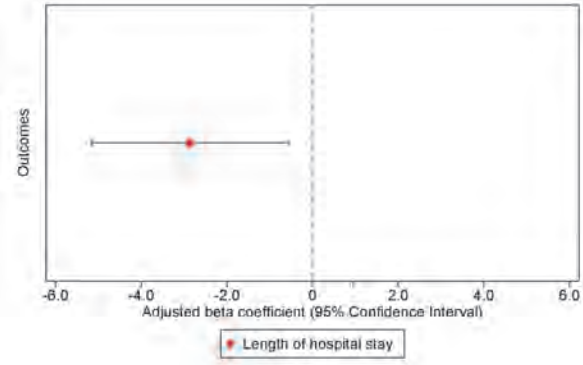
FIGURE 2 Multivariable regression analysis to assess the association between type of stent and outcomes.

FIGURE 2A. Results of multivariable logistic regression analysis to assess the association between type of stent and EBD-related cholangitis and postoperative pancreatic fistula.



Odds ratio of EBD-related cholangitis is adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), site of origin, and neoadjuvant therapy. Odds ratio for postoperative pancreatic fistula adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, neoadjuvant therapy, site of origin, pancreatic duct diameter, and pancreatic texture.

FIGURE 2B. Results of multivariable linear regression analysis to assess the association between type of stent and length of hospital stay.



The beta coefficient of length of hospital stay is adjusted for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, site of origin, neoadjvant therapy, pancreatic texture, and major postoperative complications.

TABLE 3. Postoperative outcomes.

Variable	All patients (n = 575), n (%)	SEMS* (n =246), n (%)	Plastic stents (n =329), n (%)	Pooled p-value
Major postoperative complication	148 (25.7)	58 (23.6)	90 (27.4)	0.316
Any complication during hospital admission/30 days after surgery	363 (63.1)	161 (65.4)	202 (61.4)	0.397
Postoperative pancreatic fistula, grade B/C	85 (14.8)	24 (9.8)	61 (18.5)	**0.004**
Delayed gastric emptying, grade B/C	110 (19.1)	39 (15.9)	72 (21.9)	0.100
Post pancreatectomy hemorrhage, grade B/C	33 (5.7)	11 (4.5)	23 (7.0)	0.236
Bile leakage, grade B/C	25 (4.3)	13 (5.3)	12 (3.6)	0.351
Chyle leak, grade B/C	44 (7.7)	18 (7.3)	25 (7.6)	0.776
Pneumonia	34 (5.9)	18 (7.3)	16 (4.9)	0.245
Wound infection	89 (15.5)	41 (16.7)	48 (14.6)	0.487
Intensive care unit admission	49 (8.5)	20 (8.1)	29 (8.8)	0.652
Reintervention	141 (24.5)	54 (22.0)	87 (26.4)	0.211
Endoscopic	26 (5.2)	13 (5.3)	14 (4.3)	0.553
Radiological	109 (19.0)	40 (16.3)	69 (21.0)	0.164
Reoperation	40 (7.0)	15 (6.1)	25 (7.6)	0.529
In-hospital mortality	8 (1.4)	4 (1.6)	4 (1.2)	0.603
Length of hospital stay, mean (SE)	16.0 (0.6)	14.0 (0.6)	17.4 (1.0)	**0.005**
Readmission within 30 days after discharge	80 (13.9)	32 (13.0)	48 (14.6)	0.598

Bold numbers indicate statistical significance; numbers in the SEMS and plastic stent group do not always equal the total cohort, because of rounding due to the imputation. * SEMS: self-expandable metal stents.

DISCUSSION

This nationwide study shows that in 2017 and 2018 in the Netherlands, SEMS were placed in less than half of all patients who received EBD prior to pancreatoduodenectomy. The rate of overall EBD-related complications were similar between SEMS and plastic stents, but patients receiving SEMS had a lower odds of cholangitis, less postoperative pancreatic fistula, and a shorter postoperative hospital stay. No association between SEMS and post-ERCP pancreatitis rate could be demonstrated, neither in the small subgroup analysis of patient that received a covered SEMS.

As demonstrated in a multicenter randomized controlled trial including 196 patients, early surgery without preoperative biliary drainage in patients with cancer of the pancreatic head is the preferred treatment, because routine preoperative biliary drainage increased the rate of complications from 39% to 74%.[1] Still, preoperative EBD was performed in 54.4% of all patients who underwent PD in this study. Unfortunately, the exact indication for stent placement could not be assessed because this variable was not registered in the audit. Data from the Surveillance, Epidemiology, and End Results (SEER) tumor registry showed that in 2004-2007 the rate of preoperative EBD was 40%.[14] The nationwide audit from Germany showed a preoperative EBD percentage of 38.9% for pancreatic ductal adenocarcinoma in 2014-2016.[15] Monocenter studies showed that respectively 47.6% (2005-2016) and 55% (2006-2016)

initially underwent preoperative biliary drainage.[16,17] The relatively high percentage of preoperative drainage in the current study might be a reflection of lack of awareness of the proper indication as stated in the guidelines.[2]

The European guideline published in 2018 explicitly recommends the use of SEMS in patients who undergo preoperative EBD.[2] This recommendation is mainly based on a meta-analysis that showed significantly lower rates of endoscopic reinterventions and postoperative pancreatic fistula in patients treated with SEMS compared to plastic stents (3.4% vs. 14.8% and 5.1% vs. 11.8%, respectively).[18] This study shows, however, that over 50% of all patients still received a plastic stent. Which is particularly remarkable as currently neoadjuvant chemo(radio)therapy is increasingly administered to patients with pancreatic cancer. In the Netherlands both the recently completed PREOPANC-1 trial (NL3525; https://www.trialregister.nl/trial/3525) and the ongoing PREOPANC-2 trial (NL7094; https://www.trialregister.nl/trial/7094) advise the use of (fully covered) SEMS prior to start of neoadjuvant treatment.[19] Naturally, the percentage of patients with neoadjuvant therapy was higher in the SEMS group, but still a considerable proportion of patients with neoadjuvant therapy received a plastic stent (35%). Even though data revealed that delay until start of neoadjuvant treatment was shorter in patients with a SEMS and stent patency was longer.[3,20] There could be several reasons for these relatively high percentages of plastic stents in all patients and the subgroup with neoadjuvant therapy. First, most patients received a stent before being discussed in the MDT meeting in a pancreatic center (69.6%). If drainage is performed before staging, a plastic stent is often preferred by the radiologist as scattering from the metallic stent might hamper adequate interpretation of tumor staging. After staging, but before pathological confirmation, as well plastic as fully covered SEMS could be placed. In this scenario the European guideline recommends against uncovered SEMS, because these cannot be removed without surgery.[2] Second, the higher costs of initial SEMS placement compared to plastic stent placement probably also play a major role in the current findings. Dutch costs for initial stent placement for palliation including secondary procedures in case of initial failure were €1973 for a SEMS and €1042 for a plastic stent (p=0.001).[21] However, cost-effectiveness of SEMS placement has been demonstrated in patients who received neoadjuvant therapy (United States' costs of the index ERCP, procedural adverse events, and adverse events from stent occlusion based on actual hospital charges: fully covered SEMS €36.978 vs. uncovered SEMS €37.304 vs. plastic €35.937), as the stent itself is more expensive, but SEMS have higher patency rates and render less adverse events.[3,22] Finally, the new guideline was published in September 2018 and therefore the implementation time was short, however, the results of the Dutch randomized trial were already published in 2016 and were given much attention in the Netherlands.[2,23] As it is known that implementation of new or updated guidelines often requires several years and is affected by multiple factors, e.g. quality of guidelines and characteristics

of health care professionals such as age and country of training.[24,25] Even in a small and organized country as the Netherlands, it has been shown that one year after implementation guideline compliance in pancreatic cancer was poor.[24] This is also shown for other countries and cancer types.[26–28] A nationwide implementation strategy addressing both pancreatic centers and regional referral networks might increase the use of SEMS, as recommended by the European guideline, and is currently carried out within the PACAP-1 trial.[29]

Several baseline characteristics differed between patients in the SEMS and plastic stent groups. Differences in pancreatic texture and site of origin were probably related to neoadjuvant therapy. The higher ASA score of patients with SEMS remains unexplained. The moment of registration of the ASA score is unknown. It could be that in patients with neoadjuvant therapy the ASA score increases during treatment and that this score is registered after treatment shortly before resection. More patients with a SEMS received neoadjuvant therapy and it might be speculated that this (partly) causes the higher ASA score.

In this study, a similar rate of overall EBD-related complications was found in the SEMS and plastic stent groups, but patients receiving plastic stents had statistically significantly more EBD-related cholangitis compared to patients receiving SEMS. This might also be the explanation for the longer time to surgery in patients with a plastic stent. Surprisingly, the percentage of reinterventions was not higher in the plastic stent group. This could have been caused by an under registration, as the DPCA is a surgical audit in which gastroenterological variables may be registered less accurate.

It has been shown in previous studies that the frequency of EBD-related pancreatitis was higher in patients with SEMS as compared to plastic stents.[23,30] SEMS and particularly fully covered SEMS could hamper pancreatic duct out flow as compared to plastic stents which could increase the risk of post-ERCP pancreatitis.[31] In this nationwide study, it was not demonstrated that the post-ERCP pancreatitis rate was higher in patients with a SEMS, which was also confirmed by several other studies.[32,33] Currently, the multicenter SPHINX trial in the Netherlands is assessing whether an endoscopic sphincterotomy prior to biliary fully covered SEMS placement could decrease the incidence of post-ERCP pancreatitis (NL5130; https://www.trialregister.nl/trial/5130).

Major postoperative complications were similar between the SEMS group and plastic stent group. These results were comparable to the results of a meta-analysis.[18] Literature is contradictive about the association between type of stent and postoperative pancreatic fistula.[18,23,34] In the current cohort, after adjustment for patient characteristics (i.e. age, sex, BMI, and ASA score), hospital volume, neoadjuvant

therapy, and other risk factors (i.e. BMI, pancreatic texture, and pancreatic duct diameter; in accordance with the alternative fistula risk score) in multivariable analysis, the odds of postoperative pancreatic fistula was statistically significantly lower for patient who received a SEMS.[13] It is thought that the higher odds of postoperative pancreatic fistula is related to pancreatic texture. The current binary classification of pancreatic texture does not cover all variations in pancreatic texture. After expansion of the SEMS, the pancreatic duct experiences more pressure and therefore fibrosis of the pancreatic texture increases. More fibrosis is likely related to less postoperative fistula.

The length of hospital stay was approximately three days shorter in patients who received a SEMS as compared to a plastic stent which is clinically relevant, because it reflects improved recovery and may result in decreased hospital costs. This has not been previously described.[35] Although not completely clear this might be related to an increased rate of postoperative pancreatic fistula grade A, which is not covered in the Clavien Dindo score ≥3, and hence a longer time to functional recovery after surgery with plastic stents.

This study had several limitations. First, the retrospective character of this study causes missing information about for example center of stent placement, exact indication for EBD, severity of EBD-related complications, details about reinterventions for EBD-related complications, and stent replacement. Currently, to improve DPCA data quality even further, gastroenterological variables and definitions of EBD-related complications are critically reviewed by gastroenterologists and surgeons from the Dutch Pancreatic Cancer Group. Second, only patients who underwent a PD were included and therefore selection bias might have been introduced. Therefore, patients who had serious complications due to preoperative EBD and were not able to undergo surgery were not registered in the DPCA. This proportion of patients might be, however, negligible as in a randomized setting there was only 1 out of 120 patients who did not undergo surgery after initial preoperative EBD due to stent related complications.[1,23] The main strength of this study is the mandatory, nationwide aspect of the DPCA including data on all pancreatic resections in the Netherlands. A previous study reported a high quality of DPCA data.[36]

In conclusion, this nationwide study found that EBD prior to pancreatoduodenectomy still frequently involved plastic stents. SEMS placement seemed to be associated with lower risks of cholangitis, less postoperative pancreatic fistula, and a shorter postoperative hospital stay but not with an increased risk of pancreatitis. A nationwide implementation strategy addressing both pancreatic centers and regional referral networks might increase the use of SEMS, as recommended by the European guideline.

ACKNOWLEDGEMENTS

The authors thank all participants of the Dutch Pancreatic Cancer Audit for their dedicated data collection.

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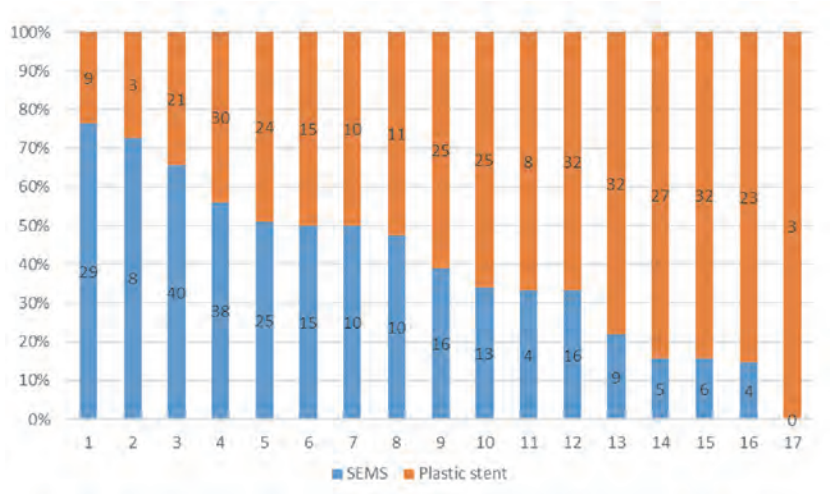
SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FIGURE 1. Variation in nationwide use of SEMS and plastic stents in 2017-2018 for endoscopic biliary drainage in patients undergoing pancreatoduodenectomy for pancreatic head and periampullary cancer in 17 pancreatic centers in the Netherlands.



The numbers in the bar charts represent the actual numbers of placed stents per pancreatic center. Stents could be placed either in the referring center or the pancreatic center.

SUPPLEMENTARY TABLE 1. Complications related to endoscopic biliary drainage in covered vs. uncovered self-expandable metal stents.

Variable	Covered (n =197) n (%)	Uncovered (n =50) n (%)	Pooled p-value
Any complication	38 (19.3)	6 (12.0)	0.279
Pancreatitis	21 (10.7)	1 (2.0)	0.128
Cholangitis	9 (4.6)	1 (2.0)	0.325
Perforation	2 (1.0)	1 (2.0)	-*
Hemorrhage	6 (3.0)	2 (4.0)	0.599
Occlusion	8 (4.0)	3 (6.0)	0.617
Reintervention	17 (8.6)	5 (10.0)	0.588

* Not enough events for statistical analysis

CHAPTER 5

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

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Trials. 2020 Apr 16;21(1):334.

ABSTRACT

Background: Pancreatic cancer has a very poor prognosis. Best practices for the use of chemotherapy, enzyme replacement therapy, and biliary drainage have been identified but their implementation in daily clinical practice is often suboptimal. We hypothesized that a nationwide program to enhance implementation of these best practices in pancreatic cancer care improves survival and quality of life.

Methods: PACAP-1 is a nationwide multicenter stepped-wedge cluster randomized controlled superiority trial. In a per center stepwise and randomized manner, best practices in pancreatic cancer care regarding the use of (neo)adjuvant and palliative chemotherapy, pancreatic enzyme replacement therapy, and metal biliary stents are implemented in all 17 Dutch pancreatic centers and their regional referral networks during a six week initiation period. Per pancreatic center, one multidisciplinary team functions as reference for the other centers in the network. Key best practices were identified from literature, three years of data from existing nationwide registries within the Dutch Pancreatic Cancer Project (PACAP), and national expert meetings. The best practices follow the Dutch guideline on pancreatic cancer and the current state of the literature, and can be executed within daily clinical practice The implementation process include monitoring, return visits, and provider feedback in combination with education and reminders.. Patient outcomes and compliance are monitored within the PACAP registries. Primary outcome is one-year overall survival (for all disease stages). Secondary outcomes include quality of life, three- and five-year overall survival, and guideline compliance. An improvement of 10% of one-year overall survival was considered clinically relevant. A 25 months study duration was chosen, which provides 80% statistical power for an mortality reduction of 10.0% in the 17 pancreatic cancer centers, with a required sample size of 2142 patients, corresponding with a 6.6% mortality reduction and 4769 patients nationwide.

Discussion: The PACAP-1 trial is designed to evaluate whether a nationwide program for enhanced implementation of best practices in pancreatic cancer care can improve one-year overall survival and quality of life.

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

BACKGROUND

It is estimated that pancreatic cancer will be the second most common cause of cancer-related mortality by 2030 in Europe[1]. Without treatment, the median survival is only three to six months. Some 15-20% of patients with pancreatic cancer are amenable to surgical resection combined with adjuvant chemotherapy[2]. However, even after resection, the median overall survival is only 11-25 months[1, 3]. In patients in whom it is possible to perform a microscopic radical resection median survival increases to three to four years[3-5].

The Dutch Pancreatic Cancer Project

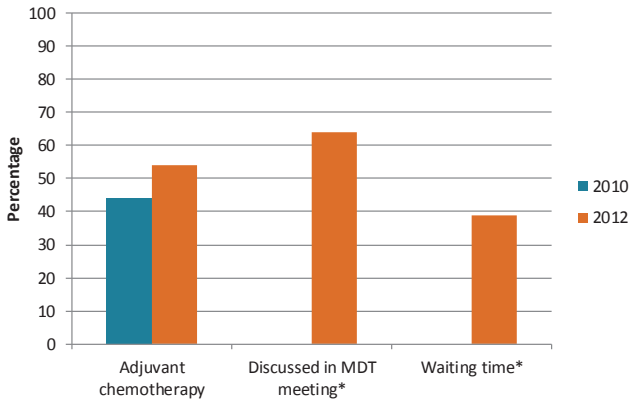
The Dutch Pancreatic Cancer Project (PACAP) aims to improve outcomes of patients in all stages of pancreatic cancer. PACAP was launched in 2013 as an initiative of the national multidisciplinary Dutch Pancreatic Cancer Group (DPCG, www.dpcg.nl). In a period of six years, PACAP aimed primarily to improve outcome and quality of life for pancreatic cancer patients in the Netherlands. This is achieved through one of the largest nationwide collaborative outcomes registration and biobanking projects on pancreatic cancer in the world, which provides unique opportunities for improving care for these patients and developing new diagnostic and treatment strategies. From the start, PACAP included several registries, including the Dutch Pancreatic Cancer Audit (DPCA), the Netherlands Cancer Registry (NCR), the Dutch Pancreas Biobank (PancreasParel), Patient Reported Outcome Measures (PROMs) and an online expert panel[6-8]. Details on PACAP registries are listed in APPENDIX 1.

The PACAP-1 trial

In 2014, 78% of 2393 patients diagnosed with pancreatic cancer in the Netherlands died within one year (www.cijfersoverkanker.nl). These numbers illustrate the severity of this disease and the need for improvement of treatment and clinical outcomes. From literature and the first three years of PACAP, fairly straightforward points of improvement in care and guideline compliance for patients with pancreatic cancer in the Netherlands were identified. Systematic reviews of guideline dissemination and implementation strategies showed that compliance by health-care workers, specifically medical doctors, is poor[9, 10]. A recent study demonstrated that compliance with the 2012 Dutch pancreatic cancer guideline was low (Figure 1)[11]. In addition, regional differences in (type of) treatment and clinical outcomes have been identified. For example, the use of adjuvant chemotherapy after pancreatoduodenectomy for pancreatic cancer per DPCG center varied between 26-74% in 1195 Dutch patients (2008-2013)[12]. Significant differences were also present in the type of palliative chemotherapy given to 345 patients with metastatic disease (Figure 2). Patients with metastatic disease who were treated in high-volume chemotherapy or surgical centers had better survival compared to lower volume centers[13]. While administration of palliative systemic chemotherapy doubled in the elderly in the

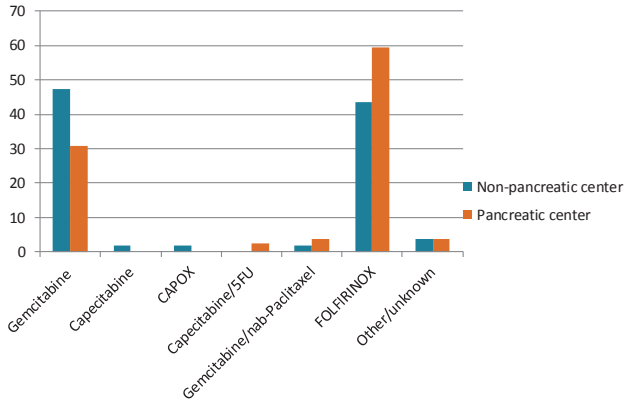
Netherlands between 2005 and 2013 (13% vs. 30%), it was still relatively low as compared with population based-studies from other Western countries[14].

FIGURE 1. Guideline compliance among 2,564 patients treated for pancreatic or periampullary cancer in the Netherlands in 2010 and 2012. MDT = multidisciplinary team. Definition adjuvant chemotherapy: percentage of patients receiving adjuvant chemotherapy after tumor resection for pancreatic carcinoma. Definition discussed in MDT meeting: percentage of patients discussed within a MDT meeting. Definition waiting time: percentage of patients who started treatment within three weeks of final MDT meeting.



* Not available for 2010.

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



CAPOX = capecitabine and oxaliplatin. 5FU = 5-fluorouracil. FOLFIRINOX = folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin.

The PACAP-1 trial aims to enhance the implementation of key best practices in the 17 Dutch pancreatic centers with their associated regional networks, using a nationwide stepped-wedge cluster randomized controlled trial (RCT). PACAP-1 is unique that it involves all relevant medical specialties and all Dutch hospitals treating patients with pancreatic cancer. PACAP-1 will use the registries already included in PACAP to audit current practice and improve adherence to best practices and synoptic reporting in the Netherlands for pancreatic cancer patients, including the Dutch evidence-based guideline on pancreatic cancer[15]. Most importantly, with the PACAP infrastructure, the level of implementation, compliance and the effect on patient outcomes can be assessed. We hypothesize that survival and quality of life will improve for pancreatic cancer patients in the Netherlands by a program to enhance implementation of best practices.

METHODS

Study setting

The PACAP-1 trial will implement best-practices to and collect data from all hospitals (e.g., academic, top-clinical, general) in the Netherlands. A list of the DPCG centers where pancreatic surgery is performed can be found at www.dpcg.nl.

Primary aim

The primary aim of PACAP-1 is to evaluate whether a nationwide program for enhanced implementation of best practices can improve one-year overall survival by 10% in all pancreatic cancer patients in the Netherlands. Ten percent was considered to be clinically relevant.

Secondary aims

Secondary aims are to evaluate whether enhanced implementation of key best practices can improve quality of life (main secondary objective) and clinical outcomes (three- and five-year overall survival, and treatment complications). Another aim is to improve the use of nationwide standardized 'best practice' reports by radiologists, surgeons, pathologists, medical oncologists and gastroenterologists. Hereby, we aim to optimize data registry with key parameter and synoptic reporting that will lead to efficient and high-quality data collection. Finally, we aim to improve participation in DPCG RCTs, especially those which aim to improve survival and/or quality of life.

PACAP-1 trial design

The PACAP-1 trial is a nationwide stepped-wedge cluster RCT which aims for enhanced implementation of best practices in all 17 DPCG pancreatic cancer centers and their respective referral networks. Per pancreatic center and network, one regional pancreatic cancer team serves as reference for the other

centers in the network. The pancreatic cancer team included at least a medical oncologist, a gastroenterologist, and a surgeon, regularly together with a specialized nurse. This trial was designed in adherence to the CONSORT statement for cluster randomized trials[16] and extension for stepped-wedge trials[17], and SPIRIT guidelines for clinical trials[18]. For an overview of PACAP-1, see the SPIRIT figure (Figure 3) and the SPIRIT checklist (Supplementary materials).

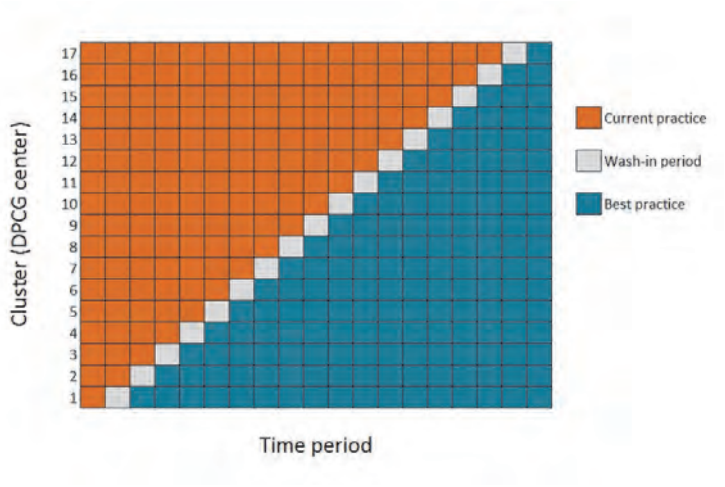
FIGURE 3. Schedule of enrolment, interventions, and assessments of PACAP-1 according to SPIRIT guidelines.

	STUDY PERIOD											
	Enrolment	Allocation	Post-allocation							Close-out	Close-out	Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	<..>	t_{18}	t_{19}	t_{19} + 1 year	t_{19} + 2 year	t_{19} + 5 year
ENROLMENT:												
Eligibility screen	X											
Cluster consent	X											
Approval local Ethical Boards	X											
Cluster randomization		X										
INTERVENTIONS:												
Current practice phase			X									
Cross-over cluster 1				X								
Cross-over cluster 2					X							
Cross-over cluster 3						X						
<< ..... >>							X					
Cross-over cluster 17								X				
Best practice phase									X			
ASSESSMENTS:												
Baseline variables	X	X	←	—	—	—	—	—	→			
Intervention outcomes			←	—	—	—	—	—	→	X	X	X
Process measure outcomes			←	—	—	—	—	—	→	X	X	X
Registry outcomes			←	—	—	—	—	—	→	X	X	X

A schematic overview of the stepped-wedge trial design is provided in Figure 4. In a step-wise manner, each cluster will cross-over from control (current practice) to intervention (best practice) phase. Each cluster contains one DPCG center and its referral region (see Figure 5), and therefore the number of sequences is equal to the number of participating centers. At start of the study, all clusters will be in the control phase. After 25 months, all 17 clusters will have crossed over to the intervention phase.

The duration of the trial is determined by the required sample size. Details of the sample size calculation are described in chapter 'Sample size calculation'. The order in which the clusters will cross-over is randomized[19, 20].

FIGURE 4. Schematic representation of PACAP-1 stepped-wedge cluster randomized controlled trial.



DPCG = Dutch Pancreatic Cancer Group.

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

Study population

All patients with pancreatic cancer in the Netherlands.

Patient inclusion criteria

Patients with pathologically or clinically diagnosed pancreatic ductal adenocarcinoma, all ages and all stages.

Patient exclusion criteria

None.

Center inclusion criteria

All 17 centers of the DPCG with their respective referral network. Each DPCG center performs at least 20 pancreatoduodenectomies (PDs) annually. Each center already has a coordinating role for pancreatic cancer for its regional network (Figure 5). It is expected that the enhanced implementation of best practices will have an impact in the entire local network. A survey was conducted among DPCG centers to identify peripheral centers that mainly refer to their DPCG center. Outcomes of this survey were checked with NCR data and discrepancies only occurred for two centers. With these centers and the particular DPCG centers, it was discussed in what region the center would fit best.

Center exclusion criteria

There are no specific center exclusion criteria.

FIGURE 5. Schematic representation of 17 Dutch Pancreatic Cancer Group centers (large dots) and their respective referral networks and centers (smaller dots) per color.

NB. Referral centers may refer patients to more than one pancreatic center and therefore this figure is only for illustration.

Study endpoints

Primary endpoint

The primary endpoint is one-year overall survival.

Secondary endpoints

Secondary study endpoints are divided in intervention (e.g. quality of life, 3- and 5- year survival, and treatment complications such as chemotherapy toxicity), process measure (e.g. proportion of post-pancreatectomy patients receiving adjuvant chemotherapy, and proportion of patients requiring biliary drainage receiving a metal stent), registry (e.g. proportion of patients registered for PROMs or in DPCA, and proportion of patients where the CT-scan checklist was used), and other outcomes (e.g. proportion of patients included in other DPCG prospective trials), see Supplementary materials for a detailed list of the secondary endpoints.

Sample size calculation

PACAP-1 is a superiority trial with one-year overall survival as primary endpoint, which will be extracted from NCR survival data. The sample size calculation was based on the data from Table 1.

TABLE 1. Unpublished data from the Netherlands Cancer Registry of new patients diagnosed with pancreatic cancer in the year 2014.

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

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

The required sample size was calculated using the formula for stepped-wedge designs[21]. Sample sizes were calculated for different effect sizes, different intra-cluster coefficients, for 80% or 90% power, and for the DPCG centers and for all of the Netherlands separately, using a cluster autocorrelation (CAC) of 1[22] and a two-sided alpha of 0.05 (see Table 2). Subsequently, it was reversely calculated which effect sizes could be determined with 80% and 90% power given a fixed study duration (hence a fixed sample size) of 25 months for the different other assumptions (Table 2). For logistical reasons inherent to successful implementation of different (discipline transcending) interventions, a shorter study duration was not considered.

TABLE 2. Power for effect size given fixed sample size.

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

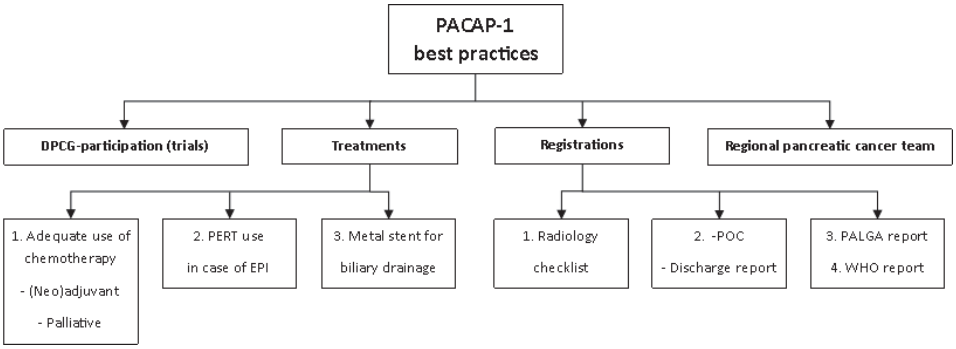
N = sample size, p0 = current one-year mortality, p1 = expected one-year mortality, RD = risk difference, ICC = intra-cluster correlation coefficient, CAC = cluster autocorrelation, DPCG = Dutch Pancreatic Cancer Group, NL = the Netherlands.

An improvement of 10% of one-year overall survival for all patients with pancreatic cancer in the Netherlands is considered clinically relevant, and could be established following the PACAP-1 interventions. A 25 months study duration was chosen, which provides 80% statistical power for an absolute mortality reduction of 10.0% and 90% power for a reduction of 11.5% in the 17 pancreatic cancer centers, with a required sample size of 2142 patients. For all of the Netherlands, assuming the intracluster correlation coefficient (ICC) will be higher, the corresponding sample size provides 80% power for an absolute mortality reduction of 6.6% and 90% power for a reduction of 7.6% (Table 2).

Intervention phase: PACAP-1 best practices

To determine key best practices, points of improvement for three key medical specialties (medical oncology, gastroenterology and surgery) were identified from literature and the first three years of PACAP (July 2014 – July 2017). These are divided in intervention and registry categories (Figure 6). Best-practice-treatments are aimed to improve survival, clinical outcomes and quality of life. Best-practice-registrations are aimed to optimize data registry with key parameter and synoptic reporting that will lead to efficient and high-quality data collection. PACAP-1 interventions are listed in APPENDIX 3 per medical specialism. An overview of PACAP-projects is presented in APPENDIX 1. Background and details per best practice are found in the Supplementary materials.

FIGURE 6. Schematic representation of PACAP-1 best practices.



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

Best practice treatments

All treatments follow the current state of the Dutch guideline on pancreatic cancer[15] and the literature.

Treatment-1: Optimal patient information and use of (neoadjuvant, adjuvant and palliative) chemotherapy

Treatment-2: Pancreatic enzyme replacement therapy (PERT) and referral to dietician in case of exocrine pancreatic insufficiency (EPI)

Treatment-3: Metal stents for biliary drainage

Best practice registration

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

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

Registration-3: Use of nationwide standard for synoptic reporting pancreatic cancer pathology from PALGA; the nationwide network and registry of histo- and cytopathology of the Netherlands

Registration-4: Report of World Health Organization (WHO) performance status

Additional best practices

Other-1: Inclusion of pancreatic cancer patients in PACAP PROMs registry

Other-2: Participation in PancreasParel biobank

Other-3: Pathologic confirmation in patients with (suspected) metastatic and locally advanced pancreatic cancer (LAPC)

Other-4: Participation in DPCG RCTs

Control phase: current practices

Current practice will be left to the discretion of the healthcare providers in the control phase. Centers will not learn the details of the best practices until the six weeks wash-in period of their region.

National expert meeting

In preparation of the PACAP-1 trial, a national expert meeting was organized for one oncologist and/or one surgeon per DPCG center to improve support and buy-in, and to optimize the design of the trial including the three intervention best practices (i.e. 1) optimizing chemotherapy, 2) EPI treatment and 3) biliary drainage with metal stents). To minimize contamination in the study we chose to invite only one specialist per center. Oncologists and surgeons working in 11 DPCG centers, and a representative of the Netherlands Comprehensive Cancer Organization (IKNL) were present. Specialists from the other six DPCG centers were informed on discussed topics by email and agreed. Specific details on best practices were not shared, but extensive background and logistic information was provided, and an elaborate discussion on what best practices should entail, was conducted. Ultimately, consensus was reached on the trial design and crucial parts of the three intervention best practices were identified. The shared opinion of the experts was that PACAP-1 should aim for the following points:

1. Optimization of patient information and use of chemotherapy
    a. 70% of patients with a resected tumor should receive adjuvant chemotherapy
    b. 60% of patients with LAPC should receive chemotherapy
    c. 40% of patients with metastasized disease should receive palliative chemotherapy
    d. All pancreatic cancer patients should be discussed in a DPCG or regional multidisciplinary team (MDT), with the exception of a small predefined subgroup (i.e. metastasized patients with WHO performance status III-IV)
2. Optimization of PERT and referral to dietician
3. Optimization of use of metal stents for biliary drainage

Randomization, blinding and treatment allocation

The same randomization order is used as in the PORSCH trial (NCT03400280), a stepped-wedge cluster RCT on the standard of care for postoperative complication after pancreatic surgery and the PACAP-1 trial which runs near simultaneously in all DPCG centers in the Netherlands. The reason to use the same randomization order was to obtain an equally long period of optimized standard of care for postoperative complications after pancreatic surgery before switching to the PACAP-1 intervention phase, resulting in homogenous treatment impact throughout centers. Randomization of the 17 pancreatic centers was performed using R statistics software. Stratification was used for center volume of pancreatic resections a year (>45 vs. ≤45). The median value of 45 was based on data from the DPCA

2014-2015). The randomization sequence was unknown to all participating centers and clinicians. Because of the design of PACAP-1, it is not feasible to blind healthcare providers to the best practice treatments and registrations. All PACAP-1 research data is obtained from existing encoded PACAP registries (NCR, DPCA and PROMs), warranting (pseudo-)anonymization of patients.

Study procedures

No specific study procedures are used, and no concomitant care and interventions are prohibited during the trial. All best practices are part of current clinical care. PACAP-1 aims to assess the impact of enhanced implementation of current best practices. Therefore, the aim is to improve standard of care compliance by informing, stimulating and reminding local clinicians per cluster to follow best practice interventions outlined by PACAP-1. Best practice procedures, identified from literature and PACAP, include all interventions documented in chapter 'Intervention phase: best practices' and APPENDIX 3. Treatment as usual according to best practice will continue after the study finishes.

Withdrawal centers

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

Replacement centers after withdrawal

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

Study duration

Planning of the PACAP-1 trial started in PACAP year three (November 2016) and the actual accrual of patients started in May 2018 after obtaining local approval in all participating centers. The implementation phase of the trial will run for 25 months, and the expected implementation end date is July 2020. Follow-up for the primary endpoint will last up until July 2021 and for secondary endpoints up until July 2025.

Statistical analyses

Outcomes of all patients with pancreatic cancer in the Netherlands will be evaluated before and after wash-in period (i.e. current practice vs. best practice). Patients will be assigned to current or best practice based on the date of first treatment related to pancreatic cancer (i.e. biliary stent placement, chemotherapy or primary resection). In case of no treatment or best-supportive care, date of diagnosis will determine assignment to current or best practice. Follow-up time is based on date of diagnosis for all patients. For patients diagnosed in a non-DPCG center, the assignment to current or best practice will depend on the affiliated DPCG center, which will be determined before the start of the study. Primary analysis will be performed with an intention-to-treat analysis according to the randomization order and cross-over dates. If implementation is not performed as scheduled, secondary analysis will be performed according to a per protocol analysis. In the primary analysis, we will use the intention to treat principle and patients will be assigned control or intervention according to what was applicable at the time they received their first cancer treatment (i.e. biliary drainage, chemotherapy, or resection). In a secondary per protocol analysis, patients that started in the control period but received part of their cancer treatment during the intervention period will be assigned to the intervention group (e.g. patients who underwent resection in the current practice phase, yet started adjuvant chemotherapy in the best practice phase). Patients diagnosed during the wash-in period will be described but will be excluded from the primary analysis, yet will be included in a secondary analysis. The primary comparison between current and best practice will be performed for patients from all hospitals in the Netherlands. Effect estimates with 95% confidence intervals (CI) will be reported. All p-values will be based on a two-sided test. P-values of less than 0.05 will be considered statistically significant.

Handling of missing data

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

Baseline characteristics

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

Primary outcome

One year overall survival will be analyzed with mixed-effects Cox proportional hazards regression models using a random intercept for hospital and a random slope on intervention effect for hospital. The analysis will be adjusted for (calendar) time and for the following baseline characteristics: age at diagnosis and tumor stage at diagnosis using the Union for International Cancer Control (UICC) tumor/node/metastasis (TNM) eighth edition (2018) classification and staging system for pancreatic cancer.

Secondary outcomes

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

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

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

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

Subgroup and sensitivity analyses

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

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

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

Interim analysis

No interim analysis will be performed for study outcomes. A study progression analysis will be performed to assess the number of inclusions at the time point when 50% of inclusions are expected. In the case that <47.5% of inclusions are acquired at that time point, the length of the steps as described in chapter 'Study design' will be increased for the remaining time of PACAP-1. As a result, sample size will be reached and statistical power will be maintained. Furthermore, if necessary, when PORSCH increases the length of the steps, PACAP-1 will do so too, to maintain a minimum time difference of five months between wash-in phases of both studies in the same cluster.

Safety reporting

PACAP-1 does not introduce new or experimental interventions. Therefore, this trial is not expected to introduce any additional safety or health risk for patients compared to regular care and hence no specific safety reporting is performed. There is no anticipated harm and compensation for trial participation.

Handling and storage of data and documents

Data will be collected through DPCA, NCR and PROMs.

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

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

PROM questionnaires are completed by patients either on paper or online with the first quality of life evaluation at baseline before index treatment. After that, questionnaires will be sent out every three

months in the first year, every six months in the second year, and every 12 months for subsequent years. After collection of paper questionnaires at the AMC, storage and digitalization happens at Profiles (subdivision of IKNL focusing on quality of life, https://www.profilesregistry.nl/). Online completed questionnaires are primarily collected at Profiles. Patients sign an informed consent form for participation. The informed consents are available from the corresponding author on request. Coded data will be obtained from Profiles by the PACAP-1 research team at request. Profiles and the PACAP-coordinating investigators are the only ones with access to the coding key.

Composition of the data monitoring committee, its role and reporting structure

Because PACAP-1 does not introduce new or experimental interventions and implements best-practices from current literature and guidelines on a health care workers level, no data monitoring committee was needed.

Public disclosure and publication policy

Final manuscript and co-authorship

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

Publications and other studies performed during the trial

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

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

chemoradiotherapy in patients with resectable and borderline resectable pancreatic cancer has already started including patients. This could influence outcomes of PACAP-1 and will be taken into account in the statistical analyses if possible.

DISCUSSION

PACAP-1 is a nationwide multicenter randomized controlled stepped-wedge superiority trial with the aim to improve overall survival and quality of life of patients with all stages of pancreatic adenocarcinoma in the Netherlands by enhanced implementation of best-practices.

Rationale for stepped-wedge cluster randomized design

A structured audit combined with provider feedback, education, outreach visits and reminders has been shown to be the most effective implementation strategy for change in patients' care[23]. RCTs are considered the most robust research design for establishing a causal relationship. However, educational interventions at the level of the physician preclude the use of individual randomization due to contamination of the control group. Therefore, a variant of this research method is increasingly used; the stepped-wedge cluster RCT[24]. Data collection in such large multicenter (stepped-wedge) RCTs is, however, often challenging. Therefore, collection through multicenter registries such as PACAP has recently gained interest from researchers as it is a practical way to improve feasibility and at the same time reduce costs for large multicenter RCTs[25]. In a systematic review, evaluating 25 studies, it was found that the stepped-wedge cluster RCT design has mainly been applied in evaluating interventions in routine practice[24]. Individual randomization was mostly not deemed possible for the risk of contamination of the control group. Also, using 'classical' parallel-group design was not desirable because the PACAP-1 trial aims to implement already previously identified and universally acknowledged 'best practices' in the entire population. In a stepped-wedge cluster RCT, clusters (e.g. centers) are randomly allocated a time when they start with the intervention. The order wherein the clusters start with the intervention is based on a randomization process, thus effectively resulting in a staged implementation in all clusters participating in the trial. This design is especially useful where phased implementation is preferable (e.g. because simultaneous implementation in more clusters is not possible due to logistic reasons), and implementation in all clusters is essential, such as with enhanced implementation of best practices. Additionally, this design makes differentiation from time-effects possible and after calculating the statistical efficiency for PACAP-1, the power achieved with a stepped-wedge cluster RCT was considerably larger than that of a parallel cluster randomized trial.

Challenges

In the design of the trial, we faced several challenges. First, to avoid contamination, in the design of this stepped-wedge trial, only a select group of DPCG experts from every specialty was involved. Although an important aspect of this trial is nationwide support and buy-in, it was actually not desirable to involve a large group of clinicians throughout the country before the actual wash-in phase of their particular center and network. A downside of this could be that there is less involvement and awareness on the trial.

Second, the Netherlands was divided into 17 regions according to the 17 DPCG centers with their respective referral networks. The referral centers usually have one main DPCG center they refer to, however, there might be some cross-over between regions due to geographical reasons, wish of the patient, or other reasons. This will lead to some unavoidable contamination of the trial information.

Third, with the aim to improve survival and quality of life, implementation of a package of best-practices, based on nationwide PACAP data, seemed the best strategy. This will, however, make it difficult to determine the effectiveness of each intervention separately. In addition, we advise to include patients in ongoing DPCG trials (e.g. PREOPANC-2) with the similar aim of survival improvement, while the individual trials advise to actively participate in PACAP-1 best-practices if already implemented. A measured effect of increased survival may therefore be partly due to the PACAP-1 enhanced implementation and partly due to the different individual trials. PREOPANC-2 is an individually randomized trial and will therefore not suffer from imbalances in patient management due to the PACAP-1 trial. However, if over time the proportion of patients enrolled in PREOPANC-2 changes, this might confound the prognosis of patients in the PACAP-1 trial. To account for this, a sensitivity analysis will be performed, but separate effects can never be measured in detail.

Fourth, every step in this trial, including the wash-in period, accounts for six weeks. Therefore, a delay between date of diagnosis or date of resection, and date of commencement of chemotherapy of longer than six weeks will lead to an attenuated measurement of the implementation effect. For example, patients who undergo resection a week before the wash-in phase and adjuvant chemotherapy is started eight weeks after surgery, are included in the current-practice group according to intention to treat, yet are treated as the best-practice group. In the Netherlands, median time to adjuvant chemotherapy is 6 to 7 weeks[12], yet due to logistical reasons it was not feasible to prolong steps. To assess the impact of a certain delay, intention to treat as well as per protocol analyses will be performed.

Fifth, the PACAP-1 trial was designed parallel to the PORSCH trial, both concurrent nationwide stepped-wedge trials. PACAP-1 used the identical randomization order as in the PORSCH trial. We have

considered to perform an independent randomization for PACAP-1. However, that would very likely have resulted in unacceptable outcomes; i) possibly both trials would have to implement the same DPCG center simultaneously which is too much information at once and clinicians may lose their trial dedication, ii) multiple combinations of the implementation order per DPCG center would be developed (e.g. first PACAP-1 / second PORSCH, or vice versa, or PACAP-1 / PORSCH at the same time) causing bias in trial results, and iii) it ignores the fact that the PORSCH algorithm (or something similar) will probably be the standard of care for postoperative complication management in the Netherlands. Therefore, we believe that PACAP-1 best practices should ideally be implemented in regions that are already in the best practice phase of the PORSCH trial. The possibility to delay the onset of PACAP-1 was deemed unacceptable for a guideline implementation program.

Sixth, during the trial there will be updates of two guidelines in care of pancreatic cancer (i.e. the national guideline on pancreatic cancer diagnostics and treatment, and the international ESGE guideline on biliary drainage). This led to more awareness of pancreatic cancer care in current practice and best practice phase centers. As best practice centers are already more attentive, probably the effect of this indirect contamination is larger in current practice centers and may therefore eliminate part of the implementation effect. Sensitivity analyses before and after the publication of both updated guidelines will be performed, but due to attention to these processes over a longer time period, it will be difficult to account for this effect accurately.

Seventh, due to ongoing centralization, centers may stop performing pancreatic surgery. Such centers will, however, remain as oncological center for patients with not-resectable pancreatic cancer. In such a scenario, the randomization order will not be changed, as only 20% of patients undergo a resection and this is according to the intention to treat principle.

Eight, current practice may change during any trial that runs for a longer period of time. In PACAP-1 for example, the advice on adjuvant strategy in the national guideline could change during the trial to modified FOLFIRINOX based on the recent trial by Conroy et al.[26]. As modified FOLFIRINOX has shown to improve survival compared to older chemotherapy regimens, however, this change will likely only positively influence survival in our cohort and therefore may result in biased outcomes.

Implications and future aims

PACAP-1 is expected to increase awareness and knowledge on best practices and pancreatic cancer care overall, from university pancreatic centers to smaller non-pancreatic centers. This may lead to enhanced implementation of both PACAP-1 best practices and other regional aspects that came to light due to

this trial (e.g. necessity of establishing a regional pancreatic MDT meeting). For this study, a pancreatic cancer team was identified in every region which could lead to improved multidisciplinary communication throughout and between the different networks. This study also identified dieticians in each network. A next step in implementing best practices could be education of all (para-)medical caregivers (e.g. general practitioners, physiotherapist, home care, etcetera), to improve awareness and knowledge on pancreatic cancer care.

TRIAL STATUS

PACAP-1 was registered with ClinicalTrials.gov on May 1st, 2018 with the identifier NCT03513705. The actual study and recruitment start date was May 22nd, 2018. The estimated recruitment completion date is July 9th, 2020. To date, 13 / 17 regional networks have undergone the implementation phase and the trial is on schedule.

DECLARATIONS

Ethics approval and consent to participate

This trial is designed and will be conducted in accordance to the requirements of the Helsinki Declaration and Good Clinical Practice. The aim of PACAP-1 is to evaluate the effect of enhanced implementation of best practices for pancreatic cancer care. The interventions proposed are currently standard of care according to literature and guidelines, and for participation in PROMs only completing questionnaires is required. The focus of this trial was to educate and stimulate local clinicians to follow known best practice and optimize data registry. As this trial introduces nationwide implementation of best practices at cluster level, all pancreatic cancer patients presented in the DPCG centers and their region will participate. As patients in PACAP-1 are not subject to novel treatment and no precepts for behavior are imposed, this research does not fall under the Medical Research Involving Human Subjects Act (WMO). This was supported by the Medical Ethical Committee of the Amsterdam UMC, location AMC (December 18, 2017, W17_454#17.526). Ethical boards of all other participating centers approved of performing the PACAP-1 trial. Thus, informed consent of individual patients will not be asked specifically in PACAP-1. In addition, collection of PACAP-1 data will happen through existing encoded PACAP registries (i.e. DPCA, NCR and PROMs) for which no informed consent is required. However, cluster consent of the pancreatic cancer team from every DPCG center was obtained[27].

Additional consent provisions for collection and use of participant data and biological specimens

Within PACAP for the PancreasParel Biobank, a separate informed consent will be asked. For PACAP-1, no additional specimens will be collected and therefore no additional informed consent is needed.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available through the scientific committee of the DPCG but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the DPCG.

Competing interests

Judith de Vos-Geelen has received non-financial support from Servier, and has received institutional research funding from Servier, all outside the submitted work. Other authors declare that they have no competing interests

Funding

This research was funded by a grant from the Dutch Cancer Society (grant number UVA2013-5842). The Dutch Cancer Society played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. (https://www.kwf.nl/node/20)

Authors' contributions

TM, FS, AL, LG, CW, JH, CE, JW, HL, MB made substantial contributions to conception and design of data, analysis and interpretation of data, and drafting the study protocol. All authors made substantial contributions to acquisition of data, revising and approving of the study protocol and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection and C.H.C. Dejong for intellectual input.

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SUPPLEMENTARY MATERIAL

Supplementary material is available online.

PART II

QUALITY OF LIFE AND CLINICAL OUTCOMES AFTER PANCREATIC SURGERY

CHAPTER 6

The effect of centralization and regionalization of pancreatic surgery on resection rates and survival

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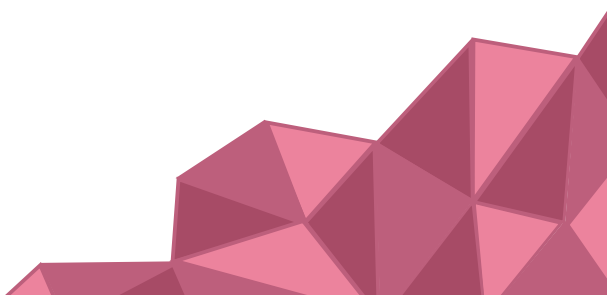
British Journal of Surgery. 2020.



ABSTRACT

Background: Centralization of pancreatic surgery in the Netherlands has been ongoing since 2011. The aim of this study is to assess how centralization affected the likelihood of resection and survival of patients with non-metastatic pancreatic head and periampullary cancer diagnosed in hospitals with and without pancreatic surgery services.

Methods: This observational cohort study used nationwide data from the Netherlands Cancer Registry (2009-2017) and included patients diagnosed with non-metastatic pancreatic head or periampullary cancer. Period of diagnosis was divided into three time periods (2009-2011, 2012-2014, and 2015-2017). Hospital of diagnosis was classified as pancreatic or non-pancreatic surgery centre. Analyses were performed by multivariable logistic and Cox regression models.

Results: In total, 10 079 patients were included of whom 3 114 (31 per cent) were diagnosed in pancreatic surgery centres. From 2009-2011 to 2015-2017, the number of patients undergoing resection increased from 1267/3169 to 1705/3566 (40 to 48 per cent, p-trend<0·001). In multivariable analysis, in 2015-2017, unlike the periods before, patients diagnosed in pancreatic and non-pancreatic surgery centres had a similar likelihood of resection (OR 1·08, 95 per cent CI 0·90-1·28, p=0·422). In this period, however, overall survival was higher in patients diagnosed in pancreatic surgery centres compared to non-pancreatic surgery centres (HR 0·92, 95 per cent CI 0·85-0·99, p=0·047).

Conclusion: After centralization of pancreatic surgery, the resection rate for patients with pancreatic head and periampullary cancer diagnosed in non-pancreatic surgery centres increased and became similar to pancreatic surgery centres. Overall survival remained higher in patients diagnosed in pancreatic surgery centres.

INTRODUCTION

The incidence of pancreatic ductal adenocarcinoma and periampullary cancer has increased over the last two decades, resulting in increasing number of patients amenable for cancer directed treatment.[1] Pancreatic surgery in combination with systemic chemotherapy provides the best outlook for long-term survival but is associated with a relatively high risk of complications.[2–4] Studies have demonstrated a clear relation between hospital volume and postoperative mortality.[5–7] To address this issue, centralization of pancreatic surgery occurred in many countries, resulting in increased resection rates and reduced in-hospital mortality.[8–10] Based on these volume-outcome relations, centralization of pancreatic surgery was initiated in the Netherlands in 2011 with the advice to apply a threshold of at least 20 pancreatoduodenectomies (PDs) per year. This volume standard became officially mandatory in 2013.

However, patients diagnosed with non-metastatic pancreatic cancer (2005-2013) in a Dutch hospital without pancreatic surgery services had a lower likelihood to undergo surgery as opposed to patients who were diagnosed in a centre performing pancreatic surgery.[11] A frequently mentioned strategy to reduce this undesired practice variation is increased regionalization with regular inter-hospital multidisciplinary team meetings, online video meetings, and easy accessible consultation of pancreatic cancer experts for referral hospitals. In addition, the Dutch Pancreatic Cancer Group (DPCG) was established in 2011 to improve quality of care, and clinical and translational research.[12] All centres performing pancreatic surgery in the Netherlands are incorporated within the DPCG and play an important role in their regional networks.

It is currently unknown whether the ongoing centralization and regionalization has equalized the surgical resection rate and consequently improved survival for patients with non-metastatic pancreatic head and periampullary cancer across centres in the Netherlands. Therefore, the aim of this study is to assess whether the resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma who were diagnosed in pancreatic surgery versus non-pancreatic surgery centres has changed between 2009-2017, and whether this influenced survival patterns.

METHODS

Study design

This observational nationwide cohort study used data from the Netherlands Cancer Registry (NCR), a prospective population-based database, which covers all Dutch hospitals (i.e. a population of 17.3 million in 2019). All patients with newly diagnosed malignancies are identified from the national pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses and included in

the NCR. Trained administrators routinely collect data about patient, tumour, and treatment characteristics from hospital records. This study was reported in accordance with the STROBE guidelines.[13]

Study population

The International Classification of Diseases for Oncology, 3th edition (ICD-O-3), was used to categorize patients with pancreatic head or periampullary carcinoma (ICD-O-3 C25.0, C24.1, C24.0-distal cholangiocarcinoma, C17.0 and morphology codes 'adenocarcinoma', Supplementary material). All patients who had non-metastatic disease or who underwent surgery with curative intent (together defined as patients with non-metastatic pancreatic head and periampullary cancer on imaging) and were diagnosed between 2009 and 2017 were included.[14] Surgery with curative intent included both patients undergoing "exploration only" (i.e., surgery without resection because of locally advanced or disseminated disease) and those with "resection of the primary tumour". Both patients with borderline resectable tumours and locally advanced pancreatic cancers were included, because information on the extend of vessel involvement was lacking and patients with locally advanced disease could not be excluded properly. Patients younger than 18 years at time of diagnosis, patients with neuroendocrine tumours and metastatic disease from other primary tumours, or patients diagnosed during autopsy were excluded. Patients were also excluded if they did not undergo surgery and died within 30 days after diagnosis (probably not surgical candidates).

Data definitions

Period of diagnosis was divided in three groups: 2009-2011, 2012-2014, and 2015-2017, respectively corresponding with a 'baseline status' without nationwide centralization of pancreatic surgery (34/78 hospitals performing pancreatic surgery), the shift to the start of nationwide centralization with a mandatory volume standard introduced in 2011 (24/78 hospitals), and current ongoing centralization (18-19/78 hospitals). Hospital of diagnosis was defined as the hospital of first visit or clinical diagnosis and classified into "pancreatic surgery" and "non-pancreatic surgery" centres. Pancreatic surgery centres are hospitals performing pancreatic surgery and participating in the DPCG. This category label was based on the classification in 2017: 18 pancreatic surgery centres and 59 non-pancreatic surgery. Time trends were analysed with this hospital category fixed, using even for the earlier time periods the category labels as assigned in 2017, to avoid any "category migration". Socioeconomic status (SES) was based on social deprivation scores per 4-digit postal code (reference data from The Netherlands Institute of Social Research) and categorized into three SES groups (high: 1st-3rd, intermediate 4th-7th, low: 8th-10th deciles). In the NCR, staging was classified according to the TNM classification at the time of registration (6th edition of UICC TNM staging during 2009, 7th edition of UICC TNM staging during

2010-2016, 8th edition of UICC TNM staging during 2017).[15–17] Both the clinical and pathological stage was presented according to the 7th edition, because most patients were classified accordingly. For patients who underwent resection, the clinical TNM classification was used if the pathological TNM stage was missing or if patients received neoadjuvant treatment. If T or N status was missing, Extent of Disease (EoD, a one-digit summary stage: local, regional, metastatic) was used for staging. Surgery refers to surgery with curative intent, which is defined as described above. Use of chemotherapy was only presented for patients with pancreatic ductal adenocarcinoma, because in the study period no guideline recommendations on adjuvant chemotherapy were available in the Netherlands for patients with tumours of the ampulla of Vater, distal bile duct, or duodenum. Survival data were obtained by annual crosscheck with the Municipal Personal Records Database, which contains the vital status of all Dutch inhabitants. Survival was calculated as the time between the date of diagnosis and date of death, or censored when alive at the last check of their vital status (1 February 2020).

Study outcomes

The resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma diagnosed in pancreatic surgery versus non-pancreatic surgery centres in 2009-2001, 2012-2014 and 2016-2017. Moreover, also survival in patients diagnosed in these centres over the periods was analysed.

Statistical analysis

Baseline characteristics were presented using descriptive statistics. Normally distributed continuous data was compared using a Students t-test and presented as means with standard deviations (SD). Non-normally distributed continuous data was compared using the Mann Whitney U test and presented as medians with interquartile ranges (IQR). Categorical data was presented as frequencies with percentages and compared using the Chi-square test. The association between diagnosis in a pancreatic surgery versus non-pancreatic surgery centre and the resection rate was analysed with multivariable logistic regression models stratified per period of diagnosis and was adjusted for patient characteristics (age, sex, and SES), tumour location, and clinical T and N-stage. Overall survival was analysed by means of Kaplan-Meier curves and compared with log-rank tests. To demonstrate whether the association between non-pancreatic surgery versus pancreatic surgery centre and survival after centralization changed over time, multivariable Cox regression models were performed and stratified by period of diagnosis. These models were adjusted for patient characteristics, tumour location, and tumour stage. Since the completeness of the NCR probably improved over the years (i.e. including more patients without pathological confirmation and elderly) sensitivity analyses were performed for patients with pathologically verified tumours and for patients under 75 years to assess whether this affected the

results, but also for patients with pancreatic ductal adenocarcinoma to exclude influences of other pathological tumours (e.g. Ampulla of Vater and duodenum). The resection rate in patients with non-metastatic pancreatic head or periampullary carcinoma in pancreatic surgery versus non-pancreatic surgery centres in 2009-2001, 2012-2014 and 2016-2017 was also analysed after multiple imputation (with predictive mean matching and creation of 30 dummy sets) for clinical T and N status, because of the relatively high percentage of unknowns in these groups (35 and 21 per cent). The results were reported as odds ratio (OR) with corresponding 95 per cent confidence interval (CI) in logistic regression and as hazard ratio (HR) with corresponding 95 per cent CI in Cox regression. All p-values were based on a 2-sided test and p-values of <0·05 were considered statistically significant. Data was analysed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armong, N.Y., USA).

TABLE 1. Baseline characteristics of all patients with non-metastatic pancreatic head and periampullary cancer and stratified for diagnosis in a pancreatic surgery or non-pancreatic surgery centres.

	All patients n = 10 079	**Pancreatic surgery centre n = 3 114 (31)**	**Non-pancreatic surgery centre n = 6 965 (69)**	**p- value**
Female	4 827 (48)	1 448 (47)	3 379 (49)	0·061
Age, median (IQR), years	71 (63-79)	70 (62-77)	72 (64-80)	**<0·001**
Social economic status				**<0·001**
High	3 115 (31)	886 (29)	2 229 (32)	
Medium	4 084 (41)	1 241 (40)	2 843 (41)	
Low	2 855 (28)	969 (31)	1 886 (27)	
Missing	25 (0·2)	18 (0·6)	7 (0·1)	
Primary tumour location				0·460
Head of pancreas	6 853 (68)	2 091 (67)	4 762 (68)	
Ampulla of Vater	1 271 (13)	405 (13)	866 (12)	
Distal bile duct	1 268 (13)	411 (13)	857 (12)	
Duodenum	687 (7)	207 (7)	480 (7)	
Clinical T-stage[a]				0·804
T1	1 076 (11)	340 (11)	736 (11)	
T2	1 561 (16)	472 (15)	1 089 (16)	
T3	1 786 (18)	561 (18)	1 225 (18)	
T2/3	476 (5)	152 (5)	324 (5)	
T4	1 698 (17)	504 (16)	1 194 (17)	
Unknown	3 482 (35)	1 085 (35)	2 397 (34)	
Clinical N-stage[a]				**0·003**
N0	6 090 (60)	1 957 (63)	4 133 (59)	
N1	1 885 (19)	539 (17)	1 346 (19)	
Unknown	2 104 (21)	618 (20)	1 486 (21)	
Pathological tumor stage[ab]				**0·046**
Stage I	695 (15)	255 (16)	440 (15)	
Stage II	3 036 (66)	1 099 (67)	1 937 (66)	
Stage II/III	227 (5)	70 (4)	157 (5)	
Stage III	474 (10)	151 (9)	323 (11)	
Stage IV	126 (3)	57 (4)	69 (2)	
Unknown	29 (1)	9 (1)	20 (1)	

Tumour stage[c]				**<0·001**
Stage I	1 892 (19)	524 (17)	1 368 (20)	
Stage II	4 147 (41)	1 404 (45)	2 743 (39)	
Stage II/III	841 (8)	222 (7)	619 (9)	
Stage III	1 595 (16)	479 (15)	1,116 (16)	
Stage IV	784 (8)	254 (8)	530 (8)	
Unknown	820 (8)	231 (7)	589 (9)	
Surgery				
Resection primary tumour	4 587 (46)	1 641 (53)	2 946 (42)	**<0·001**
Exploration only, no resection	1 213 (12)	392 (13)	821 (12)	
No surgery	4 279 (43)	1 081 (35)	3 198 (46)	
Resection[d]				0·143
Adjuvant chemotherapy	1 274 (53)	463 (51)	811 (54)	
Neoadjuvant chemo(radio)therapy	59 (2)	18 (2)	41 (3)	
Neoadjuvant and adjuvant chemo(radio)therapy	83 (3)	26 (3)	57 (4)	
No (neo)adjuvant therapy	1 007 (42)	400 (44)	607 (40)	
No resection[e]				0·427
Chemotherapy	821 (35)	258 (36)	563 (35)	
No chemotherapy	1 518 (65)	453 (64)	1 065 (65)	
Period of diagnosis				0·407
2009-2011	3 169 (31)	993 (32)	2 176 (31)	
2012-2014	3 344 (33)	1 049 (34)	2 295 (33)	
2015-2017	3 566 (35)	1 072 (34)	2 494 (36)	

Values are numbers with percentages within parentheses unless indicated otherwise.
[a] Tumor stage according to the TNM 7 classification; [b] Only in patients who underwent resection (n=4 587); [c] Tumor stage based on the clinical stage for patients who did not undergo resection and the pathological stadium for patients who underwent resection; [d] Only in patients with pancreatic ductal adenocarcinoma who underwent resection of primary tumor (n=2 423); [e] Only in patients with pancreatic ductal adenocarcinoma who did not undergo resection, thus including those who only underwent exploration (n=2 339).

RESULTS

Between 2009 and 2017, 10 079 patients were diagnosed with non-metastatic pancreatic head and periampullary cancer. The number of patients increased over time (2009-2011: 3 169 (31 per cent), 2012-2014: 3 344 (33 per cent), and 2015-2017: 3 566 (35 per cent), p-trend=0.158), whereas the number of hospitals performing pancreatoduodenectomies decreased (2009-2011: 34 hospitals with a median of 29 PDs in 3 years (IQR 5-47), 2012-2014: 24 hospitals with a median of 59 PDs (IQR 42-87), and 2015-2017: 18-19 hospitals with a median of 83 PDs (IQR 70-108). The hospital categories of 2017 were fixed for labelling of pancreatic surgery centres, regardless of time period, and used in further analysis. Patients were diagnosed in up to 78 hospitals with a median of 12 diagnoses (IQR 8-20) per hospital annually. In total, 4 827 patients were female (48 per cent) and the median age was 71 years (Table 1). Of all patients, 5 800 underwent surgery with curative intent (58 per cent) of whom 4 587 underwent resection of the primary tumour (79 per cent); the remaining patients underwent an exploration without resection.

In total, 3 114 patients were diagnosed in a pancreatic surgery centre (31 per cent) and 6 965 patients in a non-pancreatic surgery centre (69 per cent). In pancreatic surgery centres, resection was performed in 1 641 patients (53 per cent) which was higher as compared to non-pancreatic surgery centres (2 946 patients (42 per cent), p<0·001) with similar proportions of patients undergoing exploration (12 and 13 per cent, respectively). The proportion of patients with pancreatic ductal adenocarcinoma receiving chemotherapy was comparable between the centres, both for patients who underwent resection as those who did not (Table 1).

Treatment over time

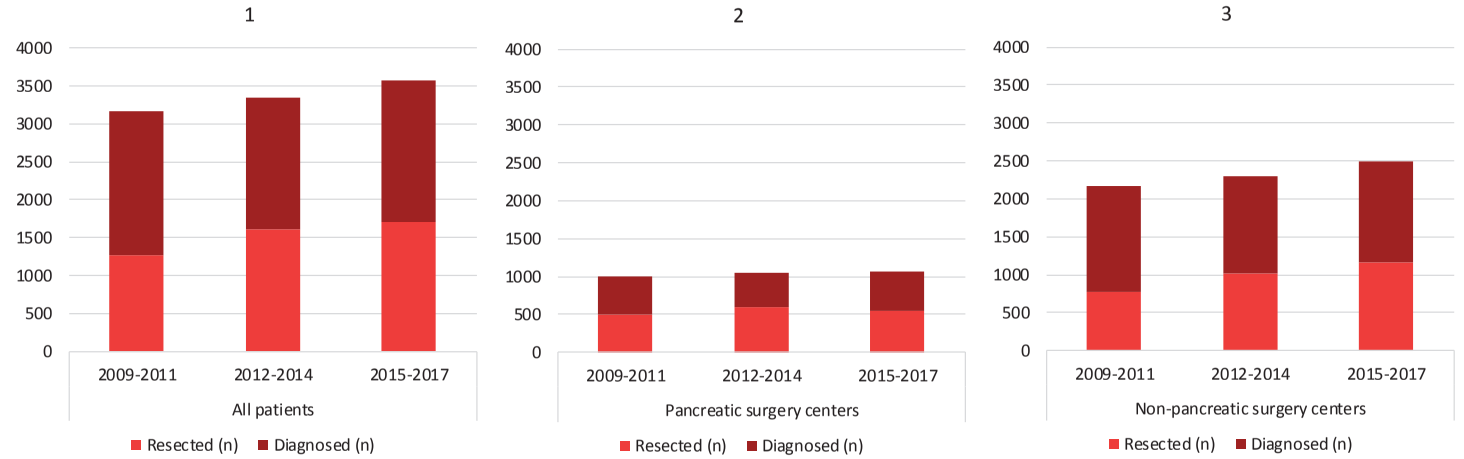
Figure 1A shows that the absolute number of patients who were diagnosed with non-metastatic pancreatic head and periampullary cancer increased from 3 169 in 2009-2011 to 3 566 in 2015-2017. The increase of diagnoses did not significantly differ between non-pancreatic surgery (2 176 to 2 494 respectively, 14 per cent increase) compared to pancreatic surgery centres (993 to 1 072 respectively, 8 per cent increase, p-trend=0·249). Over the three periods of diagnosis, the percentage of patients undergoing surgery (resection or exploration only) did not significantly change (55 versus 60 versus 57 per cent), p-trend=0·096), whereas the percentage of patients undergoing resection increased from 40 to 48 per cent (p-trend <0·001, Figure 1B). In patients with pancreatic ductal adenocarcinoma who underwent resection (n=2 423), the use of neoadjuvant chemotherapy increased over the periods (2 to 11 per cent, p-trend<0·001) and similarly, treatment with adjuvant chemotherapy did (50 to 58 per cent, p-trend=0·001). Chemotherapy was started in 821 out of 2 339 patients (35 per cent) with pancreatic ductal adenocarcinoma who did not undergo resection and increased from 31 to 41 per cent (p-trend<0·001).

Resection rate in pancreatic and non-pancreatic surgery centres

The resection rate in patients diagnosed in non-pancreatic surgery centres increased between 2009-2011 to 2015-2017 (35 to 46 per cent, p-trend<0·001), reaching a level being more comparable with pancreatic surgery centres in the most recent period (Figure 1B). In multivariable analyses, the resection rate was higher in pancreatic surgery centres in 2009-2011 (OR 1·70, 95 per cent CI 1·39-2·08, p<0·001) and 2012-2014 (OR 1·49, 95 per cent CI 1·24-1·78, p<0·001), when compared to non-pancreatic surgery centres, but this association disappeared in 2015-2017 (OR 1·08, 95 per cent CI 0·90-1·28, p=0·422, Table 2). As sensitivity analyses showed similar associations (Supplementary Table 1), possible incompleteness of the NCR in early years and missing data in clinical T and N status did not affect the results.

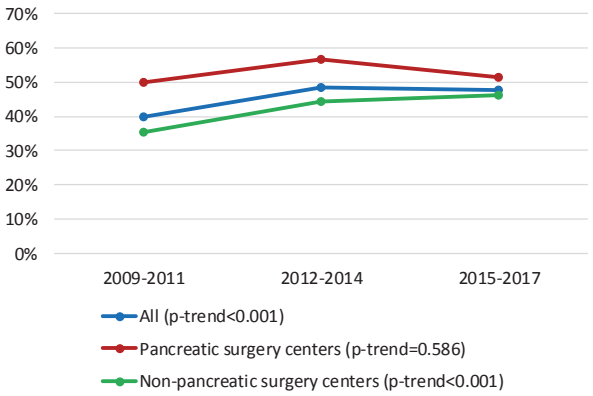
FIGURE 1

FIGURE 1A. Absolute numbers of patients diagnosed and resected in all patients (1), patients diagnosed in pancreatic surgery centres (2) and in non-pancreatic surgery centres (3) per period.



The number of patients who are diagnosed are represented by the total bar chart (light and dark coloured).

FIGURE 1B. Resection percentages in all patients, patients diagnosed in pancreatic surgery centres and in non-pancreatic surgery centres per period.



Survival in pancreatic and non-pancreatic surgery centres

Median overall survival was higher in patients diagnosed in pancreatic surgery centres as compared to non-pancreatic surgery centres, regardless of the period of diagnosis (Table 3). Within the three periods, survival did not significantly improve in pancreatic surgery centres and was 11·1 months (IQR 10·1-12·0) in 2009-2011, 13·0 months (IQR 11·9-14·1) in 2012-2014, and 12·6 months (IQR 11·5-13·6) in 2015-2017 (p=0·654, Figure 2A). Survival did improve in non-pancreatic surgery centres from 9·7 months (IQR 9·3-10·4) to 10·3 months (IQR 9·8-10·9) to 10·7 months (IQR 10·1-11·4) respectively (Figure 2B, p=0·001).

In multivariable analyses, survival was higher in pancreatic surgery centres in 2015-2017 (HR for mortality 0·92, 95 per cent CI 0·85-0·99, p=0·047, Table 3) compared to non-pancreatic surgery centres. Sensitivity analyses showed no significant association between pancreatic surgery centre versus non-pancreatic surgery centre and survival in 2015-2017, in patients with pathologically verified tumours, patients under 75 years only, and patients with pancreatic ductal adenocarcinoma (Supplementary Table 2).

TABLE 2. Multivariable logistic regression analyses to assess the association between diagnosis in a pancreatic surgery centre and pancreatic resection.

			Univariable		Multivariable[a]	
	Patients	Resection	OR	p-value	OR	p-value
Period 2009-2011[b]						
All	3 169	1 267 (40)				
Non-pancreatic surgery centre	2 176	772 (35)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	993	495 (50)	**1·81 (1·55-2·11)**	**<0·001**	**1·70 (1·39-2·08)**	**<0·001**
Period 2012-2014[c]						
All	3 344	1 615 (48)				
Non-pancreatic surgery centre	2 295	1 018 (44)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	1 049	597 (57)	**1·66 (1·43-1·92)**	**<0·001**	**1·49 (1·24-1·78)**	**<0·001**
Period 2015-2017[d]						
All	3 566	1 705 (48)				
Non-pancreatic surgery centre	2 494	1 156 (46)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	1 072	549 (51)	**1·22 (1·05-1·40)**	**0·008**	1·08 (0·90-1·28)	0·422

Values are numbers with percentages within parentheses or odds ratios with 95 per cent confidence intervals within parenthesis. Bold numbers indicate statistical significance. OR: odds ratio. [a] Adjusted for patient characteristics (age, sex, SES), tumour location (pancreas versus periampullary), and clinical T and N-stage; [b] Multivariable analysis calculated in 3 162 patients (SES unknown in 7 patients); [c] Multivariable analysis calculated in 3 334 patients (SES unknown in 10 patients); [d] Multivariable analysis calculated in 3 558 patients (SES unknown in 8 patients)

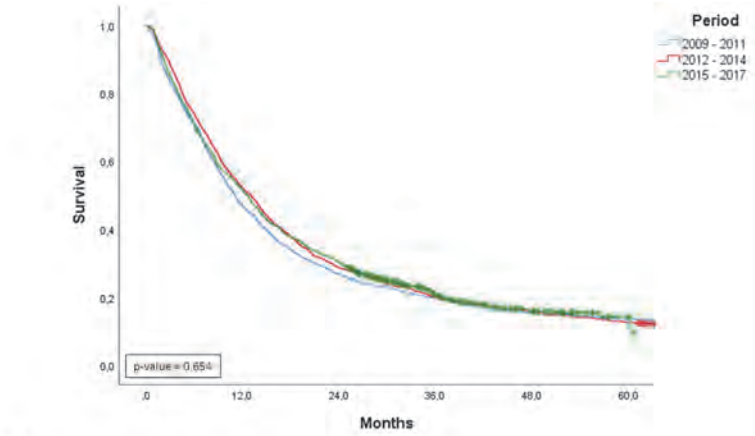
TABLE 3. Multivariable Cox regression analyses to assess the association between diagnosis in a pancreatic surgery centre and mortality.

			Univariable		Multivariable[a]	
	Patients	Median OS	HR	p-value	HR	p-value
Period 2009-2011[b]						
All	3 162	10·2 (9·7-10·7)				
Non-pancreatic surgery centre	2 174	9·9 (9·3-10·4)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	988	11·1 (10·1-12·0)	**0·85 (0·78-0·92)**	**<0·001**	0·94 (0·87-1·02)	0·148
Period 2012-2014[c]						
All	3 334	10·9 (10·3-11·4)				
Non-pancreatic surgery centre	2 292	10·3 (9·8-10·9)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	1 042	13·0 (11·9-14·1)	**0·90 (0·84-0·98)**	**0·010**	0·93 (0·86-1·00)	0·056
Period 2015-2017[d]						
All	3 558	11·2 (10·1-11·4)				
Non-pancreatic surgery centre	2 492	10·7 (10·1-11·4)	1·00 (reference)		1·00 (reference)	
Pancreatic surgery centre	1 066	12·6 (11·5-13·6)	**0·90 (0·83-0·97)**	**0·008**	**0·92 (0·85-0·99)**	**0·047**

Values median overall survival or hazard ratios with 95 per cent confidence intervals within parenthesis. Bold numbers indicate statistical significance. OS: overall survival, HR: hazard ratio. [a] Adjusted for patient characteristics (age, sex, SES), tumour location (pancreas versus periampullary), and tumour stage; [b] Analysis calculated in 3 162 patients (survival status and SES unknown in 7 patients); [c] Analysis calculated in 3 334 patients (survival status and SES unknown in 10 patients); [d] Analysis calculated in 3 558 patients (survival status and SES unknown in 8 patients).

FIGURE 2

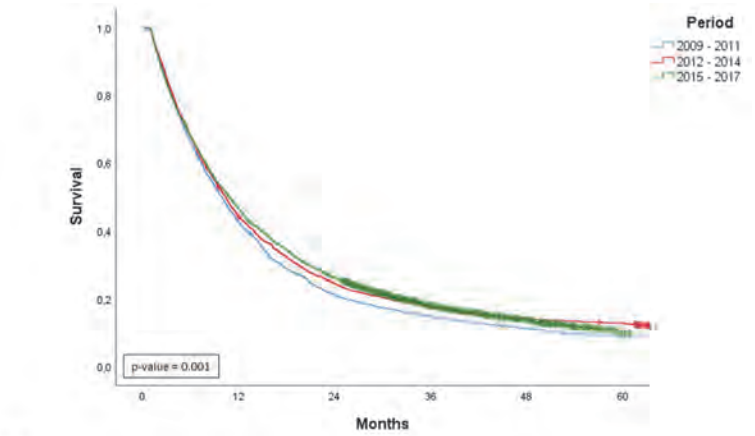
FIGURE 2A. Kaplan Meier survival curve of all patients with non-metastatic pancreatic head and periampullary cancer stratified per period of diagnosis in pancreatic surgery centres



At risk						
2009-2011	988	466	263	197	151	135
2012-2014	1042	545	298	208	166	133
2015-2017	1066	552	323	144	59	5

Survival unknown in 18 patients

FIGURE 2B. Kaplan Meier survival curve of all patients with non-metastatic pancreatic head and periampullary cancer stratified per period of diagnosis in non-pancreatic surgery centres



At risk						
2009-2011	2174	923	459	320	243	193
2012-2014	2292	1008	559	397	323	292
2015-2017	2492	1155	647	300	120	4

Survival unknown in 7 patients

DISCUSSION

This population-based observational cohort study showed that in the period 2015-2017, with ongoing centralization, the resection rate for pancreatic head and periampullary cancer became similar for patients diagnosed in pancreatic and non-pancreatic surgery centres. Nevertheless, overall survival of all patients diagnosed in pancreatic surgery centres remained superior as compared to patients diagnosed in non-pancreatic surgery centres in 2015-2017.

Over the study period, the rate of primary tumour resections in patients who underwent surgery increased, indicating an improved selection of patients being eligible for surgery and efficient referral patters. This could possibly be explained by centralization and regionalization.[18] The use of better diagnostic modalities with high-quality imaging and standardization of radiology image reporting within the DPCG could have contributed to increased identification of patients with metastatic pancreatic head and periampullary cancer before surgery.[19] Since the surgery rate was constant, it seems that more patients with (borderline) resectable and locally advanced tumours underwent resection due to more extended resections, venous resections, and improved surgical techniques. Consequently, the proportion of patients who underwent exploration only decreased over time. Unfortunately, the data were insufficient to identify patients with locally advanced tumours accurately. Although we could not perform additional analyses for this subgroup, it is well established that resection rates in these patients have increased since the introduction of neoadjuvant administration of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin).[20,21]

Since the introduction of the minimum annual volume of 20 pancreatoduodenectomies per centre in 2011, centralization of pancreatic surgery has been ongoing in the Netherlands. The DPCG offered a nationwide framework to optimize centralization. As a result, in 2012-2014, a temporary slightly higher rate of surgery was seen, as centres below the minimum volume stopped performing pancreatic surgery.[11,22] Following the introduction of the volume standard, regionalization of pancreatic and periampullary cancer care in general occurred, which is important since most patients (69 per cent) are diagnosed in non-pancreatic surgery centres. By 2017, 10 regional networks for hepato-pancreato-biliary cancers were present in the Netherlands, each containing one or more pancreatic surgery centres and several non-pancreatic surgery centres, respectively named Hubs and Spokes, according to the so-called “hub-and-spoke model”.[23–25] Regionalization consists of regional collaboration including improved referral patterns and inter-hospital multidisciplinary team meetings, and knowledge dissemination. Consequently, by 2015-2017 the resection rate in patients from non-pancreatic surgery centres increased and became similar to pancreatic surgery centres. This increase was mainly caused by an increased resection rate in patient who were as non-resectable during the earlier periods in non-

pancreatic surgery centres (e.g. locally advanced pancreatic cancer). This may have been related to improved inter-hospital contact and subsequent increased referral of these patients to pancreatic surgery centres.

It was hypothesised that survival would be similar for non-pancreatic and pancreatic surgery centres, because of equalized odds for resection based on improved referral patterns. Survival, however, remained higher in pancreatic surgery centres in 2015-2017, even after adjustment for possible confounders. The absolute difference in survival was only 1.9 months and the clinical relevance could be debated. The increased survival may be caused by differences in other factors within pancreatic and periampullary cancer care, i.e. implementation of more effective chemotherapies (e.g., (neo)adjuvant FOLFIRINOX), pancreatic enzyme supplementation, palliative care services, and endoscopic biliary drainage in pancreatic surgery centers.[26] It is known that the rate of receiving adjuvant chemotherapy is highly variable between pancreatic surgery centres.[27] In the Netherlands, patients are often referred back to their hospital of diagnosis to receive adjuvant chemotherapy or palliative care, taking into account patient's preference and hospital characteristics. It goes outside the scope of this study to analyse the effects of these referral patterns on survival, but this phenomenon could be a possible explanation for the observed differences. Since the effect on survival was not shown in the sensitivity analysis for pancreatic ductal adenocarcinoma only, the above-mentioned factors were probably more affected in patients with periampullary carcinoma. Increased regionalization could further strengthen trial participation and equalize implementation of new or current treatment strategies, as these often arise from clinical trials.[23] It could also be suggested that patients might receive better and faster diagnostics in a pancreatic surgery centre because of a well-designed pancreatic and periampullary cancer infrastructure. This could lead to earlier initiation of treatment resulting in improved patient outcomes. The differences in survival demonstrate that regionalization should be further improved. A step towards this improvement could be obtained via the nationwide PACAP-1 trial (NCT03513705) which aimed to enhance implementation of best practices in pancreatic cancer care.[28] Results from this nationwide stepped-wedge cluster randomized trial are not yet available, but this trial operated within pancreatic cancer networks and implemented several best practices (regarding chemotherapy, exocrine pancreatic insufficiency, and biliary drainage) with the aim to equalize and improve patient outcomes throughout the Netherlands.

This study had several limitations. First, exact reasons for referral or refraining from referral for individual patients were unknown. Future studies should obtain these data in order to improve referral patterns and to improve current outcomes. Second, the completeness of the NCR may have been improved in more recent years because of improved notification methods especially for patients

without pathological confirmation, elderly, and patients with a short survival.[29] However, this effect is probably limited, because we excluded non-treated patients who died within 30 days after diagnosis and sensitivity analyses showed similar associations between centre of diagnosis and the resection rate for patients with pathologically verified tumours and under 75 years old. Despite increasing completeness, a relatively large group of patients had an unknown clinical T and N status, which also did not affect the outcome in a sensitivity analysis after imputation of these variables. Third, some important factors in decision making for resection, such as multidisciplinary team meeting, WHO performance status, reason for no treatment (e.g. patients' preference) were not registered during the majority of the study period. Fourth, identification of patients with locally advanced pancreatic cancer became possible since 2016 and should be investigated separately in future studies. In this study it was assumed that patients with locally advanced disease were diagnosed equally over pancreatic and non-pancreatic surgery centers.

In conclusion, after centralization and regionalization in the Netherlands, the resection rate of primary tumours improved in patients first diagnosed in non-pancreatic surgery centres and is now similar to that in patients diagnosed in centres performing pancreatic surgery. Survival remained superior in pancreatic surgery centres. These findings suggest that centralization and regionalization improved care for pancreatic head and periampullary cancer patients but that further improvement of existing regional networks is required as this could further improve patient outcomes.

ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection.

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SUPPLEMENTARY MATERIAL

MORPHOLOGY CODES

According to the WHO classification patients with topography codes C25.0, C24.1, C24.0-distal, and C17.0 were included based on the morphology codes (ICD-O-3) below.

8000	Neoplasm, NOS*
8001	Tumour cells
8003	Malignant tumour, giant cell type
8010	Carcinoma, NOS
8011	Epithelioma
8012^	Large cell carcinoma, NOS
8020^	Carcinoma, undifferentiated, NOS
8021^	Carcinoma, anaplastic, NOS
8022^	Pleomorphic carcinoma
8031^	Giant cell carcinoma
8032^	Spindle cell carcinoma, NOS
8033^	Pseudosarcomatous carcinoma
8035^	Carcinoma with osteoclast-like giant cells
8041	Small cell carcinoma, NOS
8046^	Non-small cell carcinoma
8070^	Squamous cell carcinoma, NOS
8082	Lymphoepithelial carcinoma
8140^	Adenocarcinoma, NOS
8141^	Scirrhous adenocarcinoma
8143^	Superficial spreading adenocarcinoma
8144^	Adenocarcinoma, intestinal type
8145^	Carcinoma, diffuse type
8154	Mixed islet cell and exocrine adenocarcinoma
8160	Cholangiocarcinoma
8163^	Pancreatobiliary-type carcinoma
8201^	Cribiform carcinoma, NOS
8210	Adenocarcinoma in adenomatous polyp
8211^	Tubular adenocarcinoma
8255^	Adenocarcinoma with mixed subtypes
8260	Papillary adenocarcinoma, NOS
8261	Adenocarcinoma in villous adenoma
8262	Villous adenocarcinoma
8263	Adenocarcinoma in tubulovillous adenoma
8310^	Clear cell adenocarcinoma, NOS
8430	Mucoepidermoid carcinoma
8440	Cystadenocarcinoma
8441	Serous cystadenocarcinoma
8452	Solid pseudopapillary carcinoma
8453	Intraductal papillary mucinous carcinoma
8470	Mucinous cystadenocarcinoma
8471	Papillary mucinous cystadenocarcinoma
8480^	Mucinous adenocarcinoma
8481^	Mucin-producing adenocarcinoma
8490^	Signet ring cell carcinoma
8500^	Ductal carcinoma, NOS
8503	Intraductal papillary adenocarcinoma
8510^	Medullary carcinoma, NOS
8521^	Infiltrating ductular carcinoma
8523^	Infiltrating duct mixed with other types of carcinoma
8550	Acinus cell carcinoma
8552	Mixed ductal-acinar cell carcinoma
8560^	Adenosquamous carcinoma
8570^	Adenocarcinoma with squamous metaplasia
8572^	Adenocarcinoma with spindle cell metaplasia
8574	Adenocarcinoma with neuroendocrine differentiation
8575^	Metaplastic carcinoma
8576^	Hepatoid adenocarcinoma
8980	Carcinosarcoma, NOS

*NOS: not otherwise specified; ^Pancreatic ductal adenocarcinoma has topography code C25.0 and a morphology code marked with ^.

SUPPLEMENTARY TABLE 1. Multivariable logistic regression analyses to assess the association between diagnosis in a pancreatic surgery centre and pancreatic resection, sensitivity analyses in patients with pathologically verified tumours, age <75 years old, pancreatic ductal adenocarcinoma, and after imputation.

				Univariable		Multivariable[a]	
Period		**Patients**	**Resection**	**OR**	**p-value**	**OR**	**p-value**
Pathologically verified tumours							
2009-2011[b]	Pancreatic vs. non-pancreatic surgery centre	814 versus 1 552	495 (61) versus 771 (50)	**1.57 (1.32-1.87)**	**<0.001**	**1.64 (1.32-2.03)**	**<0.001**
2012-2014[c]	Pancreatic vs. non-pancreatic surgery centre	910 versus 1 745	597 (66) versus 1 017 (58)	**1.37 (1.16-1.61)**	**<0.001**	**1.13 (1.09-1.62)**	**0.004**
2015-2017[d]	Pancreatic vs. non-pancreatic surgery centre	904 versus 1 974	549 (61) versus 1 155 (59)	1.10 (0.93-1.29)	0.261	1.02 (0.84-1.23)	0.836
Age <75 years old							
2009-2011[e]	Pancreatic vs. non-pancreatic surgery centre	665 versus 1 296	400 (60) versus 627 (48)	**1.61 (1.33-1.95)**	**<0.001**	**1.57 (1.23-2.00)**	**<0.001**
2012-2014[f]	Pancreatic vs. non-pancreatic surgery centre	723 versus 1 360	477 (66) versus 813 (60)	**1.35 (1.08-1.58)**	**0.006**	**1.30 (1.03-1.64)**	**0.027**
2015-2017[g]	Pancreatic vs. non-pancreatic surgery centre	683 versus 1 419	432 (63) versus 869 (61)	**1.09 (0.90-1.32)**	**0.374**	1.01 (0.80-1.27)	0.956
Pancreatic ductal adenocarcinoma							
2009-2011[h]	Pancreatic vs. non-pancreatic surgery centre	492 vs. 947	259 (53) vs. 390 (41)	**1.59 (1.28-1.98)**	**<0.001**	**1.57 (1.19-2.05)**	**<0.001**
2012-2014[i]	Pancreatic vs. non-pancreatic surgery centre	566 vs. 1 028	344 (61) vs. 527 (51)	**1.47 (1.20-1.81)**	**<0.001**	**1.40 (1.09-1.80)**	**0.009**
2015-2017[j]	Pancreatic vs. non-pancreatic surgery centre	560 vs. 1 169	304 (54) vs. 599 (51)	1.13 (0.92-1.38)	0.236	1.07 (0.84-1.36)	0.573
After imputation[k]							
2009-2011	Pancreatic vs. non-pancreatic surgery centre	2 176 vs. 993	772 (35) vs. 495 (50)	**1.81 (1.55-2.11)**	**<0.001**	**1.68 (1.39-2.04)**	**<0.001**
2012-2014	Pancreatic vs. non-pancreatic surgery centre	2 295 vs. 1 049	1 018 (44) vs. 597 (57)	**1.66 (1.43-1.92)**	**<0.001**	**1.50 (1.25-1.79)**	**<0.001**
2015-2017	Pancreatic vs. non-pancreatic surgery centre	2 494 vs. 1 072	1 156 (46) vs. 549 (51)	**1.22 (1.05-1.40)**	**0.008**	1.08 (0.90-1.28)	0.413

Values are numbers with percentages within parentheses or odds ratios with 95 per cent confidence intervals within parenthesis. Bold numbers indicate statistical significance. OR: odds ratio. [a] Adjusted for patient characteristics (age, sex, SES), tumour location (pancreas versus periampullary), and clinical T and N-stage; [b] Multivariable analysis calculated in 2 360 patients (SES unknown in 6 patients); [c] Multivariable analysis calculated in 2 645 patients (SES unknown in 10 patients); [d] Multivariable analysis calculated in 2 871 patients (SES unknown in 7 patients); [e] Multivariable analysis calculated in 1 958 patients (SES unknown in 3 patients); [f] Multivariable analysis calculated in 2 074 patients (SES unknown in 9 patients); [g] Multivariable analysis calculated in 2 094 patients (SES unknown in 8 patients); [h] Multivariable analysis calculated in 1 434 patients (SES unknown in 5 patients); [i] Multivariable analysis calculated in 1 588 patients (SES unknown in 6 patients); [j] Multivariable analysis calculated in 1 726 patients (SES unknown in 3 patients); [k] After imputation for clinical T and N status, exclusions due to unknown values of SES are explained in the footnote of Table 2.

SUPPLEMENTARY TABLE 2. Multivariable Cox regression analyses to assess the association between diagnosis in a pancreatic surgery centre and mortality, sensitivity analyses in patients with pathologically verified tumours and age <75 years old.

Period		Patients	Median OS	Univariable HR	p-value	Multivariable[a] HR	p-value
Pathologically verified tumors							
2009-2011[b]	Pancreatic surgery centre	809/2 360	13.4 (12.0-14.8)	**0.89 (0.81-0.97)**	**0.010**	0.95 (0.87-1.04)	0.257
2012-2014[c]	Pancreatic surgery centre	903/2 645	14.3 (13.0-15.6)	0.98 (0.90-1.07)	0.736	0.98 (0.90-1.07)	0.632
2015-2017[d]	Pancreatic surgery centre	899/2 871	14.5 (13.2-15.8)	0.93 (0.85-1.02)	0.103	0.93 (0.88-1.02)	0.111
Age <75 years old							
2009-2011[e]	Pancreatic surgery centre	663/1 958	13.6 (12.2-15.0)	**0.87 (0.78-0.96)**	**0.004**	0.94 (0.85-1.04)	0.216
2012-2014[f]	Pancreatic surgery centre	717/2 074	14.9 (13.6-16.1)	1.00 (0.91-1.10)	0.967	0.98 (0.89-1.08)	0.685
2015-2017[g]	Pancreatic surgery centre	677/2 094	15.6 (13.9-17.2)	0.92 (0.83-1.02)	0.114	0.92 (0.83-1.02)	0.125
Pancreatic ductal adenocarcinoma							
2009-2011[h]	Pancreatic surgery centre	500/1 228	11.8 (10.1-13.5)	0.94 (0.84-1.05)	0.239	0.97 (0.87-1.09)	0.629
2012-2014[i]	Pancreatic surgery centre	480/1 266	13.4 (11.7-15.1)	**0.87 (0.78-0.96)**	**0.008**	0.92 (0.82-1.02)	0.109
2015-2017[j]	Pancreatic surgery centre	508/1 324	11.6 (9.4-13.9)	0.91 (0.82-1.02)	0.098	0.93 (0.84-1.04)	0.219

Values median overall survival or hazard ratios with 95 per cent confidence intervals within parenthesis. Bold numbers indicate statistical significance. OS: overall survival, HR: hazard ratio. [a] Adjusted for patient characteristics (age, sex, SES), tumour location (pancreas versus periampullary), and tumour stage; [b] Analysis calculated in 2 360 patients (survival status and SES unknown in 6 patients); [c] Analysis calculated in 2 645 patients (survival status and SES unknown in 10 patients); [d] Analysis calculated in 2 871 patients (survival status and SES unknown in 7 patients); [e] Analysis calculated in 1 958 patients (survival status and SES unknown in 3 patients); [f] Analysis calculated in 2 074 patients (survival status and SES unknown in 9 patients); [g] Analysis calculated in 3 558 patients (survival status and SES unknown in 8 patients); [h] Analysis calculated in 1 434 patients (survival status and SES unknown in 5 patients); [i] Analysis calculated in 1 588 patients (survival status and SES unknown in 6 patients); [j] Analysis calculated in 1 726 patients (survival status and SES unknown in 3 patients).

CHAPTER 7

Long-term quality of life and exocrine and endocrine pancreatic insufficiency after pancreatic surgery for benign non pancreatitis or pre-malignant disease: a multicenter, cross-sectional study

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Submitted

ABSTRACT

Introduction: Data regarding long-term quality of life and exocrine and endocrine insufficiency after pancreatic surgery for premalignant and benign (non-pancreatitis) disease are lacking.

Methods: This multicentre, cross-sectional study included patients ≥3 years after pancreatoduodenectomy or left pancreatectomy for premalignant or benign disease in six Dutch centres (2006-2016). Outcomes were measured with the EQ-5D-5L, the EORTC QLQ-C30 (differences ≥10 were clinically relevant), an exocrine and endocrine pancreatic insufficiency questionnaire, and Problem Areas in Diabetes Scale 20 (PAID20).

Results: Questionnaires were completed by 153/183 eligible patients (response rate 84 per cent) after a median follow-up of 6·3 years (IQR 4·7-8·3). Pancreatic surgery related complaints were reported by 72/153 patients and 13 patients (8 per cent) would, in hindsight, not undergo this procedure again because of these complaints. The VAS (EQ-5D-5L) was 76±17 versus 82±0·4 in the general population ($p<0·001$). The mean global health status (QLQ-C30) was 78±17 versus 78±17, respectively, $p=1·000$. Fatigue, insomnia, and diarrhoea were clinically relevantly worse in patients. Exocrine pancreatic insufficiency was reported by 62 patients (41 per cent) with full relieve of symptoms by enzyme supplementation in 48 per cent. New-onset diabetes mellitus was present in 22 patients (14 per cent). The median PAID20 score was 6·9/20 (IQR 2·5-17·8).

Conclusion: Although generic quality of life a median of six years after pancreatic resection for pre-malignant and benign (non-pancreatitis) disease was similar to the general population and diabetes-related distress was low, almost half of these patients suffer from a range of symptoms highlighting the need for long-term counselling.

INTRODUCTION

Pancreatic surgery is predominantly performed in patients with cancer, and increasingly for premalignant diseases, such as intraductal papillary mucinous neoplasm (IPMN) or mucinous cystadenoma. Moreover, pancreatic surgery is also sometimes performed for benign diseases, either because preoperative characterization cannot always distinguish between benign and (pre)malignant abnormalities or intentionally for chronic pancreatitis. Since patients who underwent pancreatic surgery for benign or premalignant diseases should have a nearly normal life expectancy, they are especially susceptible to the long-term consequences of pancreatic surgery, including exocrine and endocrine pancreatic insufficiency. Endocrine pancreatic insufficiency (i.e., new-onset diabetes mellitus (DM)) develops in 16-20 per cent of patients after pancreatoduodenectomy, regardless of the final histopathological diagnosis.[1–3] Endocrine pancreatic insufficiency requires daily treatment with antidiabetic agents and carries a risk for long-term micro- and macrovascular complications, both potentially negatively affecting quality of life (QoL).[4] Exocrine pancreatic insufficiency (EPI) develops in approximately 25 per cent of all patients after pancreatic surgery for benign diseases.[1] It results in maldigestion of fat, deficiencies in micronutrients, and deficiencies in fat-soluble vitamins.[4] Patients with EPI often present with steatorrhea, weight loss, or bowel complaints (e.g., pain and cramps), which again can negatively impair QoL.[5]

Overall QoL and exocrine and endocrine pancreatic insufficiency have been studied in patients after pancreatic resections for cancer but data on patients who underwent pancreatic surgery for premalignant and benign indications are lacking.[1,2,6] Therefore, we aimed to assess long-term QoL and exocrine and endocrine pancreatic insufficiency in patients after pancreatic surgery for premalignant or benign (non-pancreatitis) diseases.

METHODS

Study design and population

This multicentre cohort study included patients at least three years after pancreatoduodenectomy or left pancreatectomy between 2006 and 2016 for a premalignant and benign (non-pancreatitis) disease. Questionnaires were administered cross-sectionally. Patients were included from six Dutch centres for pancreatic surgery: Amsterdam UMC (locations Academic Medical Center and VU University Medical Center), Regional Academic Cancer Center Utrecht (locations St Antonius Hospital Nieuwegein and University Medical Center Utrecht Cancer Center), Catharina Hospital Eindhoven, and Medisch Spectrum Twente Enschede. Patients preoperatively diagnosed with symptomatic chronic pancreatitis (i.e. according to the M-ANNHEIM classification) were excluded because chronic pancreatitis is known to have a distinct impact on QoL and the exocrine and endocrine pancreatic function.[7–9] Patients with

an unexpected final histopathological diagnosis of focal pancreatitis/fibrosis, operated for suspected malignancy, were included. Patients with neuro-endocrine tumours were also excluded, because of the potential malignant character. Patients without valid contact information or who were mentally or physically unable to complete the questionnaire were excluded. The medical ethics review committee of the Amsterdam UMC, location Academic Medical Center, granted approval (research not subjected to the WMO (Medical Research Involving Human Subjects Act)). The study was performed in accordance with the STROBE guidelines.[10]

Data collection and definitions

Patient data were collected locally through an online electronic case report form in CASTOR (CIWIT B.V., Amsterdam). Eligible patients were contacted for participation and received, after providing written informed consent, the questionnaires assessing long-term QoL and exocrine and endocrine pancreatic insufficiency were sent by post. If patients did not respond within three weeks, they were called as a reminder. Baseline characteristics, operative, and postoperative data were collected retrospectively from medical charts from all patients who returned the questionnaires. For pancreatic surgery specific complications (i.e., postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy haemorrhage, and chyle leakage) the definitions of the International Study Group on Pancreatic Surgery (ISGPS) were used.[11–14] Bile leakage was scored as defined by the International Study Group of Liver Surgery.[15] Only grade B/C complications were considered as clinically relevant and were reported.

New-onset DM was defined as DM which developed within 6 months after partial pancreatectomy. General practitioners of patients with DM were contacted for their latest HbA1c value and current medication. All patients who used pancreatic enzyme supplementation were considered as diagnosed with EPI.

Questionnaires

Questionnaires included general questions about complaints since surgery, and if so, whether one would undergo the procedure again (Supplementary Text 1). Generic and disease-specific questionnaires were used to assess QoL. The self-rating daily heath status (visual analogue scale (VAS), 0-100 thermometer) from the EuroQoL Five-dimensions (EQ-5D-5L) assessed and compared to the Dutch general population.[16] The European Organization for Research and Treatment in Cancer Quality of Life Questionnaire Cancer (EORTC QLQ-C30) questionnaire is a multi-dimensional measure with 30 questions concerning the global health status, five functional scales, and nine symptom scales.[17] Each scale was linearly transformed into a score from 0-100 and a higher score represented a better QoL on the global health status, better functioning on the functional scales, and a higher level of

symptomatology (more symptoms) on the symptom scales. This questionnaire was included, despite being a cancer specific questionnaire, because the questions were also relevant for patients with benign disease. Outcomes were compared with corresponding results of the Dutch population of all ages and between 60 and 69 years.[18] Differences in scores of ≥10 were considered clinically relevant. The study-specific questionnaire regarding EPI contained questions about complaints of EPI, burden of disease, and treatment of EPI (Supplementary Text 1). Some study-specific questions about the development of DM and the current treatment were included (Supplementary Text 1). The Problem Areas in Diabetes Scale 20 (PAID20) measures DM-related distress with items scored on a Likert scale of 0-4.[19] The total score was transformed to a 0-100 scale with higher scores indicating higher distress. The modified Worry of Cancer Scale (WOCS) was adjusted to seven questions regarding the worry of recurrence or progression of disease. Each question was scored from 0-3 with a maximum score of 21 points and a higher score indicating more worry.

Statistical analysis

Normally distributed continuous data were compared using the t-test and presented as means with standard deviations (SD). Non-normally distributed continuous data were compared using the Mann-Whitney U test or Kruskal Wallis test and presented as medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages and compared using the Chi-square test. A subgroup analysis was performed to assess the impact of patients with focal pancreatitis/fibrosis. A P-value < 0·05 was considered statistically significant. Data were analysed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Patients

In total, 234 patients after pancreatectomy for premalignant and benign disease were alive and eligible in the six centres between 2006 and 2016. Of all 234 eligible patients, 42 patients had non-valid contact information and nine patients were excluded due to a language barrier, mental retardation, dementia, or hospital admission leaving 183 patients for potential participation. Questionnaires were returned by 153 of 183 patients (response rate 84 per cent) after a median follow-up of 6·3 years (IQR 4·7-8·3) after pancreatic surgery. The median age was 63 years (IQR 54-70) and 66 patients (43 per cent were female (Table 1). Most patients had undergone pancreatoduodenectomy (n=99, 65 per cent). Pancreatic specific complications are specified in Table 1. The most common final histopathological diagnosis was IPMN (39 per cent), followed by focal pancreatitis/fibrosis (13 per cent), and serous cystadenoma (12 per cent).

TABLE 1. Baseline, operative, and postoperative characteristics.

	Patients, n (per cent) n = 153
Female	66 (43)
Age at operation, median (IQR)	63 (54-70)
Preoperative BMI, median (IQR)	25·9 (23·9-28·7)
Missing	7
American Society of Anaesthesiologist score	
I	34 (22)
II	93 (61)
III	25 (16)
IV	1 (1)
Preoperative comorbidities	111 (73)
Cardiovascular disease	22 (20)
Pulmonary disease	20 (18)
Missing	1
Type of resection	
Pancreatoduodenectomy	99 (65)
Left pancreatectomy	50 (33)
Other*	3 (2)
Missing	1
Minimally invasive surgery	
Open	128 (84)
Laparoscopic	22 (15)
Robotic	2 (1)
Missing	1
Conversion	2 (8)
Postoperative pancreatic fistula, grade B/C	40 (27)
Missing	6
Delayed gastric emptying, grade B/C	27 (18)
Missing	3
Bile leakage, grade B/C	16 (11)
Missing	5
Post-pancreatectomy haemorrhage, grade B/C	19 (13)
Missing	6
Chyle leakage, grade B/C	6 (4)
Missing	6
Length of hospital stay, median (IQR)	11 (7-21)
Final histopathological diagnosis	
Intraductal papillary mucinous neoplasm	59 (39)
Chronic fibrosis	19 (13)
Serous cystadenoma	18 (12)
Mucinous cystadenoma	12 (8)
Adenoma	11 (7)
Other	33 (22)
Missing	1
Origin	
Pancreas	128 (85)
Ampulla of Vater	12 (8)
Distal bile duct	5 (3)
Duodenum	3 (2)
Other	4 (3)
Missing	1

* Other procedures included central pancreatectomy, radical antegrade modular pancreatosplenectomy, and enucleation.

Quality of life

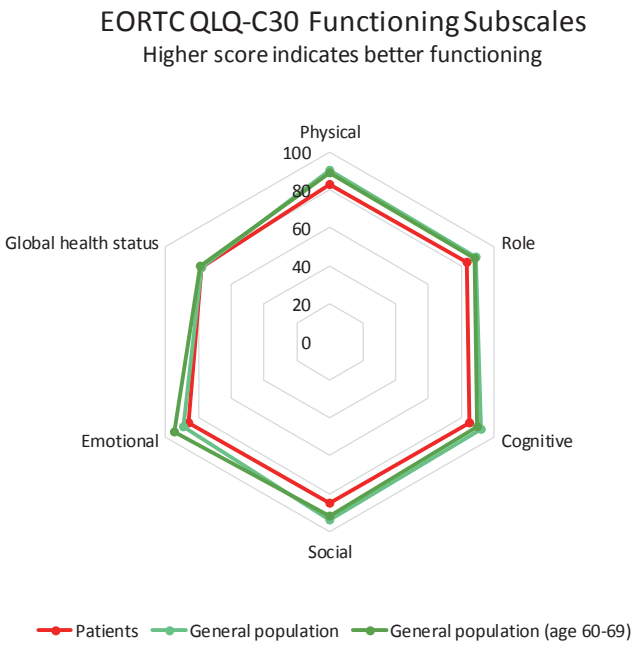
Pancreatic surgery related complaints, not further specified, were reported by 72 of 153 patients (47 per cent) and 13 of 153 patients (8 per cent) would, in hindsight, not undergo this procedure again because of these complaints. The mean daily health status (VAS) of the EQ-5D-5L was 76 (SD 17) versus 82 (SD 0·4) for all ages in the general population (p<0·001) and 81 (SD 1) for the general population aged 55-64 years (p<0·001). The results from the QLQ-C30 are shown Figure 1. On all functional subscales, patients scored significantly worse compared to the general population of all ages but none of the differences was clinically relevant. The mean global health status was 78 (SD 17) and comparable with the general population (all ages mean 78 [SD 17], p=1.000). Most symptom scores were significantly worse (i.e., higher scores) compared the general population of all ages, except for pain (Figure 1B). For fatigue, insomnia, and diarrhoea, this difference was clinically relevant. The median modified WOCS score was 1 (IQR 0-5) and indicated very little worries about recurrence of disease.

Exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency was reported by 62 patients (41 per cent, Table 2) and more often present in patients after pancreatoduodenectomy as compared to patients after left pancreatectomy (50 (51 per cent) vs. 10 (20 per cent), p<0·001) After starting enzyme supplementation, EPI related complaints disappeared in 29/62 patients (48 per cent), decreased in 21 patients (35 per cent) and were unchanged in 10 patients (17 per cent, missing data in 2 patients). At the moment of administering the questionnaire, patients with pancreatic enzyme replacement therapy had more complaints of fatty stools (50 per cent vs. 26 per cent, p=0·003) and unintentional weight loss (11 per cent vs. 2 per cent, p=0·019) than those without pancreatic enzyme therapy. All patients used capsules for the administration of pancreatic enzymes, of which only two patients opened their capsules before administration. Most patients used enzymes during their meal (range 60-63 per cent per meal) but also before or after (Table 3). More than half of all patients did not use enzymes while having a snack (n = 36, 58 per cent, missing data in one patient). In the past three months, 13 patients (21 per cent) with EPI had consulted a dietician. The initial reason was weight loss in two patients (15 per cent), DM in 6 (46 per cent), weight loss and DM in one (8 per cent), or another reason in four (31 per cent). Ten patients (16 per cent) reported to use a low-fat diet. Side effects of enzyme supplementation were noted by 13 patients (21 per cent) but these were not further specified.

FIGURE 1. EORTC QLQ-C30 mean scores in patients after a pancreatic surgery for benign or premalignant diseases in comparison with a Dutch reference population.

FIGURE 1A. EORTC QLQ-C30 Functional scales.

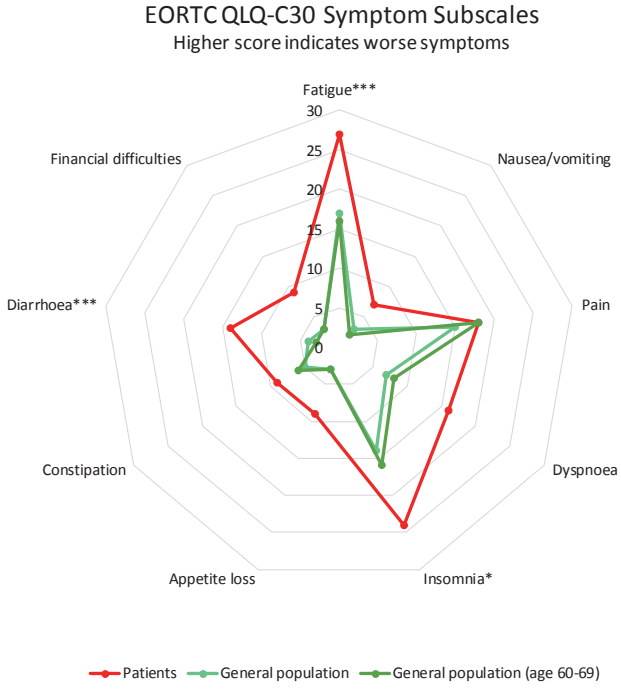


A

	Patients, mean (SD)	General population, mean (SD)	p-value	General population (age 60-69), mean[#]
Physical	83 (18)	90 (15)	**<0·001**	89
Role	83 (23)	89 (21)	**0·005**	88
Cognitive	85 (20)	92 (15)	**<0·001**	90
Social	85 (19)	94 (16)	**<0·001**	92
Emotional	86 (21)	89 (16)	**0·004**	95
Global health status	78 (17)	78 (17)	1·000	79

Bold numbers indicate statistical significance; [#] SD not presented in reference values and consequently unable to calculate p-values. Physical functioning is missing in one patient (n = 152), role functioning is missing in one patient (n = 152).

FIGURE 1B. EORTC QLQ-C30 Symptom scales.



	Patients, mean (SD)	General population, mean (SD)	p-value	General population (age 60-69), mean[#]
Fatigue***	27 (25)	17 (20)	**<0·001**	16
Nausea/vomiting	7 (16)	3 (10)	**<0·001**	2
Pain	18 (23)	15 (22)	0·107	18
Dyspnoea	16 (25)	7 (17)	**<0·001**	8
Insomnia*	24 (30)	14 (23)	**<0·001**	16
Appetite loss	9 (21)	3 (12)	**<0·001**	3
Constipation	9 (19)	5 (14)	**0·001**	6
Diarrhoea***	14 (23)	4 (14)	**<0·001**	3
Financial difficulties	9 (19)	3 (13)	**<0·001**	3

Bold numbers indicate statistical significance; [#] SD not presented in reference values and consequently unable to calculate p-values. Insomnia is missing in one patient (n = 152), constipation is missing in one patient (n = 152).

* Clinically relevant difference compared to general population of all ages
** Clinically relevant difference compared to general population aged 60-69 years
*** Clinically relevant difference compared to general population of all ages and aged 60-69 years
Reference mean values of EORTC QLQ-C30 for healthy population from reference values manuel[18]

Endocrine pancreatic insufficiency

New-onset DM was present in 22 patients (40 per cent of all patients with DM, and 14 per cent of the total cohort). Table 4 shows details about endocrine pancreatic insufficiency. The median HbA1c value of all 55 patients with DM was 60 mmol/mol (IQR 54-60). The HbA1c value did not differ between patients with preoperative DM, new-onset DM, and DM diagnosed later than 6 months after pancreatic surgery (p=0·079) with 62 mmol/mol (IQR 57-68), 64 mmol/mol (IQR 56-68), and 53 mmol/mol (IQR 48-64), respectively. The median HbA1c value was 56 mmol/mol (IQR 50-59) in patients who used tablets and 64 mmol/mol (IQR 57-69) in patients who used insulin with or without tablets (p=0·004).

TABLE 2. Exocrine pancreatic insufficiency.

	Patients with exocrine pancreatic insufficiency, n (per cent) n = 62	**Patients without exocrine pancreatic insufficiency, n (per cent) n = 91**	**p-value**
Abdominal complaints			
Abdominal rumbling	20 (32)	21 (23)	0·208
Abdominal cramps	14 (23)	20 (22)	0·930
Excessive flatulence	30 (48)	32 (35)	0·102
Fatty stools	31 (50)	24 (26)	0·003
Foul smelling stools	15 (24)	14 (15)	0·172
Unintentional weight loss	7 (11)	2 (2)	0·019
No symptoms	16 (26)	39 (43)	0·013
Abdominal pain			**0·037**
No pain	33 (54)	62 (69)	
Slightly	26 (43)	22 (24)	
Moderate	1 (2)	6 (7)	
Missing	1	1	
Use of proton pump inhibitor	36 (59)	41 (45)	0·104
Missing	1	1	
Stool frequency			0·380
≤1 times week	-	1 (1)	
1-3 times/week	4 (7)	5 (6)	
4-7 times/week	38 (62)	46 (51)	
2-3 times/ day	17 (28)	37 (41)	
≥4 times/day	2 (3)	1 (1)	
Missing	1	1	
Dosage of pancreatic enzyme capsules (FIP-E), median (IQR)*		NA	
Breakfast	25 000 (25 000-50 000)		
Lunch	40 000 (25 000-50 000)		
Dinner	50 000 (25 000-56 250)		
Snacks	0 (0-25 000)		
Determination of optimal dosage^		NA	
Based on amount of fat percentage in meal	14 (23)		
In consultation with dietician	9 (15)		
Fixed dose	45 (73)		

Bold numbers indicate statistical significance. EPI: exocrine pancreatic insufficiency, IQR: interquartile range.
* Number of missing patients was 15, 13, 15, and 12 for breakfast, lunch, diner, and snacks, respectively.
^ Multiple answers were possible and therefore the total percentage exceeds 100%.

Subgroup analysis

A subgroup analysis excluding patients with focal pancreatitis/fibrosis showed similar results (Supplementary Table 1).

TABLE 3. Timing of enzyme supplementation in 62 patients with exocrine insufficiency following pancreatic surgery.

	Before, n (per cent)	During, n (per cent)	After, n (per cent)	None, n (per cent)
Breakfast	11 (18)	38 (61)	5 (8)	8 (13)
Lunch	15 (24)	39 (63)	5 (8)	3 (5)
Snacks*	5 (8)	13 (21)	7 (11)	36 (58)
Dinner	20 (32)	37 (60)	5 (8)	-

* Data are missing in one patient.

TABLE 4. Endocrine pancreatic insufficiency.

	Patients, n (per cent) n = 55
Diabetes mellitus	
Preoperative diabetes mellitus	21 (38)
New-onset diabetes mellitus	22 (40)
Diabetes mellitus developed >6 months after pancreatic surgery	12 (22)
HbA1c value (mmol/mol), median (IQR)	60 (54-68)
Missing	1
Antidiabetic medication	
Tablets	19 (36)
Insulin	16 (30)
Tablets and insulin	18 (34)
Missing	2
PAID20	
Median value (IQR)	6·9 (2·5-17·8)
Mean (SD)	12·4 (14·2)
Missing	5

DISCUSSION

This multicentre study found that more than six years after pancreatic surgery for premalignant and benign (non-pancreatitis) disease, generic QoL was comparable to the general population and diabetes related distress was low. However, almost half of all patients reported surgery related complaints and 8 per cent of all patients would not undergo surgery again because of these complaints. Especially, pancreatic enzyme replacement therapy, used by 41 per cent of patients, led to insufficient relieve of symptoms in the majority of these patients.

Although long-term QoL has been studied after surgery for pancreatic cancer, studies solely including patients with premalignant and benign diseases or distinguishing these from patients with malignant disease are scarce. Huang et al. compared patients with other benign diseases who (i.e. cystic neoplasms, endocrine tumours, n=24) who underwent pancreatoduodenectomy between 1981 and 1997 with patients after laparoscopic cholecystectomy and found no differences in physical, physiological, and social scores.[9] The functional assessment (e.g. weight loss, abdominal pain, fatigue, and foul stool) showed worse results in patients after pancreatoduodenectomy. A more recent series (2006-2010) demonstrated that in 42 patients after pancreatoduodenectomy for non-malignant diseases, QoL was negatively impacted by complaints such as pain and diarrhoea (4·9 per cent and 7·3 per cent, respectively).[20] An Italian cohort from three centres pointed out that QoL, 24 months after pancreatoduodenectomy in 30 patients with benign diseases was better than in patients with malignant disease.[21] However, none of the studies compared outcomes with the general population. We found that generic quality of life (mean global health status QLQ-C30) scores was comparable between patients after pancreatic surgery and the general population. However, the EQ-5D-5L VAS score was worse in patients after pancreatic surgery compared with the general population. The EQ-5D-5L VAS score only questions “health today” on a scale from 0-100, whereas the QLQ-C30 questions both “health today” and “quality of life today”, both on a scale from 0-7. This might explain the difference of both score with the general population as the health status was worse but the experienced quality of life was comparable. Most function and symptom subscales (QLQ-C30) in patients were significantly worse in patients after pancreatic surgery but these difference were not clinically relevant. A clinically relevant difference was found for fatigue, insomnia, and diarrhoea. This was also found in the study comparing patients after pancreatoduodenectomy with patients after laparoscopic cholecystectomy. In addition, fatigue has been indicated as a common problem after pancreatoduodenectomy (and other major operations), regardless of a malignant or non-malignant indication for the operation.[9]

The frequency of EPI (41 per cent) in the present study was higher than previously reported in a systematic review which included patients with non-malignant diseases (25 per cent), and was more comparable to patients with malignant disease.[1,3,22] Few data are available concerning EPI in patients with benign or premalignant diseases and therefore, it is difficult to reliably compare the prevalence found in this study. Physicians, however, should be aware of the risk on developing EPI after pancreatic surgery, especially in patients after pancreatoduodenectomy. Patients receiving pancreatic enzyme supplementation at least three years after surgery (i.e., considered as having EPI) had more complaints of fatty stools and unintentional weight loss on the long-term compared to those without EPI. This could be caused by incorrect dosing or intake of pancreatic enzymes, a phenomenon frequently observed in patients with EPI. First, the median enzyme dose was 40 000 FIP-E during lunch and 50 000 FIP-E during

dinner. This means that 50 per cent of the patients used less. The advised starting dose with breakfast, lunch, or dinner is 40 000-50 000 FIP-E for patients and therefore dosing is insufficient in half of our patients.[23] Second, 20 000 FIP-E is recommended for snacks and 58 per cent of patients did not use any enzymes while having a snack. Third, the moment of enzyme administration is important and preferably enzymes are taken during the meal.[24,25] Sixty to 63 per cent of our patients took their enzymes during the main meals but the optimal effect of supplementation might not be accomplished in the other patients. Increased attention for these aspects is required and personalized care should be delivered by a dietician or nurse practitioner. In the current cohort, only 21 per cent of patients with EPI had consulted a dietician in the past three months and only in three patients this was probably related to EPI (i.e., referral for weight loss). This should be improved in current postoperative care, because even on the long-term patients still experience symptoms. Future studies should assess to what extent the guidance of a specialist dietician or nurse practitioner in the management of EPI treatment can improve symptoms of EPI.

Endocrine pancreatic insufficiency was present in 14 per cent and this was comparable to previous literature.[1–3] This is higher than the estimated crude incidence of diagnosed diabetes in United States adults (45-64 years) in 2018 which is 9·9 per 1000 persons.[26] Guidelines on DM generally recommend an HbA1c level ≤53 mmol/mol and thus glycemic control should be improved.[27,28] The median HbA1c in the present study was 60 mmol/mol and even in patients who were only treated with oral antidiabetics (i.e., which indicates less severe DM) the HbA1c value was above 53 mmol/mol. On the other hand, in a large study with patients with DM type I and II from the United States and the Netherlands the mean HbA1c value was 61 mmol/mol showing that tight glycaemic control is difficult to achieve.[19] The mean PAID20 score was 24·6 and 22·5 in Dutch patients for DM type I and type II, respectively. This was higher than the mean score of 12·4 in our cohort. This may be explained by the fact that the results of Snoek et al. are 20 years old and DM treatment has improved over the last two decades causing less distress. A more recent study from 2012 showed a mean PAID20 score of 22 in both patients with DM type I and type II patients.[29] This was still higher than our population, indicating little emotional distress regarding diabetes.

The findings of this study should be interpreted in light of some limitations. First, the retrospective collection of patients' and (post)operative characteristics might have been influenced by information bias. Second, we compared outcomes with the general population but the ideal design would have included a QoL measurement at baseline and during follow-up. Third, the inclusion period of 10 years was relatively long and surgical technique and postoperative care could have improved during this period. This was inherent to the relative rarity of pancreatic resections for premalignant and benign

diseases. Fourth, details about enzyme dosage should be interpreted with caution. Dosing of enzyme supplementation can vary per day and per meal, depending on the amount of fat ingested. However, most patients reported that dosage per meal was based on a fixed scheme and therefore we believe that the gathered data is valid. This, again, showed that flexibility in dosing should be more stimulated. Fifth, EPI was defined as using enzyme supplementation. It is known that EPI is currently underdiagnosed and probably, the actual prevalence of EPI is even higher.[8,30] Fatty stools were reported by 26 per cent of patients without EPI and this supports the presence of under diagnosis and treatment.

Strengths of the study are the relatively large cohort, the high response rate and the long follow-up. Data regarding the consequences of exocrine and endocrine pancreatic insufficiency in patients after pancreatic surgery for benign or premalignant diseases were lacking and the presented data is therefore valuable when consulting patients.[1]

In conclusion, long-term generic QoL after pancreatic surgery for premalignant and benign (non-pancreatitis) disease was similar to the general population and diabetes related distress was low, but nearly half of all patients reported surgery related complaints and 8 per cent would, in retrospect, not undergo pancreatic surgery again. The current treatment of EPI needs further attention, potentially by personalized treatment schemes given by dieticians or nurse practitioners. The current results should be used in the shared-decision making process in case surgery is considered for benign (non-pancreatitis) or premalignant pancreatic diseases.

ACKNOWLEDGEMENT

We would like to thank Anne Claire Henry for her dedicated help with the data collection in the Regional Academic Cancer Center Utrecht (St Antonius Hospital Nieuwegein and University Medical Center Utrecht Cancer Center) and prof. Sprangers, Amsterdam UMC, for her expert opinion regarding the quality of life analysis and interpretation.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1. Subgroup analyses after excluding patients with chronic fibrosis.

	Patients, n (per cent) n = 134
Daily health status (EQ-5D-5L), mean (SD)	75 (17)
Global health status (QLQ-C30), mean (SD)	78 (17)
Exocrine pancreatic insufficiency	52 (39%)
Diabetes mellitus	48 (36%)
Preoperative diabetes mellitus	16 (33%)
New-onset diabetes mellitus	20 (42%)
Diabetes mellitus developed >6 months after pancreatic surgery	12 (25%)
HbA1c value (mmol/mol), median (IQR)	58 (53-65)
Missing	1
PAID20, median (IQR)	6·3 (2·5-16·3)

SUPPLEMENTARY TEXT 1. Questionnaires.

General questions about complaints since surgery

1. Do you still have complaints related to the pancreatic surgery (e.g., diabetes mellitus or a shortage of pancreatic enzymes)?

□ Yes (move on to question 2)

□ No (move on to question 3)

2. Would you, in a similar situation, undergo the surgery again, despite your complaints related to the pancreatic surgery (e.g., diabetes mellitus or a shortage of pancreatic enzymes)?

□ Yes

□ No

□ I do not know

3. Do you believe your quality of life has been affected by your pancreatic surgery?

□ Yes

□ No

□ I do not know

Study-specific questions about diabetes mellitus

1. When were you diagnosed with diabetes mellitus?

□ Before I underwent pancreatic surgery (move on to question 3)

□ After I underwent pancreatic surgery

2. If you were diagnosed with diabetes mellitus after your pancreatic surgery: approximately how long after surgery were you diagnosed?

□ Within 3 months after surgery

□ Between 3 and 6 months after surgery

□ Between 6 months and 1 year after surgery

□ More than 1 year after surgery

3. Which type of diabetic medication(s) do you use at this moment?

□ I do not use any medication

□ I use tablets

□ I use insulin

□ I use both insulin and tablets

4. Are you supported by a physician or a nurse, specialized in diabetes, in your diabetes treatment?

□ Yes, by a physician from the hospital

□ Yes, by a nurse that is specialized in diabetes

□ Yes, by my general practitioner (GP)

□ Yes, by the assistant of the general practitioner

□ No

Study-specific questionnaire about exocrine pancreatic insufficiency

1. During the past month, which of the following complaints did you have for 3 or more days a week? (*multiple answers possible*)

□ Bowel rumblings

□ Bowel cramps

□ Excessive flatulence

□ Greasy stools (abnormal color / sticky / grease floats on it / floats)

□ Very smelly stools

□ Unintentional weight loss while eating as usual

□ None

2. Do you suffer from abdominal pain during the day?

□ Not at all

□ A little

□ Quite a bit

□ Very much

3. Do you use antacids, such as omeprazole, pantoprazole or esomeprazole, (almost) daily?

□ Yes

□ No

4. How often do you have stool?

□ Less than once a week

□ 1-3 times a week

□ 4-7 times a week

□ 2-3 times a day

□ 4 or more times a day

5. What is the aspect of your stool?

□ Separate hard lumps

□ One hard sausage-like lump

□ Smooth, soft sausage

□ Soft blobs with clear-cut edges

□ Mushy consistency with ragged edges

□ Liquid consistency (diarrhea) with no solid pieces

6. For what reason did you contacted a dietician during the past three months? (*multiple answers possible*)

□ Weight loss

□ Diabetes mellitus

□ Suspicion on impaired digestive function of the pancreas

□ Another reason, namely: _____

□ I have not been in contact with a dietician during the past three months

7. What does your diet look like?

□ I am on a high protein diet

□ I am on an energy-enriched diet

□ I am on a low-fat diet

□ I am on another kind of diet, namely: _____

□ I am not on a specific diet

8. Have you made any adjustments to your diet?

□ No

□ Yes, namely: _____

The following questions are about the use of pancreatic enzymes. If you do not use pancreatic enzyme supplementation the questionnaire ends here.

9. Which brand of pancreatic enzymes do you use?

□ Pancreaze

□ Creon

□ Panzytrat

□ Pancreatin

□ Other, namely: _____

10. What is your **daily** dosage of pancreatic enzymes?

Pay attention: this question is divided into capsules or granules.

If you use **capsules**:

	Number of capsules	Capsule dosage in mg or units of lipase
Breakfast		
Lunch		
Snacks		
Dinner		

If you use granules:

Number of spoons per day: _____

Color of the spoon:

□ Green

□ Orange

□ Transparent

11. How do you take the capsules?

□ I swallow the whole capsule

□ I open the capsule and take the granules

12. When did you (approximately) start enzyme supplementation?

□ Less than 3 months ago

□ 3 – 6 months ago

□ 7 – 12 months ago

□ 1 – 2 years ago

□ More than 2 years ago

13. At what moment during your meal do you normally take the pancreatic enzymes? *(multiple answers possible)*

Breakfast	□ Before	□ During	□ After	□ No enzymes
Lunch	□ Before	□ During	□ After	□ No enzymes
Snacks	□ Before	□ During	□ After	□ No enzymes
Dinner	□ Before	□ During	□ After	□ No enzymes

14. How do you determine the dosage of capsules or enzymes? *(multiple answers possible)*

□ Based on the amount of fat per meal

□ I discussed the dosage of capsules or enzymes with the dietician

□ I use a standard dosage (for example 2 capsules with dinner and 1 with small meals)

15. How many days of the week do you really take the pancreatic enzymes?

□ Once a week

□ 2 – 4 times a week

□ 5 – 6 times a week

□ Every day

16. Which of the following statements applies to you since you started pancreatic enzyme supplementation?

□ I have no more complaints

□ I have less complaints

□ I still have complaints

□ I have more complaints

17. Do you experience any side effects from the pancreatic enzyme supplementation, such as abdominal pain, obstipation, or rash?

□ I have no side effects

□ I have side effects

CHAPTER 8

Micronutrient deficiencies and anaemia in patients after pancreatoduodenectomy

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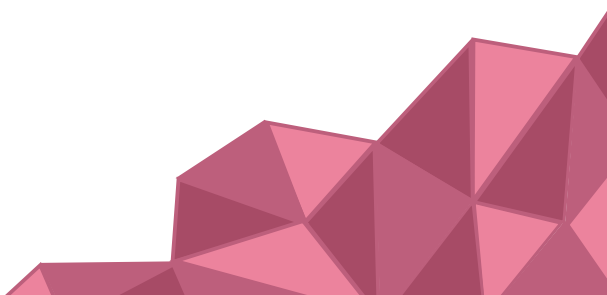
British Journal of Surgery. 2020.



Editor

In recent years, pancreatoduodenectomy (PD) is performed more often and subsequent survival of patients after pancreatic resection has improved. Increased attention for long-term consequences PD, specifically nutrition related side-effects, is therefore essential. Deficiencies may especially occur in the fat-soluble vitamins A, D, E, and K, vitamin B12, zinc, and iron. Changes in intake, cancer-related cachexia, and exocrine pancreatic insufficiency may contribute to these deficiencies. Most studies to date are performed in small cohorts, after short follow-up, or focus on only a single micronutrient.[1–3]

This single centre retrospective cohort study was conducted to assess serum levels of several micronutrients and presence of anaemia in 85 consecutive patients at least four months after PD in the Erasmus MC Rotterdam (July 2018 - December 2019). An extensive blood laboratory assessment was performed according to the local protocol. The study was performed in accordance with the STROBE guidelines.

Median follow-up was 13 months (IQR 7-28). Median age at inclusion was 68 years (IQR 61-75) and 38 patients were female (45 per cent). Pathology diagnoses included pancreatic ductal adenocarcinoma in 34 patients (40 per cent), ampullary cancer in 19 (, 22 per cent), and intraductal papillary mucinous neoplasm in 11 (13 per cent).

Median BMI decreased from 22.5 kg/m^2 (IQR 19.5-25.4) preoperatively to 20.6 kg/m^2 (IQR 17.3-22.9) postoperatively (n=47, p<0.001). Oral nutritional supplementation was prescribed to 8 patients (9 per cent). All patients received pancreatic enzyme supplementation, but exact doses were only registered in 33 patients (39 per cent). Most patients used capsules with 25 000 FIP-E lipase with a median of 4 capsules (IQR 3-6) per day.

Table 1 demonstrates the serum values and deficiencies at follow-up. In anaemic patients, the iron value was deficient in 24/41 (58 per cent) compared with 10/44 (23 per cent) with a normal haemoglobin value (p=0.001). The ferritin level was deficient in respectively 12/41 and 0/44 patients (29 versus 0 per cent, p<0.001).

This study showed that >4 months after PD, deficiencies of iron, ferritin, vitamin A, and vitamin D, and anaemia were common. This is in line with previous studies, which showed that patients >6 months after PD had deficiencies in several micronutrients.[2,3] In contrast, an earlier study demonstrated that half of all patients recovered within six months after pancreatectomy, as both nutritional status and

quality of life returned to preoperative levels.[4] However, solely albumin, protein, and transferrin were investigated.

TABLE 1. Serum levels of micronutrients and haemoglobin at follow-up after pancreatoduodenectomy.

	All patients (n = 85), median (IQR)	Reference values	Patients with deficiency, n (%)
Vitamin A	1.66 µmol/L (1.36 - 1.66)	1.25 - 3.00 µmol/L	18 (21%)
Vitamin B1	125 nmol/L (112 - 147)	70 - 140 nmol/L	0 (0%)
Vitamin B6	76 nmol/L (64 - 93)	35 - 110 nmol/L	1 (1%)
Active vitamin B12	69 pmol/L (57 - 102)	33 - 247 pmol/L	2 (4%)
Missing	36		
Total vitamin B12	315 pmol/L (230 - 419)	145 - 637 pmol/L	2 (2%)
Missing	1		
Vitamin D	56 nmol/L (38 - 74)	50 - 120 nmol/L	33 (40%)
Missing	2		
Vitamin E	26.1 µmol/L (19.4 - 32.2)	16.5 - 41.6 µmol/L	1 (3%)
Missing	55		
Haemoglobin			
Female	8.0 mmol/L (7.0 - 8.6)	7.5 - 9.50 mmol/L	13 (34%)
Male	8.1 mmol/L (6.8 - 8.9)	8.6 - 10.5 mmol/L	28 (60%)
Mean cell volume	90 fl (85 - 93)	80 - 100 fl	NA
Folic acid	19 nmol/L (13 - 26)	5 - 40 nmol/L	0 (0%)
Albumin	42 g/L (40 - 44)	35 - 50 g/L	2 (3%)
Calcium	2.36 mmol/L (2.32 - 2.42)	2.20 - 2.65 mmol/L	5 (6%)
Zinc	87 µmol/L (81 - 93)	64 - 124 µmol/L	3 (4%)
Missing	9		
Iron	11 µmol/L (8 - 15)	10 - 30 µmol/L	34 (40%)
Ferritin			
Female	65 µg/L (33 - 107)	10 - 140 µg/L	1 (3%)
Male	68 µg/L (36 - 176)	30 - 240 µg/L	11 (23%)
Transferrin	2.6 g/L (2.3 - 3.0)	2.0 - 3.5 g/L	6 (7%)a

NA: not applicable. [a] Proportion of patients with a value above the reference value; [b] Reference value for non-smokers (smokers: <10 µg/L).

Anaemia was present in a large proportion and was associated with deficiencies in iron and ferritin levels. Anaemia after PD has been previously described and related to deficient iron intake, but it could also be attributed to malabsorption of iron (after resection of the duodenum).[2,3] However, anaemia has many other underlying causes and the world-wide prevalence is around 27 per cent.

Inadequate treatment of pancreatic exocrine insufficiency might have contributed to the vitamin A and D deficiencies. Patients often use too few enzymes due to non-compliance, prescription of an insufficient dose, or bad instruction on supplementation.[5] Future studies should confirm that regular checks for fat-soluble vitamins in patients after PD in combination with consultations by a dietician or nurse practitioner could improve clinical outcome and quality of life.

The most important conclusion is that increased attention is required for long-term micronutrient deficiencies and anaemia after PD. It could be suggested to perform a standardized laboratory assessment during follow-up and supplement deficiencies that are found. Moreover, adequate supplementation of pancreatic enzymes is expected to contribute to an optimal micronutrient status. Future, prospective studies should study the impact of such a strategy in clinical practice.

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CHAPTER 9

Outcome and long-term quality of life after total pancreatectomy (PANORAMA): a nationwide cohort study

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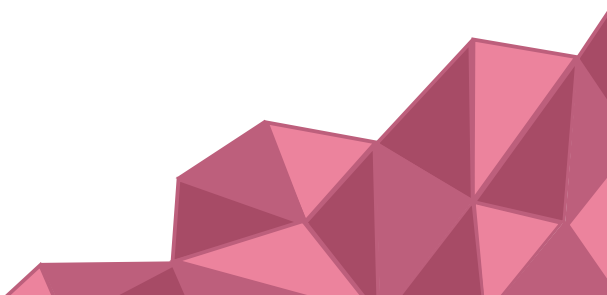
Surgery. 2019 Dec;166(6):1017-1026.



ABSTRACT

Background: The threshold to perform total pancreatectomy is rather high, predominantly because of concerns for long-term consequences of brittle diabetes on patients' quality of life. Contemporary data on postoperative outcomes, diabetes management, and long-term quality of life after total pancreatectomy from large nationwide series are, however, lacking.

Methods: We performed a nationwide, retrospective cohort study among adults who underwent total pancreatectomy in 17 Dutch centers (2006-2016). Morbidity and mortality were analyzed, and long-term quality of life was assessed cross-sectionally using the following generic and disease-specific questionnaires: the 5-level version European quality of life 5-dimension and the European Organization for Research and Treatment in Cancer Quality of Life Questionnaire Cancer. Several questionnaires specifically addressing diabetic quality of life included the Problem Areas in Diabetes Scale 20, the Diabetes Treatment Satisfaction Questionnaire-status version, and the Hypoglycemia Fear Survey-II. Results were compared with the general population and patients with type 1 diabetes.

Results: Overall, 148 patients after total pancreatectomy were included. The annual nationwide volume of total pancreatectomy increased from 5 in 2006 to 32 in 2015 ($P < 0.05$). The 30-day and 90-day mortality were 5% and 8%, respectively. The major complication rate was 32%. Quality of life questionnaires were completed by 60 patients (85%, median follow-up of 36 months). Participants reported lower global (73 vs. 78, $P = 0.03$) and daily health status (0.83 vs. 0.87, $P < 0.01$) compared to the general population. Quality of life did not differ based on time after TP (<3, 3-5, or >5 years). In general, patients were satisfied with their diabetes therapy and experienced similar diabetes-related distress as patients with type 1 diabetes.

Conclusions: This nationwide study found increased use of total pancreatectomy with a relatively high 90-day mortality. Long-term quality of life was lower compared to the general population, although differences were small. Diabetes-related distress and treatment satisfaction were similar to patients with type 1 diabetes.

INTRODUCTION

Total pancreatectomy (TP) is performed primarily in patients with pancreatic cancer, chronic pancreatitis, or as a salvage completion pancreatectomy. Currently, TP is increasingly advised in patients with intraductal papillary mucinous neoplasm (IPMN) with involvement of the entire main duct, because this condition is associated with high-grade dysplasia or pancreatic cancer in 37 to 91% of resected specimens.[1–3] In highly selected patients with locally advanced pancreatic cancer and a good response to FOLFIRINOX chemotherapy, the increased use of advanced resections with or without the use of arterial resections can potentially also increase the use of TP.[4–6]

The threshold to advise and perform TP is relatively high because of concerns for poor operative outcomes and poor quality of life (QoL) related to brittle diabetes after TP.[7,8] Although, the outcome of pancreatic surgery and the management of endocrine insufficiency may have improved in recent years, the current long-term QoL after TP from large, nationwide studies is unknown.[9–14] Likewise, exocrine pancreatic insufficiency can be treated satisfactorily with pancreatic enzyme replacement therapy.[15,16] Currently, data are only available from single center cohorts with relatively small samples (median 28 patients [interquartile range (IQR) 24-39]).[8,10,11,14,17–22] These series have reported worse QoL after TP compared to an aged-matched, healthy population, but similar QoL as reported for patients after partial pancreatectomy.[20,22] Pancreatic insufficiency and especially new-onset diabetes mellitus (DM) have a negative effect on QoL, but it is unclear whether this differs from patients with type 1 DM.[19,21,22]

The aim of this nationwide cohort study PANORAMA is to assess the short-term, postoperative outcomes and long-term impact of TP on QoL and to compare these outcomes with reference data from a healthy population and particularly in patients after pancreatoduodenectomy and patients with type 1 DM.

METHODS

Study design

This nationwide, retrospective, cohort study (PANORAMA) included all patients who underwent a TP in the 17 centers of the Dutch Pancreatic Cancer Group between 2006 and 2016. All centers perform at least 20 pancreatoduodenectomies annually. Included were patients after elective primary TP or elective completion TP (for disease recurrence). Emergency completion TP (n = 23) was excluded. Both open and minimally invasive procedures were included. The medical ethics review committee of the Amsterdam UMC, location Academic Medical Center, granted approval and waived the need for consent. The survival status of all patients was assessed on October 20 2016 from the database of the Dutch municipal personal records. This database only contains information about date and place of

death. Thereafter, all surviving patients were contacted by telephone and when they agreed to participate, received a set of validated questionnaires between October 2016 and May 2017.

Definitions

TP was defined as resection of the entire pancreas with or without splenectomy. New-onset DM was defined as newly diagnosed DM for which oral medication and/or insulin was required within 6 months after TP. Major complications were defined as a Clavien-Dindo score ≥ 3.[23] Postpancreatectomy hemorrhage, delayed gastric emptying ,and chyle leakage were defined according to the International Study Group on Pancreatic Surgery.[24–26] Only Grade B and C complications were considered to be clinically relevant. This classification was also applied for bile leakage, which was graded based on the system of the International Study Group of Liver Surgery.[27] The TNM classification was defined based on the American Joint Committee on Cancer Staging Manual, seventh edition.[28] Although a new defintion is available, it was not used in the patient records and therefore, was not used during data collection.

Data sources

Data were collected retrospectively from (digital) medical records. Baseline characteristics were age (years), sex, body mass index (kg/m^2), American Society of Anesthesiologist class, smoking and alcohol status, first symptoms, elective primary or completion TP, splenectomy, neoadjuvant therapy, preoperative DM, and pancreatic enzyme replacement therapy for exocrine pancreatic insufficiency. Postoperative outcomes included overall complications, postpancreatectomy hemorrhage, delayed gastric emptying, chyle leakage, bile leakage, operation time (minutes), duration of hospital stay (days), 30- and 90-day mortality, duration of follow-up, pathologic diagnoses (including resection margins and TNM classification), adjuvant therapy, occurrence of new-onset DM with required therapy, and start of enzyme supplementation before discharge. Causes of death for patients with IPMN >90 days after TP were retrieved whenever possible.

QoL was assessed cross-sectionally using both generic and disease-specific, self-report questionnaires. Additional collected characteristics were marital status, education level, and diagnosis. The 5-level version EuroQoL 5-dimension (EQ-5D-5L), which is a generic questionnaire, was used along with the following 4, disease-specific questionnaires: European Organization for Research and Treatment in Cancer Quality of Life Questionnaire Cancer (EORTC QLQ-C30); Problem Areas in Diabetes Scale 20 (PAID20); Hypoglycemia Fear Survey-II, and Diabetes Treatment Satisfaction Questionnaire-status version (DTSQs). The EQ-5D-5L consists of 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) each scored within 5 levels of severity and an overall self-rating

of health status (0 -100 thermometer; mean daily health score).[29] Both scores were compared with the Dutch general population.[30,31]

The EORTC QLQ-C30 questionnaire is a multi-dimensional measure that includes 30 questions covering global health status, five functional scales, and nine symptom scales.[32] Each scale is analyzed separately in which a higher score represents a better QoL on the global health status, a higher or healthier level of functioning on the functional scales, and a higher level of symptomatology (more symptoms) on the symptom scales. Results were compared to reference data of the Dutch population and patients 1 year after pancreatoduodenectomy.[33,34] The importance of differences was interpreted in accordance with Osoba et al [35]: 5-10% a little change; 10-20% moderate change; >20% very much change.
PAID20 and DTSQs are DM-specific measures. The PAID20 is a brief measure of DM-related distress with items scored on a Likert scale of 0 to 4.[36] The total PAID score is transformed to a 0 to 100 scale with higher scores indicating higher distress. Mean scores were compared to a reference population of Dutch adult patients with type 1 DM.[36] The DTSQs is an 8-item measure of current satisfaction with DM treatment, including 2 items pertaining to perceived hyper- and hypoglycemia. The maximum overall satisfaction score is 36.[37] The Hypoglycemia Fear Survey-II evaluates hypoglycemia-related fear and comprises 2 subscales, the behavior- and worry-scale. Only the worry-scale consisting of items that describe concerns that patients may have about hypoglycemic episodes was analyzed.[38]

Statistical analysis

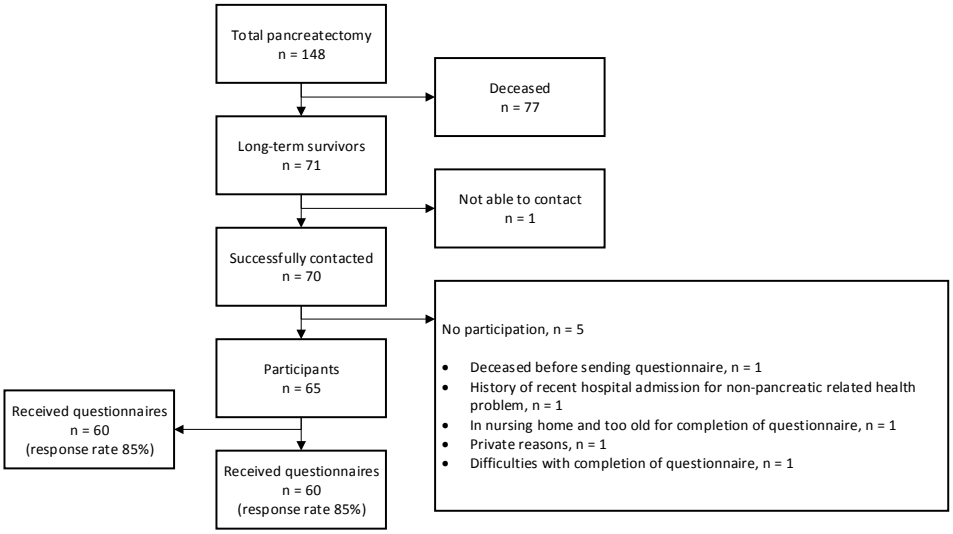
IBM SPSS version 24 (IBM Corporation, Armonk, NY) was used to analyze all data. Data on baseline characteristics and postoperative outcomes were presented for all patients, while data on QoL are presented only for patients who completed the required questionnaires. Normally distributed continuous variables were presented as means with standard deviations and non-normally distributed as medians with IQR. Categorical data were presented in frequencies with percentages. To evaluate differences between malignant and nonmalignant disease and between QoL scores of TP patients and with reference groups (eg, the general population, patients after pancreatoduodenectomy, or patients with type 1 DM), the *t* test, one-way analysis of variance, Kruskal-Wallis, or Mann-Whitney *U* test were used. Time trends in volumes of TP per year and in indications for TP were analyzed with the χ^2 for trend. Associations between period of diagnosis or center volume with major morbidity or mortality were analyzed with the χ^2 test. Centers were categorized in high or low-volume centers according to 2 strategies, (1) the 6 centers with the greatest volumes of TP were high-volume centers and the 5 centers with the least volumes were low-volume centers, and (2) centers with ≥20 TPs in the total study period were high-volume centers, and centers with <20 TPs were low-volume centers. Sensitivity analyses included assessment of QoL based on duration of follow-up (<3, ≥ 3, 3-5 or >5-year follow-up). These

cut-off points were selected to create sufficiently large groups. A second sensitivity analysis was performed by excluding patients who underwent an elective completion TP. A Kaplan-Meier analysis was used to assess overall survival in patients with IPMN and pancreatic ductal adenocarcinoma and compared using the log-rank test.

RESULTS

Between 2006 and 2016, 148 patients had undergone elective primary (n=136) or elective completion (n=12) TP with an overall median follow-up of 18 months (IQR 11-37). During the time period of this study, 77 patients (52%) had died with a median survival of 12 months (IQR 10-14, Fig 1). All 71 surviving patients were contacted, and 65 agreed to participate in the QoL assessment. Finally, 60 patients with a median follow-up of 36 months (IQR 21-56, range 6-113) completed and returned the questionnaires (response rate 85%). Overall, 38 patients (26%) had a follow-up greater than 3-years, 20 patients (14%) had a follow-up from 3-5 years, and 18 patients (12%) had a follow-up >5-years.

FIGURE 1. Flow diagram: patient selection for the assessment of long-term quality of life.



Patient characteristics

The annual volume of TP increased from 5 in 2006 to 32 in 2015 annually (*P* trend = 0.005). No trend over time was shown for type of indication for TP (pancreatic ductal adenocarcinoma versus IPMN *P* trend = 0.84 and malignant versus nonmalignant disease *P* trend = 0.73). Baseline characteristics are shown in Table 1. In 64% of all 148 patients, TP was performed for malignant disease and in 36% for nonmalignant disease

TABLE 1. Baseline characteristics of 148 patients after TP Including 60 patients with assessment of long-term QoL.

Clinical values	All TP patients (n=148)	Long-term TP patients (n=60)	Malignant (n=95)	Non-malignant (n=53)
Male, n (%)	82 (55)	28 (47)	52 (55)	30 (57)
Age at operation, median (IQR, range), years	65 (57-71, 27-85)	64 (57-68, 27-85)	65 (57-73, 35-85)	65 (57-70, 35-85)
Body mass index, mean (SD), kg/m²	24.5 (4)	24.4 (4)	24.5 (4)	24.3 (4)
American Society of Anesthesiologist class, n (%)				
1	21 (14)	14 (23)	11 (12)	10 (19)
2	84 (57)	30 (50)	56 (59)	28 (53)
3	41 (28)	14 (23)	26 (27)	15 (28)
4	2 (1.4)	2 (3)	2 (2)	-
Smoking, n (%)	47 (32)	12 (20)	32 (34)	15 (28)
Alcohol, n (%)	63 (43)	21 (35)	44 (46)	19 (36)
First symptoms, n (%)				
Abdominal pain	34 (23)	16 (27)	18 (19)	16 (30)
Weight loss	6 (4)	2 (3)	4 (4)	2 (4)
Nausea	2 (1)	1 (2)	1 (1)	1 (2)
Steatorrhea	6 (4)	3 (5)	4 (4)	2 (4)
Jaundice	23 (16)	5 (8)	21 (22)	2 (4)
New-onset diabetes mellitus	1 (1)	1 (2)	-	1 (2)
Tired	3 (2)	2 (3)	2 (2)	1 (2)
Anemia	3 (2)	2 (3)	1 (1)	2 (4)
No symptoms	27 (18)	14 (23)	11 (12)	16 (30)
> 1 symptom	40 (27)	11 (18)	31 (33)	9 (17)
Missing	3 (2)	2 (3)	2 (2)	*1 (2)*
Elective primary TP, n (%)	136 (92)	54 (90)	89 (94)	47 (89)
Elective completion TP, n (%)	12 (8)	6 (10)	6 (6)	6 (11)
Recurrence	11 (92)	6 (100)	6 (100)	5 (83)
Prophylactic (MEN-1 syndrome)	1 (8)	-		1 (17)
Type of operation, n (%)				
Open	144 (97)	56 (93)	94 (98)	50 (94)
Laparoscopic	4 (3)	4 (7)	1 (1)	3 (6)
Neoadjuvant therapy[a], n (%)	6/95 (6)	2/24 (8)	6/95 (6)	NA
FOLFIRINOX	2 (33)	1 (50)	2 (33)	
Gemcitabine	3 (50)	1 (50)	3 (50)	
Chemoradiation	1 (17)	-	1 (17)	
Missing	1	1	1	

Preoperative diabetes mellitus (type 1 and 2), n (%)	60 (41)	19 (32)	39 (41)	21 (39)
Use of insulin	10 (17)	3 (16)	9 (23)	1 (5)
Use of oral medication	33 (55)	9 (47)	22 (56)	11 (52)
Combination	17 (28)	7 (37)	8 (21)	9 (43)
Preoperative enzyme supplementation, n (%)	23 (16)	10 (17)	14 (15)	9 (17)
Marital status, n (%)				
Married		47 (78)	19 (79)[b]	28 (78)[b]
Widowed		8 (13)	3 (13)[b]	5 (14)[b]
Separated/divorced		5 (8)	2 (8)[b]	3 (8)[b]
Education level, n (%)				
Primary education		4 (7)	2 (8)[b]	2 (6)[b]
Vocational education		27 (45)	8 (33)[b]	19 (53)[b]
Secondary education		12 (20)	5 (21)[b]	7 (19)[b]
Higher education		17 (28)	9 (38)[b]	8 (22)[b]

NA, not applicable; IQR, interquartile range; SD, standard deviation; TP, total pancreatectomy; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin. [a] Only patients with malignant disease (n = 95 for all patients and n = 24 for long-term TP patients). [b] Only patients with completed questionnaires (n=24 for malignant disease and n=36 for non-malignant disease).

Postoperative outcome and survival

Major morbidity occurred in 48 patients (32%, Table 2). The 30-day mortality and 90-day mortality after TP were 5% and 8%, respectively. The cause of 90-day mortality was related to the operation in 9 patients (75%), disease-related in 2 patients (17%), and 1 patient died because of a hypoglycemic coma on postoperative day 21 (8%). The operation-related causes of death were multi-organ failure (n = 1), hemorrhagic shock due to a splenic artery bleeding (n = 1), infected chyle leak (n = 1), hepaticojejunostomy leak (n = 1), intestinal ischemia (n = 4), and in 1 patient the cause of death was unknown. Major morbidity and 30-day and 90-day mortality did not differ between periods in this study and between low volume centers (5 centers, median TPs 2 [range 1-4] during the study period) and high volume centers (6 centers, median TPs 12 [range 11-24] during the study period; Supplementary Table 1). Patients with nonmalignant disease had less blood loss during the operation compared to patients with malignant disease (1300 mL vs. 750 mL, *P*=0.022). Postoperative outcomes were essentially comparable for patients with malignant and nonmalignant disease, except for major complications and chyle leakage, the rates of which were greater in patients with malignant disease (38% vs. 21%, *P*=0.032 and 14% vs. 0%, *P*=0.03 respectively).

TABLE 2. Operative and pathology outcomes in 148 patients after TP including 60 patients with assessment of long-term QoL.

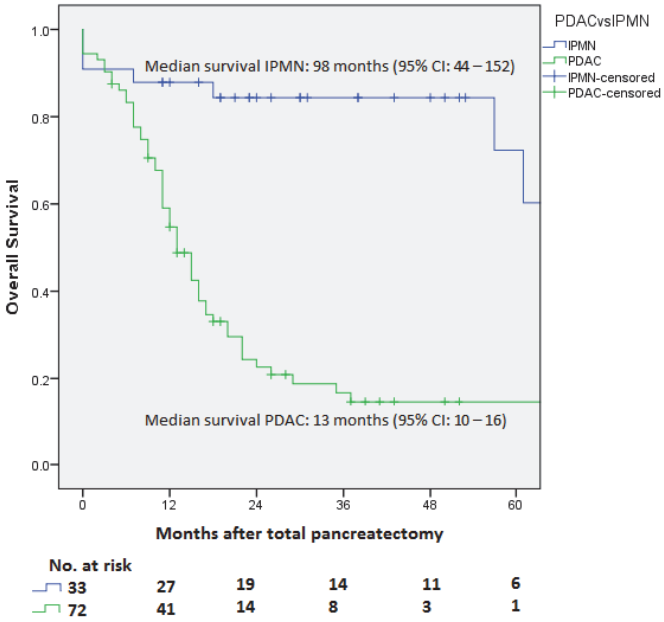
Operative and pathology outcomes	All TP patients (n=148)	Long-term TP patients (n=60)	Malignant (n=95)	Non-malignant (n=53)	P-value
Pathology, n *(%)*					
Pancreatic ductal adenocarcinoma	72 (49)	11 (18)	72 (76)		
Renal cancer metastasis	4 (3)	3 (5)	4 (4)		
Invasive IPMN	11 (7)	8 (13)	11 (12)		
Duodenal carcinoma	1 (1)	1 (2)	1 (1)		
Ampullary carcinoma	3 (2)	-	3 (3)		
Cholangiocarcinoma	4 (3)	1 (2)	4 (4)		
pNET	7 (5)	5 (8)		33 (62)	
Pancreatitis	8 (5)	4 (7)		8 (15)	
IPMN	33 (22)	23 (38)		4 (8)	
Serous cystadenoma	4 (1)	4 (7)		4 (8)	
MEN-1 syndrome	1 (1)	-		1 (2)	
Procedure time, hours, mean (SD)	5.9 (2.5)	5.3 (2.4)	6.0 (2.4)	5.7 (2.7)	0.671
Missing, n	9	5	6	3	
Blood loss, median (IQR), ml	1000 (100-2156)	550 (6-1300)	1300 (250-2500)	750 (5-1350)	**0.022**
Missing, n	16	5	12	4	
Splenectomy, n (%)	67 (45)	22 (37)	45 (47)	22 (42)	0.258
Resection margins[a], n (%)				NA	
R0, > 1 mm	66 (69)	21 (88)	66 (69)		
R1, < 1 mm	25 (26)	2 (8)	25 (26)		
R2	2 (2)	-	2 (2)		
Missing	2 (2)	1 (4)	2 (2)		
pT stage, n (%)[a]				NA	
Not applicable	25 (26)	8 (33)	25 (26)		
1	2 (2)	2 (8)	2 (2)		
2	14 (15)	5 (21)	14 (15)		
3	41 (43)	6 (25)	41 (43)		
4	9 (10)	2 (8)	9 (10)		
Missing	4 (3)	1 (4)	4 (3)		
pN1 stage, n (%)[a]	48 (50)	7 (29)	48 (50)	NA	
Adjuvant chemotherapy[a], n (%)	46 (48)	13 (54)	46 (48)	NA	

Major complications, Clavien-Dindo grade ≥ 3, n (%)	48 (32)	13 (22)	36 (38)	11 (21)	**0.032**
Clavien-Dindo Grade 3	29 (20)	11 (18)	22 (23)	7 (13)	
Clavien-Dindo Grade 4	9 (6)	2 (3)	9 (10)	-	
Clavien-Dindo Grade 5	10 (7)	0	6 (6)	4 (8)	
Postpancreatectomy hemorrhage, grade B/C, n (%)	7 (5)	3 (5)	3 (3)	4 (8)	0.228
Postoperative bile leak, grade B/C, n (%)	4 (3)	2 (3)	3 (3)	1 (2)	0.648
Postoperative chyle leak, grade B/C, n (%)	8 (5)	2 (3)	8 (14)	-	**0.030**
Delayed gastric emptying, grade B/C, n (%)	20 (14)	9 (15)	13 (14)	7 (13)	0.935
Duration of hospital stay, days, median (IQR)	16 (12-22)	13 (10-19)	16 (12-21)	15 (11-22)	0.851
New-onset diabetes mellitus, n (%)[b]	87 (57)	40 (67)	56 (59)	31 (58)	0.957
Postoperative enzyme supplementation for EPI, n (%)	130 (88)	54 (90)	83 (87)	47 (89)	0.753
30-day mortality, n (%)	8 (5)	0	5 (5)	3 (6)	0.918
90-day mortality, n (%)	12 (8)	0	8 (8)	4 (8)	0.852

IPMN, intraductal papillary mucinous neoplasm; pNET, pancreatic neuroendocrine tumor; EPI, exocrine pancreatic insufficiency; NA, not applicable; IQR, interquartile range; SD, standard deviation. Bold numbers indicate statistical significance. [a] Only patients with malignant disease (n = 95 and n=24). [b] One patient did not develop new-onset DM due to pancreatic transplantation.

Overall survival is shown in Fig 2 for pancreatic ductal adenocarcinoma and IPMN, excluding patients with invasive IPMN (n = 11). The 3-year survival rate was 18% for pancreatic ductal adenocarcinoma and 84% for IPMN. In total, 8 patients with IPMN died within our follow-up period. Three patients died within 30 days after the TP, all by operation-related causes (hemorrhagic shock due to splenic artery bleeding, intestinal ischemia, and unknown). Two other patients died of renal failure due to chronic renal insufficiency (61 months after TP) and a myocardial infarction (57 months after TP). Causes of death of the 3 remaining deceased patients with IPMN could not be retrieved. Within the group of patients with pancreatic ductal adenocarcinoma, no difference in survival was seen for T-stage 2, 3, or 4 (median overall survival 15 months [IQR 7-23], 12 months [10-14], and 13 months [8-18], p=0.891, respectively).

FIGURE 2. Overall survival after total pancreatectomy.



Overall survival of patients with pancreatic ductal adenocarcinoma and IPMN, excluding patients with invasive IPMN. IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma.

Use of enzyme supplementation increased from 16% before TP to 88% before discharge (Tables 1 and 2). Preoperative DM was present in 60 patients (41%), while after TP, new-onset DM developed in 87 patients (57%). One patient did not develop new-onset DM due to undergoing a pancreatic autologous islet transplantation.

Long-term QoL

Characteristics of the 60 patients in whom QoL could be assessed are given in Tables 1 and 2. The mean daily health status (0-100 thermometer, EQ-5D-5L) as rated by patients was 76 (±15) and was worse compared to the mean daily health status of 82 (±0.4, $P < 0.01$) in the general population as well as the mean daily health status in the same age category (55-64 years), mean 80.7 (±1.0, $P < 0.01$). The EQ-5D-5L index score (median 0.83 [IQR 0.73-0.92], mean 0.81 ± 0.16) was also less compared to the mean index score of the Dutch population index score (0.87 ± 0.17, $P < 0.01$, Table 3), but was not different when compared to Dutch patients ≥60 years (this comparison to Dutch patients ≥60 years was more equivalent to the median age of 64 in our cohort). The median QoL index rates did not differ between patients with preoperative or new-onset DM (0.85 vs. 0.83 $P = 0.93$), malignant or nonmalignant disease (0.80 vs. 0.84, $P = 0.44$), or pancreatic ductal adenocarcinoma, IPMN, or invasive IPMN (0.78 vs. 0.84 vs. 0.86, $P = 0.33$).

TABLE 3. EuroQoL EQ-5D-5L index scores in 60 patients after TP.

Groups	n	Index score (median)	IQR	*P*
Overall group	60	0.83	0.73 – 0.92	
Overall group, mean	60	0.81	0.16 (SD)	
Dutch population[a], mean	979	0.87	0.17 (SD)	**<0.05**
Dutch population (≥60 years)[a], mean	158	0.84	0.18 (SD)	0.26
< 3 years after TP	30	0.80	0.74 – 0.92	0.42
≥ 3 years	30	0.84	0.73 – 1.00	
3-5 years after TP	20	0.87	0.75 – 1.00	
> 5 years after TP	10	0.81	0.69 – 0.87	
Malignant	24	0.80	0.73 – 0.92	0.44
Non-malignant	36	0.84	0.74 – 0.98	
Pancreatic ductal adenocarcinoma	13	0.78	0.63 – 0.88	0.33
IPMN	23	0.84	0.77 – 1.00	
Invasive IPMN	6	0.86	0.73 – 1.00	
Preoperative DM	19	0.85	0.63 – 1.00	0.93
New-onset DM	41	0.83	0.74 – 0.91	

IQR indicates inter quartile range; SD, standard deviation. Higher index scores means better QoL. Bold numbers indicate statistical significance. [a] Reference value of index scores for Dutch population.[31]

The cancer-specific QLQ-C30 questionnaire showed that the overall, mean, self-rated global health status after TP differed from the general population (73 ± 18 vs. 78 ± 17; *P* = 0.03). The functional and symptom scales are outlined in Fig 3 and compare TP patients with the general population (all ages and 60-69 years) and patients after pancreatoduodenectomy. Compared to the general population, patients after TP had more financial difficulties, diarrhea, appetite loss, insomnia, dyspnea, and fatigue. Symptoms were comparable to patients who underwent pancreatoduodenectomy except for financial difficulties, insomnia, and fatigue which were worse. TP patients with pancreatic ductal adenocarcinoma were also compared to patients with IPMN (Fig 3, C-D). Comparison of patients with and without preoperative DM showed no differences in global health status and physical or social functioning (data not presented).

Diabetes-specific outcomes

Of patients with QoL assessment, 19 patients (32%) had preoperative DM, 40 patients (67%) developed new-onset DM, and one patient did not develop DM due to pancreatic autologous islet transplantation. Results of the PAID20 showed that patients after TP experienced similar mean levels of diabetes-related distress as compared to a reference type 1 DM population (24 ±21 vs. 25 ±19).

According to the Hypoglycemia Fear Survey-II worry-scale, patients were rarely worried about not recognizing low glucose, hypoglycemia during the night, or when being alone (median score of 2 out of 5). In general, patients were satisfied with their DM treatment. The median of the DTSQs was 29 (IQR 22-32). In the weeks before answering the questionnaire, 13% of patients very often thought that their glucose level was too high, and 10% felt that their glucose level was too low.

Sensitivity analyses

Sensitivity analyses showed no differences in self-reported, global health status (QLQ-C30) and daily health status or the index score (EQ-5D-5L) based on time after TP (<3, ≥3, 3-5, or >5 years), suggesting a similar QoL (Table 4). This also applies for DM-related outcomes, i.e. treatment satisfaction (DTSQs) and emotional distress (PAID20). Patients after TP achieved their most optimal QoL within 3 years after the operation and maintained this level after >5 years follow-up. Overall outcomes remained similar (data not shown) when excluding patients with an elective completion TP (n=12).

FIGURE 3. Quality of life after TP.

FIGURE 3A. QLQ-C30 Functional scales in TP patients versus the general population (all ages and 60-69 years).

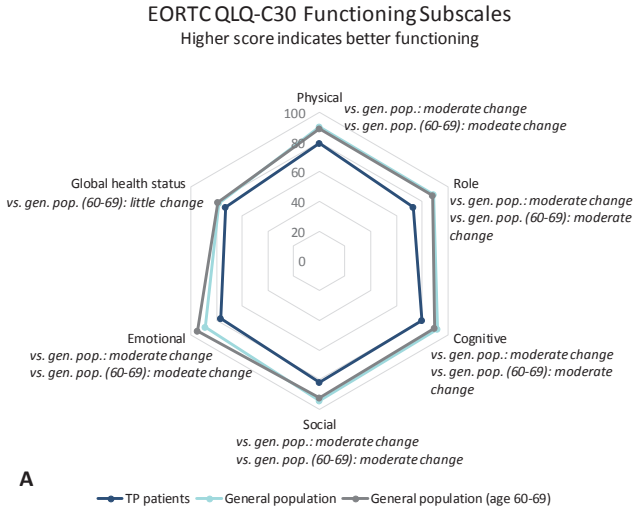


FIGURE 3B. QLQ-C30 Symptom scales in TP patients versus the general population (all ages and 60-69 years).

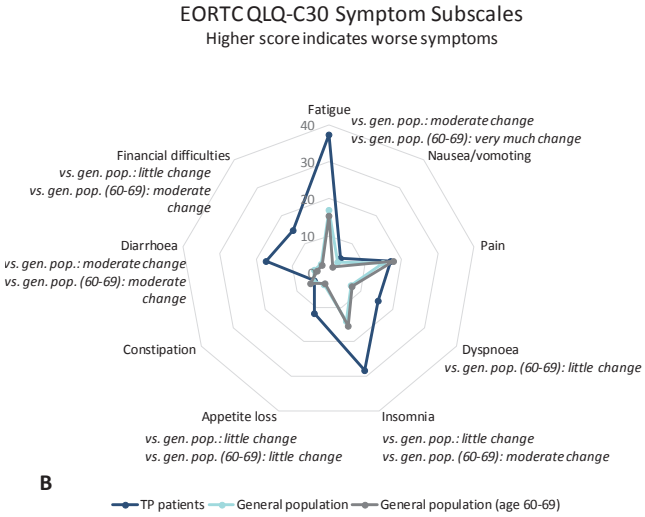
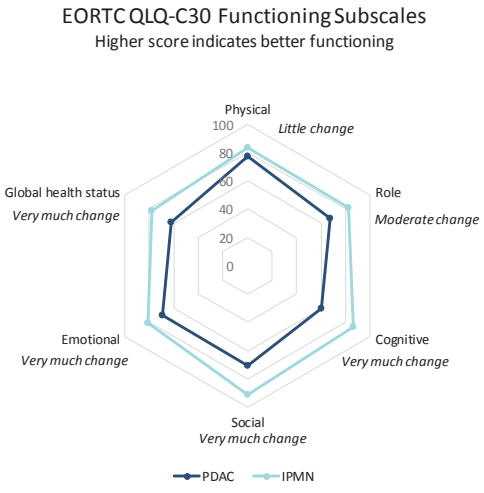


FIGURE 3C. QLQ-C30 Functional scales in pancreatic ductal adenocarcinoma patients versus IPMN patients.

FIGURE 3D. QLQ-C30 Symptom scales in pancreatic ductal adenocarcinoma patients versus IPMN patients.



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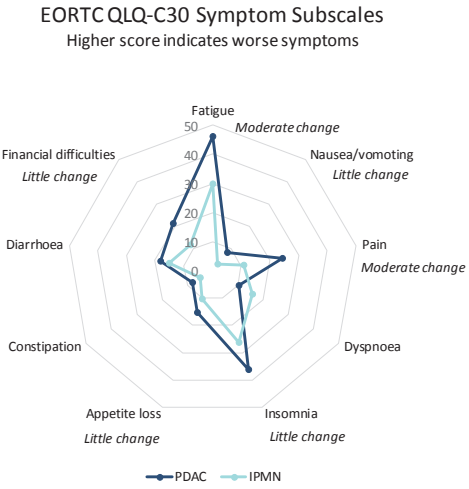

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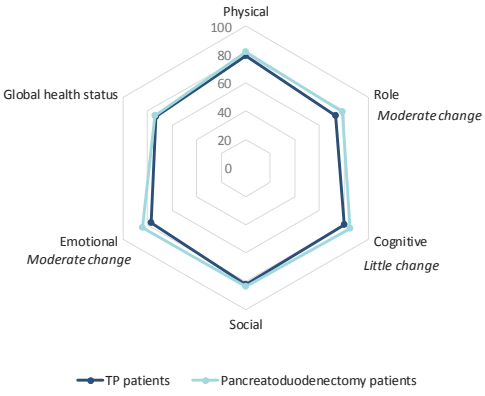
FIGURE 3E. QLQ-C30 Functional scales in TP patients versus patients one year after pancreatoduodenectomy.

FIGURE 3F. QLQ-C30 Symptom scales in TP patients versus patients one year after pancreatoduodenectomy.



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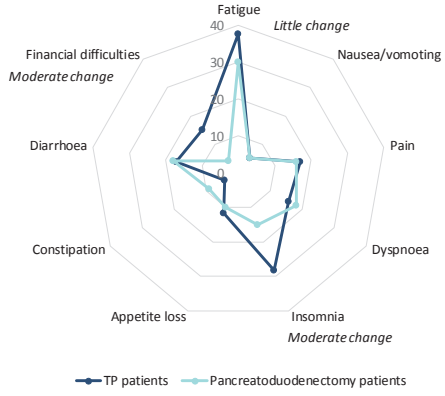

F

* Little change is 5-10% difference, moderate change is 10-20% difference, very much change is >20% difference.[35]
# Reference values of QLQ-C30 scores for healthy population from reference values manual and for patients after pancreatoduodenectomy from Heerkens et al.[33,34] † In functional subscales a higher score indicates better functioning and in symptom subscales a higher scores indicates worse symptoms.

TABLE 4. Quality of life after TP stratified for duration of follow-up.

Patients	PAID 20 Median (IQR)	DTSQs Median (IQR)	QLQ-C30 - Global health status Mean, SD	EQ-5D-5L - Index score Median (IQR)	EQ-5D-5L - Daily health status Mean, SD
All patients (n=60)	Mean 23 (SD ±20) Med. 15 (7.5-37.5)	Mean 27 (SD ±7) Med. 29 (22-32)	73, ±18	Mean 0.81 (SD ±0.16) Med. 0.83 (0.73-0.92)	76, ±15
<3 years after TP (n=30)	14 (8-40)*	28 (21-32)*	71, ±20	0.80 (0.74-0.92)	75, ±14
≥3 years after TP (n =30)	20 (5-38)	30 (24-32)	74, ±17	0.84 (0.73-1.0)	76, ±16
3-5 years after TP (n=20)	20 (5-44)	30 (23-32)	73, ±19	0.87 (0.75-1.0)	76, ±16
>5 years after TP (n=10)	18 (6-37)	31 (24-33)	79, ±11	0.81 (0.69-0.87)	77, ±16
P-value^	0.87	0.54	0.49	0.42	0.78

IQR, interquartile range; SD, standard deviation; Med., median. * One patient did not develop DM. ^ Comparison between the < 3 and ≥ 3 years follow-up periods.

DISCUSSION

This first nationwide multicenter study on TP found an 8% 90-day mortality and a worse, self-rated, global health status compared to a reference population, involving more symptoms and functional complaints. Patients were, however, satisfied with their DM therapy and had similar DM-related distress as patients with type 1 DM. No differences in QoL within 3 years or >3 years after TP were detected.

As expected, global health status (QLQ-C30) and mean daily health status (EQ-5D-5L) were statistically worse in patients after TP compared to the general population (compared to both overall and age-specific reference scores). QoL in terms of functional and symptom scales (QLQ-C30) and the mean index score of the EQ-5D-5L were also somewhat worse in TP patients, except for the mean index score compared to Dutch patients ≥ 60 years; however, the clinical importance of these small differences is difficult to ascertain and warrants further research. The global health status (QLQ-C30) for patients after TP for malignant or nonmalignant indications was nearly similar to a recent study on TP.[20] Comparable to our results Hartwig et al[17] found, in a large single-center study, lower scores for functioning and symptom scales but only in patients with malignant disease. Although the QLQ-C30 found a difference in global health status between patients with pancreatic ductal adenocarcinoma and IPMN, the EQ-5D-5L daily health status was similar in both groups. This difference may be due to the different methods of measuring the health status in the 2 questionnaires. EQ-5D-5L results were reported only in a single center study comparing TP and pancreatoduodenectomy for both malignant and non-malignant disease.[18] This study showed that the 35 patients after TP had a mean score of 0.87 compared to 0.83 in 84 patients after pancreatoduodenectomy. These findings were comparable to the mean score of

0.81 in 60 patients after TP in the present study. QoL measured by the QLQ-C30 was better in patients operated for IPMN compared to pancreatic ductal adenocarcinoma, probably because patients are aware of their poor overall chance of survival. Outcomes of TP appeared to be similar between all different time periods (<3, ≥3, 3-5, or >5 years) after TP. Nevertheless, QoL after 3 and 5 years was only measured in relatively few patients, and results should be interpreted with caution. The QoL results are important for clinicians and patients in the context of shared-decision making in daily clinical practice.

Historically, the bad reputation of so-called brittle DM treatment has been one of the main reasons to avoid TP, whereas more recent studies described marked improvement of treatment options for DM in patients after TP.[9–11] We found no indication that DM distress is greater among patients after TP compared to patients with type 1 DM. Moreover, patients after TP are satisfied with their DM treatment, with a mean DTSQs of 27 (±7). This score is comparable to Nicolucci et al[39] who found a mean score of 30.1 (±5.1) in patients with continuous, subcutaneous insulin infusion and 26.2 (±6.1) in patients with multiple daily injections. These are promising results for patients who have an indication for TP because of IPMN, because these patients are not eligible for islet auto-transplantation. Moreover, islet auto-transplantation is not commonly performed in the Netherlands. The long-term risks of DM, however, are considerable and not to mention that 1 patient died during the postoperative period of a hypoglycemic coma. Data on causes of death after the postoperative period were not available, so it is unknown whether more hypoglycemia related deaths occurred in the long-term follow-up. Treatment of brittle diabetes also depends on the experience of the endocrinologist treating patients after TP. Probably, the most specialized endocrinologists for patients after TP are located in pancreatic surgery centers. During the study, insulin pumps and continuous glucose monitoring were used increasingly and might have decreased the frequency of hypoglycemic episodes after TP. The closed-loop insulin system is not yet available in the Netherlands.[40] Despite new technologies, low distress, and treatment satisfaction, therapeutic consequences and long-term sequelae of the obligate apancreatic state should still be considered as a serious consequence of TP, especially because at least 1 patient died of hypoglycemia in the current series.

Exocrine pancreatic insufficiency appeared to be undertreated, because only 88% of patients received pancreatic enzyme replacement therapy prior to discharge. This treatment may have been started after hospital discharge when oral intake had been fully resumed, but it is known that exocrine insufficiency is often undertreated.[41] Notably, in our cohort, >17% of patients had complaints of diarrhea (QLQ-C30), which might be caused by exocrine insufficiency; the diarrhea could also have other causes (eg, neurologic damage due to the operation). It could cautiously be speculated that little emphasis is given to the treatment of exocrine insufficiency in patients after TP. To achieve optimal enzyme replacement

therapy, clinicians should start with a prescription followed by referral to a dietician to help with correct dosage and to emphasize the importance of compliance.

Endocrine and exocrine insufficiency were present preoperatively in 41% and 16% of patients, and could have influenced QoL. Because no baseline QoL was measured, we could not assess whether this influenced QoL in our cohort. We can only speculate whether QoL recovers quickly postoperatively, similar to patients after partial pancreatectomy.[34]

Compared to earlier multicenter studies that reported on the outcome after TP, the 30-day mortality in this study is somewhat less (5% vs 8.5%-17.9%).[37–39] Only Datta et al [9] reported a lesser 1.6% 30-day mortality after TP. These earlier multicenter studies did not report on 90-day mortality. The present study found a 90-day mortality of 8%, which is comparable to some single-center series (0-20%).[6,8,9,11,42–44] Some investigators assume better short-term results of TP than after a partial pancreatectomy, because no pancreato-enteric anastomosis is performed. Van Roessel et al reviewed single-center studies with at least 500 consecutive pancreatoduodenectomies and showed that 30-day mortality or in-hospital mortality was considerably less than in our cohort of patients after TP.[45] Especially because TP is often performed for suspected malignant disease or is also performed even prophylactically, it could be argued that the mortality rates in our cohort are unacceptable. In our series, 3 of the 33 patients with IPMN died in the 30 days postoperatively. Therefore, the indication for TP should be well-considered. Potentially, mortality rates could be decreased by centralization. Our study showed no difference for being operated in centers with a relatively high-volume compared to centers with relatively low-volumes, but there was a trend toward a lesser 90-day mortality in the high-volume centers. A clear effect probably lacks, because even in the hospital with the highest volume, only 24 TPs were performed during the total study period of 10 years, which results in a very low annual volume. Unfortunately, little data about the cause of death after the period of hospitalization was available of the patients with IPMN who died on the long-term.

Major morbidity occurred in 32% of patients in the present study which was comparable to the rate of major complications after pancreatoduodenectomy.[46,47] This percentage is also largely comparable with current literature on TP.[11,20,48] Reddy et al[49] found that 41% of patients undergoing TP for pancreatic cancer developed a Clavien-Dindo complication score ≥ 3 , which is comparable to the 38% after TP for pancreatic cancer in this study. Patients who underwent TP for non-malignant disease had fewer major complications, but long-term DM and QoL outcomes were comparable. This finding is important to consider when making the decision to perform TP in patient with non-malignant disease. Even more

important, however, is the 90-day mortality which though not different between the groups was still quite high (malignant- 8/95 patients, 8% and non-malignant 4/53 patients, 8%).

Our study also confirmed the apparent increased tendency to perform TP in more recent years in the Nethererlands.[17] The trend was not explained by a change in indications, because the ratio of TPs for malignant versus non-malignant or specifically pancreatic ductal adenocarcinoma versus IPMN was constant over time. It might be related to previously described improved short- and long-term postoperative outcomes.[12–14] It could also be speculated that the incidence of TP increased due to the belief by the surgeons that TP would avoid the complications of postoperative pancreatic fistula after extended resections with vascular reconstructions, which were increasingly performed during the study period.

Because of the complications and 90-day mortality of TP, other surgical treatment options should also be considered before performing TP in patients with non-malignant disease; pancreatoduodenectomy or even parenchyma-sparing resections should at least be discussed. Beger et al[50] showed that parenchyma-sparing pancreatic head resections in patients with premalignant or selected, low grade malignancies had low postoperative morbidity and was associated with histopathologically complete tumor resection. In contrast, for patients with main-duct IPMN with involvement of the entire pancreatic duct or multiple nodules in the pancreatic duct, TP is the recommended treatment.

Our study had several limitations. First, this was a retrospective study, which could have led to incomplete data retrieval, however, because the emphasis in this study was (current) QoL obtained with questionnaires and data on survival were obtained via the Dutch municipal personal records, the loss of data was presumably small. Second, patients were operated over a 10-year period during which the surgical procedure and postoperative care has improved. Such a large time-span is essentially inherent to the relative rarity of the operation of TP in this nationwide cohort. A shorter inclusion period could have been obtained with the participation of only very high-volume centers, but this approach would have affected the generalizability of our results, which now reflect daily clinical practice in the Netherlands. Third, this study would have been more informative if a baseline QoL assessment with a prospective follow-up was performed; such a design would have allowed us to compare QoL before and after TP, but also would have meant we could have assessed QoL in patients who already died at the time we performed the present study, because their QoL was undoubtedly worse. Last, the effect of DM treatment was measured by subjective reports, which though appropriate for QoL purposes, lacked objective information, (eg, average daily doses, HbA1c levels, and the status of DM complications).

The strengths of this study include the nationwide, multicenter design, resulting in a relatively large sample size with an acceptable response rate and the use of well-validated and multiple questionnaires. Moreover, this is the first nationwide study to assess long-term QoL after TP. Previous studies on QoL after TP were all single-center studies with a median of 28 patients (IQR 24-39) and a follow-up ranging from 23 to 104 months.[8,10,11,14,17–22]

In conclusion, this nationwide cohort study found that in long-term survivors after TP, the reported QoL was worse compared to a healthy reference population of all ages. The differences, though, were small and the clinical relevance is unknown. The global health status showed no difference in patients after TP when compared to patients one year after pancreatoduodenectomy, despite slightly more symptoms and functional complaints. Rather concerning, however, was the 90-day mortality of 8% which is high compared to mortality rates after pancreatoduodenectomy in high-volume centers. DM-related QoL and distress were comparable to patients with type 1 DM. The data from this study enrich the information which can be provided to patients and their relatives to facilitate shared decision-making when faced with the decision to undergo TP, but also shows that there is room for improvement of postoperative outcomes.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1. Differences in major morbidity and mortality between period of diagnosis in patients diagnosed in high- of low-volume centers.

		Major complications		30-day mortality		90-day mortality	
	n	Percentage	p-value	Percentage	p-value	Percentage	p-value
2006-2010	34	32%	0.998	6%	0.795	9%	0.921
2011-2015	105	32%		5%		8%	
Centers with lowest volume	5 centers 13 patients	23%	0.679	0%	0.441	15%	0.183
Centers with highest volumes	6 centers 91 patients	29%		4%		6%	
Low-volume <20 patients	15 centers 123 patients	33%	0.620	6%	0.733	10%	0.280
High-volume ≥20 patients	2 centers 25 patients	29%		4%		4%	

CHAPTER 10

Clinical outcomes after total pancreatectomy: a prospective multicenter pan-European snapshot study

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Annals of Surgery. 2020 Nov 9.

ABSTRACT

Objective: To assess outcomes among patients undergoing total pancreatectomy (TP) including predictors for complications and in-hospital mortality.

Background: Current studies on TP mostly originate from high-volume centers and span long time periods and therefore may not reflect daily practice.

Methods: This prospective pan-European snapshot study included patients who underwent elective (primary or completion) TP in 43 centers in 16 European countries (June 2018-June 2019). Subgroup analysis included cut-off values for annual volume of pancreatoduodenectomies (<60 vs. ≥60). Predictors for major complications and in-hospital mortality were assessed in multivariable logistic regression.

Results: In total, 277 patients underwent TP, mostly for malignant disease (73%). Major postoperative complications occurred in 70 patients (25%). Median hospital stay was 12 days (IQR 9-18) and 40 patients were readmitted (15%). In-hospital mortality was 5% and 90-day mortality 8%. In the subgroup analysis, in-hospital mortality was lower in patients operated in centers with ≥60 pancreatoduodenectomies compared <60 (4% vs. 10%, p=0.046). In multivariable analysis, annual volume <60 pancreatoduodenectomies (OR 3.78, 95%CI 1.18-12.16, p=0.026), age (OR 1.07, 95%CI 1.01-1.14, p=0.046), and estimated blood loss ≥2L (OR 11.89, 95%CI 2.64-53.61, p=0.001) were associated with in-hospital mortality. ASA ≥3 (OR 2.87, 95%CI 1.56-5.26, p=0.001) and estimated blood loss ≥2L (OR 3.52, 95%CI 1.25-9.90, p=0.017) were associated with major complications.

Conclusion: This pan-European prospective snapshot study found a 5% in-hospital mortality after TP. The identified predictors for mortality, including low-volume centers, age, and increased blood loss, may be used to improve outcomes.

INTRODUCTION

Total pancreatectomy (TP) is mostly performed for diseases involving the entire pancreas, for example, main duct intraductal papillary neoplasm (IPMN), chronic pancreatitis, or pancreatic cancer.[1–3] There is, however, a reluctance to perform TP, because of high postoperative mortality, and the resulting life-long endocrine and exocrine pancreatic insufficiency.[4,5]

Current data on major morbidity and in-hospital mortality after TP are conflicting. A recent systematic review reported that overall morbidity ranged from 36% to 69% and mortality from 0% to 27%.[6] In contrast, a study that only included patients from 2 high-volume centers reported a low 2.1% 30-day mortality after TP in the years 2000-2014.[7] These study results are clearly heterogeneous and may not reflect current practice in recent years. Furthermore, the influence of center volume is unclear. This lack of data is inherent to the fact that TP is a relatively rare procedure. To properly inform patients, reliable and recent real-world data are required.

The relatively new snapshot study is a cross-sectional study design which enables an actual insight into current practice by collecting data in a short period of time in a large number of centers and therefore creates greater generalizability than randomized controlled trials or longitudinal studies.[8,9] Snapshot studies are based on collaborative research and supported by the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). The aim of this pan-European snapshot study was to assess short-term postoperative outcomes after elective TP.

METHODS

Patients and design

A prospective multicenter pan-European study was conducted according to the snapshot design. The aim was to collect a large dataset in a short time period using collaborative research and to create greater generalizability than single-center studies running over longer periods of time.[8,9] All members of the European-African Hepato-Pancreato-Biliary Association were invited to participate. The participating centers included all consecutive patients who underwent elective TP for either malignant or non-malignant disease between June 1, 2018 until June 30, 2019. Patients undergoing elective primary TP, elective completion (after a previous partial pancreatic resection) TP, and in whom an intraoperative decision to extend the planned resection to TP were included. Patients who underwent TP in an emergency setting were excluded. This study is reported in accordance with the STROBE guidelines.[10] The ethics committee of the University Hospital of Guadalajara, Spain waived the need for informed consent.

Data collection and definitions

Patient data were collected locally through an online electronic case report form in CASTOR (CIWIT B.V., Amsterdam). Baseline characteristics collected included sex, age, body mass index (kg/m2), previous abdominal surgery, comorbidity (pulmonary, cardiovascular, and gastrointestinal, and hepatic), American Society of Anesthesiologists (ASA) physical status, preoperative diabetes mellitus and neoadjuvant chemo(radio)therapy. Preoperative imaging was reviewed for tumor location and tumor involvement of vascular structures and other organs. Intraoperative outcomes were the type of surgery (open or minimally invasive), type of TP (elective primary, elective completion, intraoperative decision to perform TP), splenectomy, vein resection (portal vein or superior mesenteric vein), arterial resection (common or proper hepatic artery, accessory or aberrant hepatic artery, celiac trunk, or superior mesenteric artery), additional organ resection, estimated blood loss (including a categorical distribution in <2L and ≥2L), and operation time. Pathological outcomes were tumor origin, histology, resection margin, tumor differentiation, T-stage according to the 7th edition of AJCC TNM staging, and lymph node ratio.[11] Postoperative outcomes were collected up to 90 days postoperatively and during readmission when applicable. Collected outcomes included complications (ie, general and pancreas-specific complications), hospital stay (days), readmission, and mortality. Major postoperative complications were defined as a Clavien-Dindo (CD) score ≥3.[12] Pancreatic surgery-specific complications (only grades B and C) included delayed gastric emptying, post-pancreatectomy hemorrhage, and bile leakage and were defined by the International Study Group on Pancreatic Surgery.[13–16] Mortality is presented as in-hospital and 90-day mortality. In-hospital mortality was defined as a patient who deceased during the initial hospital stay or, in case of earlier discharge, within 30 days after TP. Use of adjuvant chemotherapy was recorded. Data about endocrine and exocrine pancreatic insufficiency were collected at 3 and 6 months postoperatively. Annual center volume was based on the mean annual volume of pancreatoduodenectomies in 2018 and 2019. High or lower-volume centers were defined based on two previously used cut-off values, specifically <40 (lower-volume) or ≥40 (high-volume), or <60 (lower-volume) or ≥60 (very high-volume) pancreatoduodenectomies annually.[17–19]

Systematic literature search

To compare our results to the current literature, PubMed was systemically searched for all published series which included at least 100 TPs, regardless of the study period and indication. Systematic reviews and studies with overlapping cohorts were excluded. Outcomes extracted per study included study period, study design, number of patients, indication, the percentages of complications, postpancreatectomy hemorrhage, bile leakage, delayed gastric emptying, mortality, and long-term survival. Outcomes were compared with our study results.

Statistical analysis

Baseline characteristics are presented using descriptive statistics and compared using the Students t-test, Mann Whitney U test, or Chi-square test, as appropriate. Subgroup analysis were performed to assess the clinical outcomes in patients diagnosed with IPMN, in patients operated in very high-volume, high-volume, and lower-volume centers (cut-offs based on annual volume 60 and 40 pancreatoduodenectomies), and in patients with elective TP compared with patients with an intraoperative decision to perform TP. Predictors within patient characteristics, hospital volume, and intraoperative outcomes for major complications or in-hospital mortality were identified in univariable logistic regression models. Variables with a p-value <0.10 in univariable analyses were entered in the multivariable regression models and backward step selection was used. The results are reported as odds ratio (OR) with corresponding 95% confidence interval (CI). All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

During the 13-month study period, 277 patients who underwent TP were prospectively included from 43 centers in 16 European countries. The patients had a median age of 68 years (IQR 57-73) and 161 (58%) were male (Table 1). Preoperative diabetes mellitus was present in 101 patients (37%). During the study period, the median number of TPs per hospital was 3 (IQR 2-6) and the median annual number of pancreatoduodenectomies was 32 (IQR 17-78). An annual center volume of ≥40 pancreatoduodenectomies was reached in 18 centers, which performed a total of 217 TPs (78%) with a median of 7 TPs (IQR 5-15) per center. An annual center volume of ≥60 pancreatoduodenectomies was reached in 14 centers, which performed 193 TPs (70%) with a median of 8 TPs (IQR 5-23) per center (eFigure 1).

Perioperative outcomes

Results on intraoperative, pathological, and postoperative outcomes are presented in Table 2-4. TPs were performed by an open approach in 265 patients (96%). Neoadjuvant chemotherapy was given to 42 patients (15%). Vein resection was performed in 58 patients (21%) and arterial resection in 12 patients (4%), both mostly for malignant disease.

Major complications were reported in 70 patients (25%) and mostly consisted of CD grade 3 complications (n=40, 57%). A postpancreatectomy hemorrhage occurred in 11 patients (4%), bile leakage in 17 patients (6%), and delayed gastric emptying in 20 patients (7%). Within 90 days after TP, 40 patients (15%) were readmitted of whom 15 patients (38%) had a complication with CD≥3. The median duration of readmission was 8 days (IQR 5-13). The in-hospital and 90-day mortality were 5%

(n=15) and 8% (n=21), respectively. Causes of death of the 6 patients who died after initial hospital stay but within 90 days, were aspiration pneumonia accompanied by a diabetic ketoacidosis, complication of a second operation for acute arterial ischemia of the lower limb, sepsis with multiorgan failure after start of chemotherapy, multiorgan failure due to cardiac decompensation, portal vein and superior mesenteric vein thrombosis, and early recurrence of pancreatic cancer. At final pathological diagnosis, 202 patients (73%) had malignant disease. Among all patients with adenocarcinoma, 113 received any type of adjuvant chemo(radio)therapy (63%). Patients with a CD score ≥3 had a lower percentage of receiving adjuvant chemo(radio)therapy compared the other patients (40% vs. 72%, p<0.001).

TABLE 1. Patient characteristics.

	All patients (n=277)
Male	161 (58%)
Age at operation, median (IQR), years	68 (57-73)
BMI, median (IQR), kg/m^2	24 (22-27)
Indication	
Adenocarcinoma	153 (55%)
IPMN	78 (28%)
Neuroendocrine tumor	9 (3%)
Chronic pancreatitis	14 (5%)
Mucinous cystic neoplasm	2 (0.7%)
Solid pseudopapillary neoplasm	2 (0.7%)
Other	18 (7%)
Missing	1
Previous abdominal surgery	150 (55%)
Missing	5
Comorbidity	
Cardiovascular	124 (45%)
Gastrointestinal and hepatic	47 (17%)
Pulmonary	31 (11%)
ASA score	
I	27 (10%)
II	160 (58%)
III	88 (32%)
IV	2 (1%)
Preoperative diabetes mellitus	101 (36%)
Insulin dependent	51 (50%)
Non-insulin dependent	42 (42%)
Unknown type	8 (8%)
Vascular contact on CT or MRI	72 (27%)
Missing	9
Additional organ involvement on CT or MRI	14 (5%)
Missing	9
Neoadjuvant therapy	42 (15%)
Chemotherapy	29 (69%)
Chemoradiotherapy	13 (31%)
Missing	1

Values are numbers with percentages within parentheses unless indicated otherwise. BMI indicates body mass index.

At 3 months follow-up, 256 patients were alive and questions regarding endocrine and exocrine insufficiency were completed in 238 patients (data were missing in 18 patients). New-onset diabetes mellitus was present in 157 patients (66%), and preoperative diabetes had worsened in 42 patients (16%) and was unchanged in 39 patients (16%). Pancreatic enzyme replacement therapy was given to 230 patients (97%).

TABLE 2. Intraoperative characteristics.

	All patients (n=277)
Type of surgery	
Open surgery	266 (96%)
Minimally invasive surgery	11 (4%)
Type of TP	
Intraoperative decision to perform TP	132 (48%)
Elective primary	127 (46%)
Elective completion	18 (7%)
Splenectomy	214 (77%)
Vein resection	58 (21%)
End-to-end anastomosis	33 (57%)
Wedge	18 (31%)
Segment resection, end-to-end anastomosis with graft	7 (12%)
Missing	4
Arterial resection	12 (4%)
Common or proper hepatic artery	5 (42%)
Superior mesenteric artery	4 (33%)
Accessory hepatic artery	2 (17%)
Celiac trunk	1 (8%)
Additional organ resection	
Partial gastrectomy (beyond Whipple)[a]	16 (6%)
Colon segment resection	2 (1%)
Extended right hemicolectomy	4 (1%)
Other	13 (5%)
Estimated blood loss, median (IQR), L	0.4 (0.3-0.8)
<2L	228 (93%)
≥2L	17 (6%)
Missing	32
Operation time, median (IQR), minutes	405 (303-499)
Missing	4

Values are numbers with percentages within parentheses unless indicated otherwise. [a] Subtotal gastrectomy or antrectomy.

Subgroup analysis

In the 41 patients who underwent TP because of IPMN, major complications occurred in 7 patients (17%), and both in-hospital and 90-day mortality was 0% (Table 5). Patients in high-volume centers (≥40 pancreatoduodenectomies annually) had similar postoperative outcomes compared with lower-volume centers, except for hospital stay (12 days (IQR 8-17) vs. 14 days (11-21), p=0.003). In very high-volume centers (≥60 pancreatoduodenectomies annually) postoperative major complications were similar compared with lower-volume centers but in-hospital mortality was lower (4% vs. 10% in lower-volume

centers, p=0.046), and 90-day mortality was 6% vs. 12%, respectively (p=0.073). There were no differences in outcomes between patients with elective primary TP compared with patients with an intraoperative decision to perform TP, except for diabetes-related hypoglycemia during initial hospitalization or readmission (9% vs. 20%, respectively, p=0.007). The group of 17 patients who underwent elective completion TP was too small to take into account in this subgroup analysis.

TABLE 3. Pathological outcomes.

		All patients (n=277)
Origin		
	Pancreas	241 (87%)
	Ampulla of Vater	15 (5%)
	Distal bile duct	6 (2%)
	Duodenum	2 (1%)
	Other[a]	13 (5%)
Malignant		202 (73%)
Histology		
	Adenocarcinoma	183 (66%)
	IPMN	41 (15%)
	Neuroendocrine tumor grade 1 and 2	15 (5%)
	Neuroendocrine tumor grade 3	-
	Chronic pancreatitis	14 (5%)
	Metastasis of renal cell carcinoma	10 (4%)
	Mucinous cystic neoplasm	1 (0.4%)
	Solid pseudopapillary neoplasm	1 (0.4%)
	Serous cystadenoma	1 (0.4%)
	Other	10 (4%)
IPMN[b]		
	Mixed type	17 (6%)
	Main duct	15 (5%)
	Side branch	6 (2%)
Missing		3
Resection margin[c]		
	R0	121 (60%)
	R1	74 (37%)
	R2	6 (3%)
Missing		1
Tumor differentiation[d]		
	Well differentiated	16 (9%)
	Moderately differentiated	89 (52%)
	Poorly differentiated	62 (36%)
	Undifferentiated	5 (3%)
Missing		11
T stage[d]		
	T1	15 (9%)
	T2	62 (39%)
	T3	79 (49%)
	T4	5 (3%)
Missing		22
Lymph node ratio[d], median (IQR)		0.08 (0-0.19)

Values are numbers with percentages within parentheses unless indicated otherwise. TNM staging is according to tumor origin and based on the 7th edition of AJCC TNM staging TNM classification. [a] Originating from kidney, stomach, vena cava inferior or gallbladder; [b] IPMN details are based on the preoperative CT or MRI; [c] Only in patients with malignant disease (n=202); [d] Only patients with adenocarcinoma (n=183).

TABLE 4. Postoperative outcomes.

	All patients (n=277)
Patients with a major complication	70 (25%)
Clavien-Dindo grade 3	40 (57%)
Clavien-Dindo grade 4	15 (21%)
Clavien-Dindo grade 5	15 (21%)
Post-pancreatectomy hemorrhage	11 (4%)
Bile leakage	17 (6%)
Delayed gastric emptying	20 (7%)
Other complications	
Abdominal surgical site infection	37 (13%)
Diabetes related hypoglycemia	44 (16%)
Hospital stay[a], median (IQR)	12 (9-18)
Readmission within 90 days	40 (15%)
Missing	2
In-hospital mortality	15 (5%)
90-day mortality	21 (8%)
Adjuvant chemo(radio)therapy[b]	113 (63%)
Missing	5
Diabetes mellitus[c]	238 (100%)
New-onset diabetes mellitus	157 (66%)
Unchanged diabetes mellitus	39 (16%)
Worsened diabetes mellitus	42 (18%)
Postoperative pancreatic enzyme replacement therapy for exocrine insufficiency[c]	230 (97%)

Values are numbers with percentages within parentheses unless indicated otherwise. TNM staging is according to tumor origin and based on the 7th edition of AJCC TNM staging TNM classification. [a] Only calculated in patients who did not die during hospital admission (n= 262); [b] Only in patients with adenocarcinoma (n=183); [c] Data are only presented for patients with a completed 3 month follow-up for endocrine and exocrine insufficiency (n=238).

Multivariable analyses

Based on the results in the subgroup analysis, hospital volume <60 or ≥60 was assessed within the multivariable analysis. Factors associated with major postoperative complications were ASA≥3 (OR 2.87, 95%CI 1.56-5.26, p=0.001), and estimated blood loss ≥2L (OR 3.52, 95%CI 1.25-9.90, p=0.017, eTable 1). In-hospital mortality was related to age (OR 1.07, 95% CI 1.01-1.14, p=0.046), estimated blood loss ≥2L (OR 11.89, 95%CI 2.64-53.61, p=0.001) and lower-volume centers (<60 pancreatoduodenectomies, OR 3.78, 95% CI 1.18-12.16, p=0.026, eTable 1). Vein or arterial resections were not associated with major postoperative outcomes and in-hospital mortality.

Systematic literature search

The systematic review retrieved 7 studies which included at least 100 TPs (Table 6). All studies were retrospective (including one post-hoc analysis of a prospective database). One study included series from 2 different countries. All studies had an inclusion period beyond 5 years. The number of included patients ranged from 100 to 813. Most studies included both malignant as nonmalignant disease. The pancreatic specific complications postpancreatectomy hemorrhage and bile leakage in our cohort were comparable to literature, but the rate of delayed gastric emptying rate in our study was lower. Mortality

in our study was comparable with most published series, although 1 study had a lower 90-day mortality (3%), whereas 1 other study had a higher rate (11%).

DISCUSSION

This prospective multicenter pan-European snapshot study found a 5% in-hospital mortality after TP. The international snapshot approach allowed for inclusion of 277 patients from 16 countries in a relatively short period of only 13 months, hereby assuring data representative of current clinical practice. The multivariable analysis found an association between in-hospital mortality and annual center volume for pancreatoduodenectomy of <60, age, and estimated blood loss ≥2L.

In this study, the decision to perform TP in patients with malignant disease was mostly made intraoperatively (eg, in order to obtain a radical resection), thus striving for optimal survival outcomes.[20,21] TP is also increasingly considered in patients with main-duct IPMN, which was associated with lower (0%) mortality.[1,20] Generally, TP may be more often considered in recent years because of perceived improved surgical outcomes, increased use of surgery in patients with locally advanced pancreatic cancer, and better management of exocrine and endocrine insufficiency.[7,22,23]

The present study found high rates of postoperative complications and 90-day mortality after TP. In the total cohort, causes for mortality were not only surgery-related but sometimes also disease-related (eg, cancer recurrence). In an earlier series, postoperative complications were associated with a higher age and longer operation time, and there were no independent risk factors identified for mortality.[7] In contrary, a large monocenter series demonstrated that perioperative mortality was related to high blood loss, longer operative time (≥7 hours) and arterial resection.[23] Independent predictors for major complications in the current study were ASA score and estimated blood loss ≥2L, and predictors for in-hospital mortality included center volume, age and estimated blood loss ≥2L. These risk factors should be taken into account during patient selection and the decision to refer patients. We found no association with arterial or vein resections and outcome, which could be related to the low number of 12 patients with arterial resection and 58 patients with vein resection. Also, malignant disease was not related to worse outcomes. No differences were observed in morbidity and mortality between patients who underwent elective primary TP or in whom it was intraoperatively decided to perform TP. An intraoperative decision to perform a TP is therefore feasible. However, because morbidity and mortality after TP are high, this decision should be very well-considered and this option should be discussed with patients prior to surgery.

TABLE 5. Subgroup analysis.

	Total cohort (n=277)	IPMN (n=41)	Center volume based on ≥40 pancreatoduodenectomies annually			Center volume based on ≥60 pancreatoduodenectomies annually			Type of total pancreatectomy		
			High-volume centers (n=217)	Lower-volume centers (n=60)	p-value	High-volume centers (n=193)	Lower-volume centers (n=84)	p-value	Elective primary TP (n=127)	Intraoperative decision to perform TP (n=132)	p-value
Major complications	70 (25%)	7 (17%)	53 (25%)	17 (28%)	0.537	43 (22%)	27 (32%)	0.083	30 (24%)	35 (26%)	0.591
Clavien-Dindo grade 3	40 (57%)	6 (67%)	33 (62%)	7 (41%)		27 (63%)	13 (48%)		15 (50%)	22 (63%)	
Clavien-Dindo grade 4	15 (21%)	1 (22%)	9 (17%)	6 (35%)		9 (21%)	6 (22%)		7 (23%)	6 (17%)	
Clavien-Dindo grade 5	15 (21%)	-	11 (21%)	4 (24%)		7 (16%)	8 (30%)		8 (27%)	7 (20%)	
Post pancreatectomy hemorrhage	11 (4%)	1 (2%)	9 (4%)	2 (3%)	0.775	5 (3%)	6 (7%)	0.075	7 (6%)	3 (2%)	0.176
Bile leakage	17 (6%)	2 (5%)	13 (6%)	4 (7%)	0.847	9 (5%)	8 (10%)	0.121	9 (7%)	7 (5%)	0.551
Delayed gastric emptying	20 (7%)	3 (7%)	16 (7%)	4 (7%)	0.852	16 (8%)	4 (5%)	0.297	8 (6%)	10 (8%)	0.686
Other complications											
Abdominal surgical site infection	37 (13%)	3 (7%)	30 (14%)	7 (12%)	0.664	28 (15%)	9 (11%)	0.394	16 (13%)	19 (14%)	0.673
Diabetes related hypoglycemia	44 (16%)	9 (22%)	38 (18%)	6 (10%)	0.159	38 (20%)	6 (7%)	**0.009**	11 (9%)	27 (20%)	**0.007**
Readmission within 90 days	40 (15%)	7 (17%)	35 (16%)	5 (8%)	0.136	34 (18%)	6 (7%)	**0.024**	14 (11%)	21 (16%)	0.231
Missing	2		1	1		1	1			2	
Hospital stay[a], days, median (IQR)	12 (9-18)	11 (9-14)	12 (8-17)	14 (11-21)	**0.003**	12 (9-17)	14 (10-21)	**0.014**	13 (10-17)	12 (9-19)	0.228
In-hospital mortality	15 (5%)	-	12 (6%)	3 (5%)	0.872	7 (4%)	8 (10%)	**0.046**	8 (6%)	6 (5%)	0.533
90-day mortality	21 (8%)	-	16 (7%)	5 (8%)	0.804	11 (6%)	10 (12%)	0.073	10 (8%)	10 (8%)	0.928

Values are numbers with percentages within parentheses unless indicated otherwise. [a] Only calculated in patients who did not die during hospital admission.

TABLE 6. Comparison with published cohorts including at least 100 total pancreatectomies.

Author	Inclusion period	Country	Mono or multicenter	Retrospective or prospective	Patients, n	Indications for TP	Complications, n (%)	PPH, %	BL, %	DGE, %	Mortality, n (%)	Long-term survival
Reddy et al.[22]	1970-2007 37 years	Johns Hopkins Hospital, USA	Monocenter	Retrospective	100	Pancreatic adenocarcinoma	Surgical morbidity 69% CD≥3 28%	14%		11%	30-day 8%	Median survival 13 months 5-year 19%
Nathan et al.[24]	1998-2004 6 years	USA	Multicenter (SEER)	Retrospective	376	Pancreatic adenocarcinoma	-	-	-	-	30-day 7% 90-day 11%	Median survival per location: Head 15 months Body/tail 12 months Unspecified 11 months
Murphy et al.[25]	1998-2006 8 years	USA	Multicenter (NIS)	Retrospective	4013 *Weighted (actual inclusion 813)*	Malignant and non-malignant	Major complications[a] 28%	4%	-	-	In-hospital 9%	-
Johnston et al.[26]	1998-2011 13 years	USA	Multicenter (NCDB)	Retrospective	5726	Pancreatic adenocarcinoma	-	-	-	-	30-day 6%	Median survival 15 months 5-year survival 12%
Hartwig et al.[23]	2001-2012 11 years	University of Heidelberg, Germany	Monocenter	Post hoc analysis of prospective database	434	Malignant and non-malignant	Nonsurgical morbidity 38% Surgical morbidity 37%	7%	6%	18%	30-day 5% In-hospital 12%	Median survival 24 months 5-year non-malignant 94% 5-year adenocarcinoma 15%
Pulvirenti et al.[7]	2001-2013 12 years	Johns Hopkins Hospital, and University of Verona (binational)	Bicenter	Retrospective	329	Malignant and non-malignant	Morbidity 59% CD≥3 23%	6%	2%	14%	30-day 2% 90-day 3%	-
Scholten et al.[4]	2006-2016 10 years	The Netherlands	Multicenter	Retrospective	148	Malignant and non-malignant	CD≥3 32%	5%	3%	14%	30-day 5% 90-day 8%	Median survival per diagnosis: IPMN 98 months PDAC 13 months
Current study	2018-2019 1 year and 1 month	Pan-European (international)	Multicenter	Prospective	277	Malignant and non-malignant	CD≥3 25%	4%	6%	7%	In-hospital 5% 90-day 8%	-

BL indicates bile leakage; DGE, delayed gastric emptying; NCDB, U.S. National cancer Database; NIS, Nationwide Inpatient Sample; PDAC, pancreatic ductal adenocarcinoma; SEER, surveillance, epidemiology, and end results;. [a] Major post-operative complications in this study were defined by specific diagnoses with codes based on their validation as true complications rather than comorbidities by the methods described by Lawthers et al.[32]

To place the current findings in perspective, a systematic literature search was performed. Compared with the included series, this present study stands out because of its prospective and international multicenter design and short inclusion period with a relatively high number of patients. Our findings are comparable to previous literature in terms of morbidity and mortality and thus outcomes of TP seem not to have substantially improved over the latter years. Mortality in 3 registry studies from the USA was similar to our findings (mortality 6-11%).[24–26] Mortality in high-volume centers was lower than in our cohort.[7] Studies from the world's highest volume centers are less useful for daily clinical practice. The association between outcome and volume was confirmed in our subgroup analyses which showed more favorable results in centers with an annual pancreatoduodenectomy volume of ≥60. The rate of major complications did not differ between very high and lower-volume centers (cut-off ≥60), although mortality rates were lower in very high-volume centers. This could be explained by a lower failure to rescue rate (ie, better treatment of patients with a major complications) in very high-volume centers as was already shown for pancreatoduodenectomy.[27,28] These findings further support the concept of centralization of major pancreatic surgery.

Comparison of our results with patients after pancreatoduodenectomy in the Dutch and German audit, showed similar rates of postpancreatectomy hemorrhage and lower rates of delayed gastric emptying. This may be surprising since post-pancreatectomy hemorrhage is related to postoperative pancreatic fistula, which by definition cannot occur after TP. In-hospital mortality after pancreatoduodenectomy was 4.3% and 3.9% in respectively the German and Dutch audit and thus lower than after TP, except for very high-volume centers.[29] Results after pancreatoduodenectomy within the Swedish registry showed a lower major complication (15.3%) and 90-day mortality (3.5%) as compared with the current study.[30] A systematic review comparing TP and pancreatoduodenectomy confirmed these suggestions and showed that TP had worse outcomes as compared with pancreatoduodenectomy.[31]

A recent systematic review concluded that treatment of endocrine and exocrine insufficiency after TP remains challenging.[5] In our cohort, some data on endocrine and exocrine insufficiency were collected but due to the short follow-up an accurate reflection of treatment and burdens of endocrine and exocrine insufficiency could not yet be demonstrated. Regarding exocrine insufficiency after TP, some patients did not receive pancreatic enzyme supplementation, which should be improved. The impact of long-term endocrine, exocrine insufficiency, and quality of life will have to be assessed in a longer term follow-up study.

The findings of this study should be interpreted considering some limitations. First, since participation in this study was voluntary, some selection bias toward higher-volume centers may have occurred. This

bias, if present, would only further strengthen our findings of a high 90-day mortality after TP. Second, in retrospect, some data could have been collected otherwise. TNM staging should have been scored according to the 8th edition. Third, registration bias cannot be excluded. Although all variables were defined in the online Castor system, the relatively low rate of delayed gastric emptying in our study could be related to registration bias. This could be improved by an external control, but this is obviously highly challenging in 43 centers and 16 countries, let alone the current strict privacy laws. Fourth, pancreatic surgery expertise was based on center volume of pancreatoduodenectomy, which is common in pancreatic surgery literature. The relationship between pancreatoduodenectomy and TP volume is, however, not constant and symmetrically predictable between centers. Moreover, expertise increases with other resections, such as left sided resections and enucleations, and is also depending on the capability of the intensive care unit and interventional radiology. It might be possible that expertise is underestimated based on only pancreatoduodenectomy.

The international multicenter snapshot design is one of the main strengths of the study and allowed for the inclusion of a large number of patients in a very short time period. Snapshot studies require effort from physicians and residents to register data, but also extensive study coordination to ensure complete data collection. Especially, prospective follow-up within a snapshot study complicates the ease and should be excluded from study protocols if possible. A better alternative would be to perform a second snapshot study within the same cohort with (long-term) follow-up. The large advantage of this novel design is the accurate reflection of current practice and these results add substantially to those from studies with a selected cohort, such as randomized controlled trials or series from high-volume centers. The results from our study form a solid basis for discussion about how to improve outcomes after TP.

In conclusion, this pan-European prospective snapshot study found a 5% in-hospital mortality after TP across Europe. Several risk factors for mortality and major complications were identified which could be useful for patient selection and selective patient referral.

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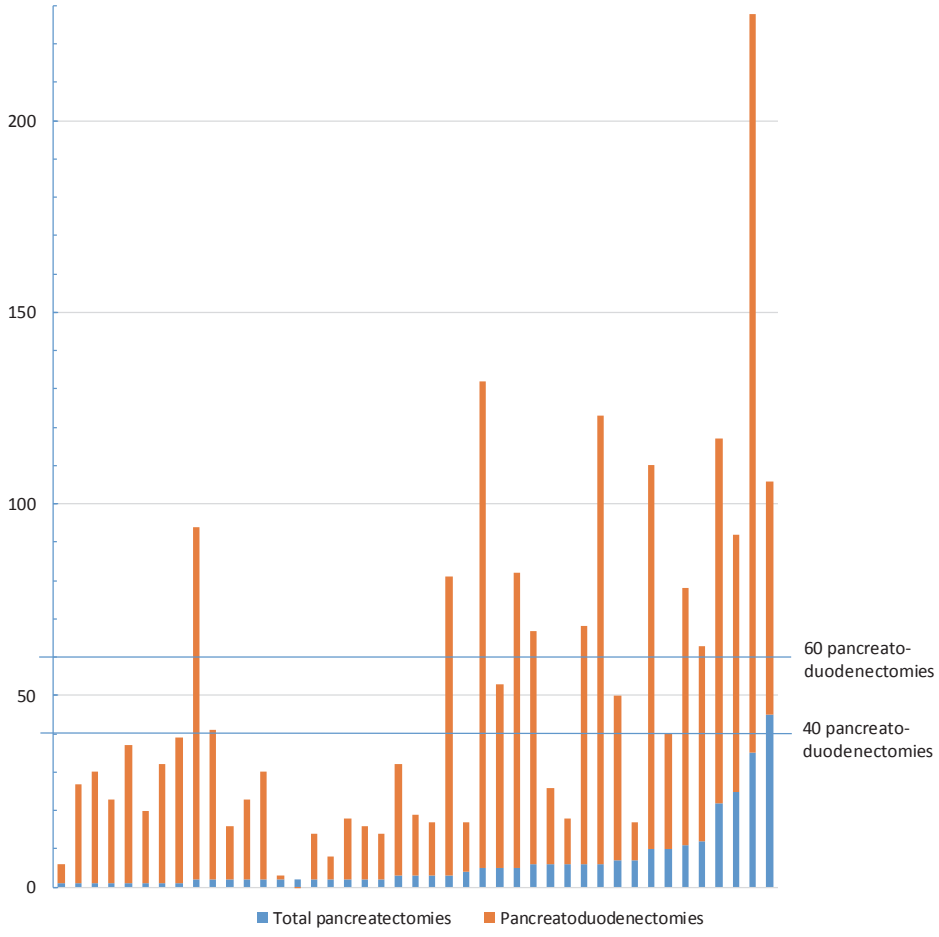
SUPPLEMENTARY MATERIAL

eFIGURE 1. Number of total pancreatectomies and pancreatoduodenectomies per center.



eTABLE 1. Multivariable logistic regression analyses with backward step selection.

	Major postoperative complications				In-hospital mortality			
	Univariable analyses OR (95%CI)	p-value	Multivariable analyses[ab] OR (95%CI)	p-value	Univariable analyses OR (95%CI)	p-value	Multivariable analyses[ab] OR (95%CI)	p-value
Male	1.53 (0.87-2.70)	.138			2.05 (0.64-6.62)	.228		
Age at operation	1.01 (0.99-1.03)	.434			**1.05 (1.00-1.11)**	**.068**	**1.07 (1.01-1.14)**	**0.046**
BMI	1.05 (0.99-1.12)	.115			**1.11 (1.01-1.23)**	**.038**		
ASA ≥3	**3.00 (1.71-5.26)**	**<.001**	**2.87 (1.56-5.26)**	**.001**	**2.51 (0.88-7.15)**	**.085**		
Neoadjuvant therapy	1.05 (0.50-2.23)	.893			2.13 (0.65-7.05)	.214		
Malignant disease	1.35 (0.71-2.54)	.359			2.51 (0.55-11.40)	.233		
Type of TP								
Elective primary	1.00 (reference)				1.00 (reference)			
Elective completion	1.24 (0.41-3.77)	.700			0.88 (0.10-7.44)	.903		
Intraoperative conversion to TP	1.17 (0.66-2.05)	.592			0.71 (0.24-2.10)	.534		
Splenectomy	1.40 (0.71-2.76)	.337			1.19 (0.33-4.35)	.795		
Any vein resection	0.80 (0.40-1.59)	.526			1.37 (0.42-4.48)	.559		
Any arterial resection	1.51 (0.44-5.17)	.514			3.88 (0.77-19.54)	.101		
Additional organ resection	0.90 (0.36-2.17)	.796			2.18 (0.58-8.20)	.251		
Operation time	1.00 (1.00-1.00)	.296			1.00 (1.00-1.00)	.556		
Estimated blood loss ≥2L	**3.81 (1.40-10.36)**	**.009**	**3.52 (1.25-9.90)**	**.017**	**6.71 (1.84-24.31)**	**.004**	**11.89 (2.64-53.61)**	**.001**
Lower-volume center (<60 pancreatoduodenectomies)	**1.65 (0.94-2.92)**	**.084**			**2.80 (0.98-7.98)**	**.055**	**3.78 (1.18-12.16)**	**.026**

All bold results of the univariable analyses were included in the multivariable analyses (p <.10). TP: total pancreatectomy; ASA: American Society of Anesthesiologist. [a] n=245 patients, because estimated blood loss was missing in 32 patients selection. [b] Results after backward step selection.

CHAPTER 11

The use and clinical outcome of total pancreatectomy in the United States of America, Germany, the Netherlands, and Sweden

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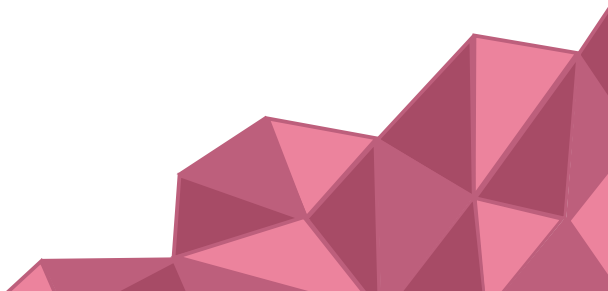
Submitted



ABSTRACT

Objective: To compare use and postoperative outcomes of total pancreatectomy (TP) among four Western countries.

Introduction: TP has high morbidity and mortality and differences among countries are currently unknown.

Methods: Patients who underwent one-stage TP were included from registries in the USA, Germany, the Netherlands, and Sweden (2014-2018). Use of TP was assessed by calculating the ratio TP to pancreatoduodenectomy. Primary outcomes were major morbidity (Clavien Dindo≥3) and in-hospital mortality. Predictors for the primary outcomes were assessed in multivariable logistic regression analyses. Sensitivity analysis assessed the impact of volume (low-volume <40 or high-volume ≥40 pancreatoduodenectomies annually; data available for the Netherlands and Germany).

Results: In total, 1579 patients underwent one-stage TP. The relative use of TP to pancreatoduodenectomy varied up to a fivefold (USA 0.03, Germany 0.15, the Netherlands 0.03, and Sweden 0.15, p<0.001). Both the indication and several baseline characteristics differed significantly among countries. Major morbidity occurred in 423 patients (26.8%) and differed (22.3%, 34.9%, 38.3%, and 15.9%, respectively, p<0.001). In-hospital mortality occurred in 85 patients (5.4%) and also differed (1.8%, 10.2%, 10.8%, 1.9%, respectively, p<0.001). Country, age ≥75, and vascular resection were predictors for in-hospital mortality. In-hospital mortality was lower in high-volume centers in the Netherlands (4.9% vs. 23.1%, p=0.002), but not in Germany (9.8% vs. 10.6%, p=0.733).

Conclusions: Considerable differences in the use of TP, patient characteristics, and postoperative outcome were noted among four Western countries. Outcomes were superior in the USA and Sweden. These large, yet unexplained, differences require further research to ultimately improve patient outcome.

INTRODUCTION

Total pancreatectomy (TP) is a relatively uncommon operation which is mostly performed for pancreatic cancer, chronic pancreatitis, or main duct intraductal papillary mucinous neoplasm (IPMN).[1–4] Most surgeons are reluctant to perform TP because of the resulting life-long endocrine and exocrine pancreatic insufficiency.[5] However, it is unknown whether the threshold to perform TP differs between surgeons and centers. For instance, some surgeons may consider a TP in case of a very challenging pancreatic anastomosis, whereas others view this as a relative contra-indication for TP. To what extent such differences could even exist between countries is unclear since nationwide data are lacking.

A recent study with 329 patients from two very high-volume centers reported a low 30-day mortality of 2.1% after TP.[6] In contrast, a recent pan-European snapshot study reported an in-hospital mortality of 5% after TP.[7] The latter study also showed that high-volume centers had better outcomes after TP. Next to hospital volume, patient characteristics may also affect postoperative outcomes. A previous comparison of 20,000 pancreatoduodenectomies from four Western registries demonstrated considerable differences in patient and tumor characteristics in the period 2014-2017.[8] It is unclear to what extent such differences also exist between patients undergoing TP.

The aim of this study is to assess differences in the use of TP, patient baseline characteristics, and in short-term postoperative outcomes after one-stage TP among four Western registries of pancreatic surgery.

METHODS

Patients and design

This cohort study combined data on patients undergoing one-stage TP from four registries on pancreatic surgery: USA (American College of Surgeons National Surgical Quality Improvement Program [ACS NSQIP], multicenter, 147 centers in 2017, including several Canadian hospitals), Germany (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie - Studien-, Dokumentations- und Qualitätszentrum [DGAV StuDoQ|Pankreas], multicenter, 54 centers in 2017), the Netherlands (Dutch Pancreatic Cancer Audit [DPCA], nationwide, 17 centers in 2017), and Sweden (Swedish National Pancreatic and Periampullary Cancer Registry [SNPPRC], nationwide, six centers in 2017).[9–12] The national coverage of these registries was reported as 66%, 20%, 93%, and 86%, respectively.[9–11,13] All patients who underwent one-stage TP from 2014 to 2018, and were registered in one of the registries, were included. From the StuDoQ database patients were included between 2014 and 2017. The study was performed in accordance with the STROBE guidelines.[14]

Data collection

Baseline characteristics, postoperative, and pathological outcomes were collected according to the previously described methods for the comparison of pancreatoduodenectomies (PD) from the four registries by this study group.[8] The use of TP per country/registry was assessed by calculating the ratio of TP to PD. Postoperative outcomes were registered during initial hospital admission, until 30 days after surgery, or until discharge if longer than 30 days. Additionally, failure to rescue rates (i.e., mortality after a major complication) were calculated, assuming that all patients with in-hospital mortality died from a major complication.[15] Annual center volume was based on the annual volume of PDs during the last year which was extracted from the registration and could only be assessed for Germany and the Netherlands. Low and high-volume centers were defined based on a previously used cut-off value of <40 (low-volume) or ≥40 (high-volume) PDs annually.[16]

Statistical analysis

Baseline characteristics, postoperative, and pathological outcomes wee presented using descriptive statistics. Normally distributed continuous data were compared using the one-way ANOVA and presented as means with standard deviations (SD). Non-normally distributed continuous data were compared using the Kruskal Wallis test and presented as medians with interquartile ranges (IQR). Categorical data are presented as frequency with percentages and were compared using the Chi-square test. Missing data were described and not imputed, and complete case analyses were performed (missing data<5% in multivariable analyses). Sensitivity analyses for major morbidity and in-hospital mortality were performed for patients with IPMN and for patients operated in high-volume vs. low-volume centers to observe the impact of volume on postoperative outcomes. Potential independent predictors for major morbidity and in-hospital mortality within patient, preoperative, and histopathological diagnosis characteristics were identified in univariable logistic regression models. Variables with a p-value <0.10 in univariable analyses were entered in the multivariable regression models and backward step selection was used. Results were reported as the odds ratio (OR) with corresponding 95% confidence interval (CI). All p-values were based on a two-sided test and p-values of <0.05 were considered statistically significant. P-values of <0.001 were considered statistically significant due to a Bonferroni correction for multiple comparisons in the analyses of baseline characteristics, postoperative, and pathological outcomes. Data was analyzed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Overall, 1579 patients after one-stage TP met the inclusion criteria. There were 663 patients from the USA (mean number per center: 5), 538 from Germany (mean: 10), 120 from the Netherlands (mean: 7),

and 258 from Sweden (mean: 43). The relative use of TP differed up to a fivefold among countries (ratio TP to PD: 0.03, 0.15, 0.03, and 0.15, respectively, p<0.001).

The median age at operation was 66 years (IQR 57-73) and 732 patients (46.4%) were female (Table 1). Laparoscopic and robotic TP, including those converted to open procedures, was performed in 68 (4.3%) and 29 patients (1.8%), respectively. Venous resections (i.e., portal vein or superior mesenteric vein) were performed in 345 patients (21.8%), arterial resections in 15 (0.9%), and venous and arterial resections in 54 (3.4%). On final histopathological diagnosis, 836 patients (52.9%) were diagnosed with a pancreatic adenocarcinoma, followed by 229 patients (14.5%) with IPMN without invasive cancer, and 176 patients (11.1%) with chronic pancreatitis. Major morbidity occurred in 423 patients (26.8%) and in-hospital mortality in 85 patients (5.4%).

Patient, preoperative, and intraoperative characteristics

Patient, preoperative, and intraoperative characteristics for each country are displayed in Table 1. Patients in the USA were younger (63 years old) compared to 68, 65, and 68 years in Germany, the Netherlands, and Sweden, respectively (p<0.001). Multiple significant differences also were observed for other patient characteristics, comorbidities, biliary stent placement, and use of neoadjuvant chemotherapy (Table 1). The proportion of patients with pancreatic adenocarcinoma as indication for TP was the lowest in the USA and Sweden (47.8%, 59.5%, 63.3%, 47.7%, p<0.001, Table 2). The proportion of patients with IPMN was the lowest in Germany (15.5%, 9.3%, 16.7%, 21.7%, p<0.001). Surgery for chronic pancreatitis was performed most often in the USA and Germany (14.5%, 11.9%, 4.2%, and 4.3%, p<0.001,). The vascular resection rate was highest in Sweden with 23.6%, 23.4%, 30.8%, 36.4%, p<0.001. Differences were shown for spleen, colon, and gastric resection as well as drain placement (Table 1).

Postoperative outcomes

Major morbidity rates differed among the countries with 22.3%, 34.9%, 38.3%, 15.9%, for USA, Germany, the Netherlands, and Sweden, respectively (p<0.001). As described in Table 2, pancreatectomy specific complications also differed among the countries. The reoperation rate was highest in Germany (8.9%, 20.3%, 13.3%, 10.5%, p<0.001), while the readmission rate was the highest in the USA (20.7%, 5.9%, 13.3%, 2.7%, respectively, p<0.001). In-hospital mortality was highest in Germany and the Netherlands (1.8%, 10.2%, 10.8%, 1.9%, respectively, p<0.001, Figure 1A). The same was found for failure to rescue rates which were 8.1%, 29.3%, 28.3%, 12.2%, respectively (p<0.001, Figure 1B).

TABLE 1. Patient, preoperative, and intraoperative characteristics.

	Total n = 1579	NSQIP USA n = 663	StuDoQ Germany n = 538	DPCA The Netherlands n = 120	SNPPCR Sweden n= 258	p-value
Age at operation, median (IQR), years	66 (57-73)	63 (54-71)	68 (59-75)	65 (58-72)	68 (60-73)	**<0.001**
Missing	5 (0.3%)			5 (4.2%)		
Female	732 (46.4%)	333 (50.2%)	228 (42.6%)	59 (49.2%)	112 (43.4%)	0.028
Missing	3 (0.2%)			3 (2.5%)		
BMI, median (IQR), kg/m^2	25.0 (22.6-28.6)	25.8 (22.8-29.8)	24.8 (22.6-27.7)	23.9 (21.8-27.9)	24.8 (22.6-27.5)	**<0.001**
Missing	17 (1.1%)	5 (0.8%)	4 (0.7%)	2 (1.7%)	6 (2.3%)	
≥10% weight loss 6 months preoperatively	376 (23.8%)	107 (16.1%)	112 (20.8%)	36 (30.0%)	121 (46.9%)	**<0.001**
Missing	42 (2.7%)		21 (3.9%)	18 (15.0%)	3 (1.2%)	
Functional health status						**<0.001**
Independent	1508 (95.5%)	652 (98.3%)	497 (92.4%)	105 (87.5%)	254 (98.4%)	
Partially dependent	45 (2.8%)	9 (1.4%)	32 (5.9%)	2 (1.7%)	2 (0.8%)	
Totally dependent	5 (0.3%)	-	4 (0.7%)	1 (0.8%)	-	
Missing	21 (1.3%)	2 (0.3%)	5 (0.9%)	12 (10.0%)	2 (0.8%)	
ASA score						**<0.001**
1	64 (4.1%)	1 (0.2%)	19 (3.5%)	9 (7.5%)	35 (13.6%)	
2	571 (36.2%)	130 (19.6%)	232 (43.1%)	72 (60.0%)	137 (53.1%)	
3	869 (55.0%)	473 (71.3%)	277 (51.5%)	37 (30.8%)	82 (31.8%)	
4	72 (4.6%)	58 (8.7%)	9 (1.7%)	2 (1.7%)	3 (1.2%)	
5	1 (0.1%)	1 (0.2%)	-	-	-	
Missing	2 (0.1%)		1 (0.2%)		1 (0.4%)	
Diabetes mellitus	594 (37.6%)	272 (41%)	200 (37.2%)	49 (40.8%)	73 (28.3%)	0.004
Missing	6 (0.4%)		2 (0.4%)	2 (1.7%)	2 (0.8%)	
COPD	78 (4.9%)	18 (2.7%)	37 (6.9%)	14 (11.7%)	9 (3.5%)	**<0.001**
Missing	9 (0.6%)		2 (0.4%)	4 (3.3%)	3 (1.2%)	
Heart failure	51 (8.6%)	3 (0.5%)	46 (8.6%)	2 (1.7%)	NA	**<0.001**
Missing	13 (1.0%)		7 (1.3%)	6 (5.0%)		
Hypertension	798 (50.5%)	331 (49.9%)	311 (57.8%)	31 (25.8%)	125 (48.4%)	**<0.001**
Missing	21 (1.3%)		2 (0.4%)	10 (8.3%)	9 (3.5%)	
Dialysis	10 (0.8%)	5 (0.8%)	5 (0.9%)	-	NA	0.587
Missing	10 (0.8)		2 (0.4%)	8 (6.7%)		
Albumin, median (IQR), g/L	39 (33-43)	38.0 (31.0-42.0)	39.3 (34.6-43.4)	39.0 (31.5-43.5)	NA	0.001
Missing	436 (33%)	95 (14.3%)	250 (46.5%)	91 (75.8%)		

Biliary stent placement						**<0.001**
No	1108 (70.2%)	468 (70.6%)	401 (74.5%)	75 (62.5%)	164 (63.6%)	
Yes – ERCP	379 (24.0%)	121 (18.3%)	133 (24.7%)	34 (28.3%)	91 (35.3%)	
Yes – PTCD	8 (0.5%)	6 (0.9%)	-	2 (1.7%)	-	
Yes – type unknown	12 (0.8%)	12 (1.8%)	-	-	-	
Missing	72 (4.6%)	56 (8.4%)	4 (0.7%)	9 (7.5%)	3 (1.2%)	
Neoadjuvant chemotherapy[a]	196 (12.4%)	110 (34.7%)	34 (10.6%)	7 (9.2%)	20 (16.3%)	**<0.001**
Missing	59 (3.7%)		1 (0.3%)	29 (38.2%)		
Neoadjuvant radiotherapy[a]	53 (7.4%)	45 (14.2%)	5 (1.6%)	3 (3.9%)	NA	**<0.001**
Missing	31 (4.3%)	1 (0.3%)	1 (0.3%)	29 (38.2%)		
Year of surgery						**<0.001**
2014	257 (16.3%)	114 (17.2%)	98 (18.2%)	26 (21.7%)	19 (7.4%)	
2015	312 (19.8%)	137 (20.7%)	110 (20.4%)	28 (23.3%)	37 (14.3%)	
2016	326 (20.6%)	126 (19.0%)	112 (20.8%)	23 (19.2%)	65 (25.%)	
2017	465 (29.4%)	154 (23.2%)	218 (40.5%)	23 (19.2%)	70 (27.1%)	
2018	219 (13.9%)	132 (19.9%)	-	20 (16.7%)	67 (26.0%)	
Operative approach						**<0.001**
Open (excluding conversion)	1477 (93.5%)	591 (89.1%)	519 (96.5%)	113 (94.2%)	254 (98.4%)	
Laparoscopic without conversion	33 (2.1%)	24 (3.6%)	5 (0.9%)	2 (1.7%)	2 (0.8%)	
Laparoscopic with conversion	35 (2.2%)	19 (2.9%)	10 (1.9%)	4 (3.3%)	2 (0.8%)	
Robotic without conversion	20 (1.3%)	20 (3.0%)	-	-	-	
Robotic with conversion	9 (0.6%)	9 (1.4%)	-	-	-	
Missing	5 (0.3%)		4 (0.7%)	1 (0.8%)		
Vascular resection						**<0.001**
No	1143 (72.4%)	489 (73.8%)	412 (76.6%)	80 (66.7%)	162 (62.8%)	
Venous (portal or SMV)	345 (21.8%)	111 (16.7%)	121 (22.5%)	34 (28.3%)	79 (30.6%)	
Arterial (celiac, hepatic, or SMA)	15 (0.9%)	11 (1.7%)	1 (0.2%)	-	3 (1.2%)	
Venous and arterial	54 (3.4%)	35 (5.3%)	4 (0.7%)	3 (2.5%)	12 (4.7%)	
Missing	22 (1.4%)	17 (2.6%)		3 (2.5%)	2 (0.8%)	
Spleen resection	582 (44.1%)	324 (48.9%)	209 (38.8%)	49 (40.8%)	NA	**<0.001**
Missing	127 (9.6%)	119 (17.9%)		8 (6.7%)		
Colon resection	54 (4.1%)	18 (2.7%)	28 (5.2%)	8 (6.7%)	NA	0.082
Missing	137 (10.4%)	119 (17.9%)		18 (15.0%)		
Partial gastrectomy	156 (11.8%)	79 (11.9%)	73 (13.6%)	4 (3.3%)	NA	0.015
Missing	138 (10.4%)	119 (17.9%)		19 (15.8%)		

Abdominal drain placed	767 (73.7%)	438 (66.1%)	NA	110 (91.7%)	219 (84.9%)	<0.001
Missing	27 (2.6%)			6 (5.0%)	17 (6.6%)	
Days in situ, median (IQR), days[b]	6.0 (4.0-9.0)	6.0 (4.0-9.0)		6 (4.5-15.5)	6.0 (4.0-8.0)	**0.083**
Missing	164/767 (21.4%)	83/438 (18.9%)		81/110 (73.6%)		

Values are numbers with percentages within parentheses unless indicated otherwise. Bold numbers indicate statistical significance after Bonferroni correction (p<0.001). NSQIP: National Surgical Quality Improvement Program; USA: United States of America; StuDoQ: Studien-, Dokumentations- und Qualitätszentrum; DPCA: Dutch Pancreatic Cancer Audit; SNPPCR: Swedish National Pancreatic and Periampullary Cancer Registry; IQR: interquartile range; NA: not applicable; ASA: American Society of Anesthesiologist; BMI: body mass inex; COPD: chronic obstructive pulmonary disease; ERCP: endoscopic retrograde cholangiopancreatography; PTCD: percutaneous transhepatic cholangiography drainage; SMV: superior mesenteric vein; SMA: superior mesenteric artery. [a] Patients with pancreatic adenocarcinoma, respectively 317, 320, 76, and 123 patients. [b] Number of days until drain removal from resection to removal.

TABLE 2. Postoperative and pathological outcomes.

	Total n = 1579	**NSQIP USA n = 663**	**StuDoQ Germany n = 538**	**DPCA The Netherlands n = 120**	**SNPPCR Sweden n= 258**	**p-value**
Postoperative outcomes						
Clavien Dindo classification						**<0.001**
No complications or Clavien Dindo <3	1127 (71.4%)	515 (77.7%)	346 (64.3%)	64 (53.3%)	202 (78.3%)	
Clavien Dindo ≥3	423 (26.8%)	148 (22.3%)	188 (34.9%)	46 (38.3%)	41 (15.9%)	
Missing	29 (1.8%)		4 (0.7%)	10 (8.3%)	15 (5.8%)	
Surgical site infection	142 (9.0%)	45 (6.8%)	66 (12.3%)	7 (5.8%)	24 (9.3%)	0.008
Missing	67 (4.2%)		16 (3.0%)	37 (30.8%)	14 (5.4%)	
Pneumonia	130 (8.2%)	45 (6.8%)	48 (8.9%)	6 (5.0%)	31 (12.0%)	**<0.001**
Missing	116 (7.3%)		5 (0.9%)	38 (31.7%)	73 (28.3%)	
Post-pancreatectomy hemorrhage, grade B/C	78 (8.5%)	NA	35 (6.5%)	6 (5.0%)	37 (14.3%)	**<0.001**
Missing	22 (2.4%)		4 (0.7%)	4 (3.3%)	14 (5.4%)	
Delayed gastric emptying, grade B/C	205 (13.0%)	104 (15.7%)	61 (11.3%)	22 (18.3%)	18 (7.0%)	0.001
Missing	36 (2.3%)	13 (2.0%)	4 (0.7%)	3 (2.5%)	16 (6.2%)	
Bile leak, grade B/C	55 (3.5%)	6 (0.9%)	34 (6.3%)	7 (5.8%)	8 (3.1%)	**<0.001**
Missing	147 (9.3%)	132 (19.9%)		1 (0.8%)	14 (5.4%)	
Radiologic intervention performed	77 (9.8%)	59 (8.9%)	NA	18 (15.0%)	NA	0.012
Missing	19 (2.4%)	6 (0.9%)		13 (10.8%)		

Organ failure	176 (11.1%)	60 (9.0%)	87 (16.2%)	19 (15.8%)	10 (3.9%)	**<0.001**
Missing	15 (0.9%)		4 (0.7%)	11 (9.2%)		
ICU admission	186 (11.8%)	NA	87 (16.2%)	23 (19.2%)	21 (8.1%)	0.003
Missing	161 (10.2%)		4 (0.7%)	11 (9.2%)	14 (5.4%)	
Reoperation	211 (13.4%)	59 (8.9%)	109 (20.3%)	16 (13.3%)	27 (10.5%)	**<0.001**
Missing	54 (3.4%)		10 (1.9%)	11 (9.2%)	33 (12.8%)	
Length of stay, median (IQR), days[a]	14.0 (9.0-20.0)	9.0 (7.0-14.0)	20.0 (15.0-27.0)	15.0 (11.0-21.0)	12.0 (8.8-17.0)	**<0.001**
Missing	16 (1.0%)	9 (1.4%)		1 (0.8%)	6 (2.3%)	
Readmission	192 (12.2%)	137 (20.7%)	32 (5.9%)	16 (13.3%)	7 (10.4%)[b]	**<0.001**
Missing	229 (14.5%)		9 (1.7%)	12 (10.0%)	17 (25.4%)	
In-hospital mortality	85 (5.4%)	12 (1.8%)	55 (10.2%)	13 (10.8%)	5 (1.9%)	**<0.001**
Missing	11 (0.7%)		1 (0.2%)	1 (0.8%)	9 (3.5%)	
Time between resection and in-hospital mortality, median (IQR), days[c]	14.0 (3.0-23.5)	16.5 (3.5-20.5)	13.0 (4.0-24.0)	10.0 (1.5-23.5)	26.0 (1.0-63.0)	0.686
Failure to rescue	85/423 (20.1%)	12/148 (8.1%)	55/188 (29.3%)	13/46 (28.3%)	5/41 (12.2%)	**<0.001**
Pathological outcomes						
Histopathological diagnosis						**<0.001**
Pancreatic adenocarcinoma	836 (52.9%)	317 (47.8%)	320 (59.5%)	76 (63.3%)	123 (47.7%)	
Periampullary cancer	50 (3.2%)	7 (1.1%)	30 (5.6%)	1 (0.8%)	12 (4.7%)	
Neuroendocrine tumor	90 (5.7%)	58 (8.7%)	16 (3.0%)	5 (4.2%)	11 (4.3%)	
IPMN	229 (14.5%)	103 (15.5%)	50 (9.3%)	20 (16.7%)	56 (21.7%)	
Chronic pancreatitis	176 (11.1%)	96 (14.5%)	64 (11.9%)	5 (4.2%)	11 (4.3%)	
Other	168 (10.6%)	71 (10.7%)	52 (9.7%)	12 (10.0%)	33 (12.8%)	
Missing	30 (1.9%)	11 (1.7%)	6 (1.1%)	1 (0.8%)	12 (4.7%)	
T-stage[d]						0.004
Tis / T0	11 (1.2%)	6 (1.9%)	4 (1.1%)	-	1 (0.7%)	
T1	76 (8.6%)	38 (11.7%)	29 (8.3%)	1 (1.3%)[e]	8 (5.9%)	
T2	156 (17.6%)	57 (17.6%)	63 (18.0%)	17 (22.1%)	19 (14.1%)	
T3	560 (63.2%)	203 (62.7%)	221 (63.1%)	45 (58.4%)	91 (67.4%)	
T4	55 (6.2%)	8 (2.5%)	27 (7.7%)	6 (7.8%)	14 (10.4%)	
Tx	3 (0.3%)	1 (0.3%)	-	-	2 (1.5%)	
Missing	25 (2.8%)	11 (3.4%)	6 (1.7%)	8 (10.4%)		
N-stage[d]						**<0.001**
N0	308 (34.8%)	143 (44.1%)	123 (35.1%)	21 (27.3%)	21 (15.6%)	
N+	553 (62.4%)	164 (50.6%)	222 (63.4%)	54 (70.1%)	113 (83.7%)	
Nx	3 (0.3%)	2 (0.6%)	-	-	1 (0.7%)	
Missing	22 (2.5%)	15 (4.6%)	5 (1.4%)	2 (2.6%)		

M-stage[d]						0.001
M0 / Mx	738 (83.3%)	225 (69.4%)	321 (91.7%)	72 (93.5%)	120 (88.9%)	
M1	38 (4.3%)	5 (1.5%)	13 (3.7%)	5 (6.5%)	15 (11.1%)	
Missing	110 (12.4%)	94 (29.0%)	16 (4.6%)			
Tumor stage[d]						**<0.001**
0	9 (1.0%)	4 (1.2%)	4 (1.1%)		1 (0.7%)	
I	110 (12.4%)	44 (13.6%)	49 (14.0%)	9 (11.7%)[f]	8 (5.9%)	
II	509 (57.4%)	163 (50.3%)	210 (60.0%)	41 (53.2%)	95 (70.4%)	
III	90 (10.2%)	7 (2.2%)	56 (16.0%)	13 (16.9%)	14 (10.4%)	
IV	38 (4.3%)	5 (1.5%)	13 (3.7%)	5 (6.5%)	15 (11.1%)	
Missing	130 (14.7%)	101 (31.2%)	18 (5.1%)	9 (11.7%)	2 (1.5%)	
Resection margin[d]		NA				**<0.001**
R0	329 (58.5%)		246 (70.3%)	35 (45.5%)	48 (35.6%)	
R1	208 (37.0%)		92 (26.3%)	36 (46.8%)	80 (59.3%)	
Missing	25 (4.4%)		12 (3.4%)	6 (7.8%)	7 (5.2%)	
Tumor size for benign tumors[g]			NA			0.078
<2 cm	37 (10.7%)	26 (14.8%)		3 (10.7%)	8 (11.8%)	
2-5 cm	61 (17.6%)	36 (20.5%)		6 (21.4%)	19 (27.9%)	
>5 cm	64 (18.4%)	27 (15.3%)		11 (39.3%)	26 (38.2%)	
Missing	185 (53.3%)	89 (49.4%)		8 (28.6%)	15 (22.1%)	

Values are numbers with percentages within parentheses unless indicated otherwise. Bold numbers indicate statistical significance after Bonferroni correction (p<0.001).
NSQIP: National Surgical Quality Improvement Program; USA: United States of America; StuDoQ: Studien-, Dokumentations- und Qualitätszentrum; DPCA: Dutch Pancreatic Cancer Audit; SNPPCR: Swedish National Pancreatic and Periampullary Cancer Registry; NA: not applicable; Surgical site infection: superficial, deep incisional, and wound disruption; ICU: intensive care unit; IQR: interquartile range; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm. [a] In patients without in-hospital mortality; [b] Only in patients operated in 2018; [c] In patients with in-hospital mortality; [d] In patients with pancreatic or periampullary adenocarcinoma, respectively 324, 350, 77, and 135 patients; [e] Patients operated in 2018 (n=14) were staged according to the TNM8 classification: 7 patients had stage T2, 5 patients stage T3, 1 patients stage T4, and in 1 patient the stage was missing; [f] Patients operated in 2018 (n=14) were staged according to the TNM8 classification: 1 patient had stage I, 5 patients stage II, and 8 patients stage III; [g] Benign and neuroendocrine tumors (excluding chronic pancreatitis), respectively 176, 75, 28, and 75 patients.

Multivariable analysis

Patients from Germany and the Netherlands, but not from Sweden, had higher odds of major morbidity compared to patients from the USA (Germany: OR 2.07, 95%CI 1.57-2.74, p<0.001; the Netherlands: OR 3.10, 95%CI 1.96-4.90, p<0.001; Sweden: OR 0.85, 95%CI 0.56-1.28, p=0.426, Table 3). Other predictors of major morbidity were ASA score ≥3 (OR 1.65, 95%CI 1.27-2.15, p<0.001), vascular resection (OR 1.70, 95%CI 1.30-2.23, p<0.001), and periampullary cancer (reference: pancreatic ductal adenocarcinoma; OR 2.91, 95%CI 1.58-5.36, p=0.001). This pattern for countries was also identified for in-hospital mortality (USA: reference; Germany: OR 5.19, 95%CI 2.73-9.89, p<0.001; the Netherlands: OR 6.41, 95%CI 2.82-14.61, p<0.001; Sweden: OR 0.94, 95%CI 0.33-2.71, p=0.911, Table 3). In addition, age ≥75 (OR 2.67, 95%CI 1.67-4.28, p<0.001) and vascular resection (OR 1.94, 95%CI 1.21-3.12), p=0.006) were associated with in-hospital mortality. Pathological diagnosis (i.e., pancreatic adenocarcinoma, IPMN, and chronic pancreatitis) was not a predictor for in-hospital mortality.

Sensitivity analysis

In 229 patients with IPMN, major morbidity was 21.0% and in-hospital mortality was 3.1% (mortality after TP for IPMN in USA 1.0% [1/103], Germany 6.0% [3/50], the Netherlands 10.0% [2/20], and Sweden 1.8% [1/55]). In total, 246 patients underwent TP in high-volume centers in Germany (8 centers) and 81 patients in the Netherlands (9 centers, Supplementary Table 1). Median center volume for Germany in 2017 was 15 PDs (IQR 5-29) and in the eight high-volume centers 47 PDs (IQR 43-52). In the Netherlands, median center volume was 40 PDs (IQR 24-60) and in the nine high-volume centers 58 PDs (IQR 42-78). In Germany, major morbidity was 33.6% in low-volume centers compared to 36.6% in high-volume (p=0.537) and in the Netherlands 51.3% vs. 32.1% (p=0.095), respectively. In-hospital mortality was not higher in low-volume centers in Germany (10.6% vs. 9.8%, p=0.733, respectively). In the Netherlands, in-hospital mortality was higher in low-volume centers (23.1% vs. 4.9%, p=0.002).

FIGURE 1. Mortality and failure to rescue among the four countries.

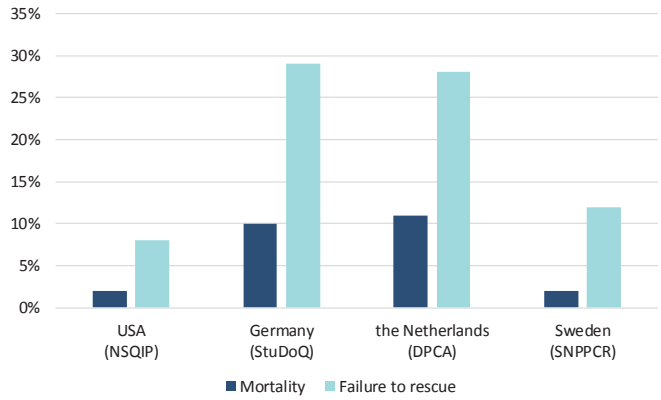


TABLE 3. Multivariable regression analyses to assess predictors for major morbidity and mortality.

	Major morbidity				Mortality			
	Univariable analysis OR (95%CI)	p-value	Multivariable analysis[a] OR (95%CI)	p-value	Univariable analysis OR (95%CI)	p-value	Multivariable analysis[b] OR (95%CI)	p-value
Country								
USA	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Germany	**1.89 (1.46-2.44)**	**<0.001**	**2.07 (1.57-2.74)**	**<0.001**	**6.19 (3.28-11.69)**	**<0.001**	**5.19 (2.73-9.89)**	**<0.001**
The Netherlands	**2.50 (1.64-3.81)**	**<0.001**	**3.10 (1.96-4.90)**	**<0.001**	**6.65 (2.96-14.97)**	**<0.001**	**6.41 (2.82-14.61)**	**<0.001**
Sweden	0.71 (0.48-1.04)	0.075	0.85 (0.56-1.28)	0.426	0.84 (0.39-3.19)	0.844	0.94 (0.33-2.71)	0.911
Age ≥75	**1.34 (1.02-1.77)**	**0.036**			**3.20 (2.04-5.04)**	**<0.001**	**2.67 (1.67-4.28)**	**<0.001**
Male	**1.27 (1.01-1.59)**	**0.041**			1.26 (0.81-1.96)	0.317		
BMI	1.00 (0.97-1.02)	0.681			1.01 (0.97-1.04)	0.681		
ASA score ≥3	**1.39 (1.10-1.75)**	**0.006**	**1.65 (1.27-2.15)**	**<0.001**	1.39 (1.10-1.75)	0.774		
Comorbidities	0.95 (0.76-1.20)	0.677			1.26 (0.81-1.96)	0.299		
Preoperative biliary drainage	0.88 (0.68-1.15)	0.359			0.89 (0.53-1.49)	0.659		
Neoadjuvant chemotherapy	0.90 (0.63-1.27)	0.536			0.75 (0.36-1.59)	0.459		
Minimally invasive surgery	0.92 (0.58-1.47)	0.723			0.54 (0.17-1.74)	0.300		
Vascular resection	**1.51 (1.18-1.93)**	**0.001**	**1.70 (1.30-2.23)**	**<0.001**	**1.74 (1.11-2.74)**	**0.017**	**1.94 (1.21-3.12)**	**0.006**
Histopathological diagnosis								
Pancreatic adenocarcinoma	1.00 (reference)		1.00 (reference)		1.00 (reference)			
Periampullary cancer	**2.73 (1.52-4.90)**	**0.001**	**2.91 (1.58-5.36)**	**0.001**	**2.39 (1.03-5.58)**	**0.043**		
Neuroendocrine tumor	0.93 (0.57-1.52)	0.760	1.27 (0.76-2.11)	0.364	0.12 (0.33-1.36)	0.124		
IPMN	**0.67 (0.47-0.96)**	**0.028**	0.93 (0.63-1.35)	0.685	0.46 (0.20-1.01)	0.054		
Chronic pancreatitis	0.87 (0.60-1.26)	0.456	1.10 (0.75-1.64)	0.620	0.42 (0.17-1.07)	0.068		
Other	0.87 (0.60-1.27)	0.470	1.08 (0.73-1.60)	0.709	0.81 (0.39-1.68)	0.575		

Bold numbers in univariable analysis indicates variables that were entered in multivariable analysis (p<0.10). Bold numbers in multivariable analysis indicates statistical significance (p<0.05). OR: Odds ratio; USA: United States of America; ASA: American Society of Anesthesiologists. [a] Multivariable analysis after backward step selection in 1507 patients. [b] Multivariable analysis after backward step selection in 1541 patients.

DISCUSSION

This largest international analysis in 1579 patients after one-stage TP found a major morbidity rate of 26.8% and an in-hospital mortality rate of 5.4%. The relative use of TP differed up to a fivefold among the four countries. Differences were also noted for patient characteristics, surgical indications, and clinical outcomes among the four countries. Outcomes were superior in the USA and Sweden compared to Germany and the Netherlands. Although partly explained by surgical volume much of these differences remains unexplained. In multivariable analyses, country and vascular resection were predictors of both major morbidity and in-hospital mortality. Evaluation of the mechanisms behind these differences may improve outcomes of patients undergoing TP.

Before attempting to interpret these results, it should be noted that these registries differ in design and some variables had to be recoded to enable comparisons among countries. As concluded in the previous comparison between these four registries, implementation of key parameters with identical definitions in the separate registries is required.[8] The Dutch and Swedish registries are nationwide with a very high coverage, whereas the NSQIP and German StuDoQ registries are multicenter with a two-third and one-fifth nationwide coverage, respectively. The NQSIP has a high presence of high-volume centers which could partly explain the high rate of neoadjuvant therapy and improved postoperative outcomes in the USA.[17] Currently, harmonization of the registries is one of the main tasks of the GAPASURG collaboration. The number of TPs per center differed widely among the countries and was especially high in Sweden with good outcomes. This could be explained by the extensive centralization of pancreatic surgery in Sweden in six university hospitals (i.e., five of which performed at least 60 PDs in 2018).[9,18] However, Sweden included more than double the number of TPs compared to the Netherlands, whereas their population is 10 million in 2018 as compared to 17 million in the Netherlands. This difference was also reflected in the TP to PD ratio, which was lower for the USA and the Netherlands compared to Germany and Sweden. This suggests a higher threshold for TP in the USA and the Netherlands, but reasons for these differences are unclear.

In line with our findings, a recent pan-European snapshot study of 277 patients after TP demonstrated rates of major morbidity of 25% and in-hospital mortality of 5%.[7] Also, a systematic review of cohorts with at least 100 TPs, found outcomes comparable to the current study: major complications 27% vs. 23-32% (current study vs. systematic review), post-pancreatectomy hemorrhage 9% vs. 4-14%, bile leak 4% vs. 2-6%, delayed gastric emptying 13% vs. 7-18%, and in-hospital mortality 5% vs. 5-9%.[7] However, in a series describing 12-year results of two very high-volume centers, 30-day and 90-day mortality rates were lower with 2% and 3%, respectively.[6] These results are in line with the results from the USA and Sweden, which both had an in-hospital mortality of 2%, yet are in contrast with the high mortality rates

in both Germany (10%) and the Netherlands (11%). The difference in mortality rates is interesting and next to age ≥75 and vascular resection, country was identified as a predictor. The relation between mortality after partial pancreatectomy and center volume is also well-established and was recently demonstrated for TP.[7,19–21] A future study could aim to develop a case-mix adjustment model to more properly compare morbidity and mortality in patients after TP, as was recently done for patients who underwent liver resection for colorectal liver metastases.[22] Case-mix factors for patients who underwent pancreatic surgery were already identified from a systematic literature search and the most important factors were selected after multidisciplinary and international discussions.[10]

The presence of high-volume centers in the USA and advanced centralization in Sweden could explain the lower in-hospital mortality.[9,17,18] The sensitivity analysis showed that in-hospital mortality was lower in the Netherlands in nine centers performing more than 40 PDs annually, confirming the effect of volume. Interestingly, sensitivity analyses in the German cohort did not show different outcomes for high-volume (≥40 PDs annually) although the volume per center was lower than in the Netherlands. Higher volume centers may have superior failure to rescue rates due to more developed perioperative care, such as improved preoperative patient selection, protocolized care, intensive care, interventional radiology, and nurse to patients ratio.[15] The lower failure to rescue rates as seen the USA and Sweden probably contributed to the lower in-hospital mortality rates.[23–25]

Major morbidity also was higher in Germany and the Netherlands, and much lower in Sweden. The low major morbidity rate after TP in Sweden is similar to the previously published results from the Swedish registry.[9] This low rate might be partially based on the indication for TP (i.e., planned vs. unplanned), a lower threshold for TP (i.e., thus also including less complicated patients), or on a registration bias.[26] Surgical morbidity was higher in patients with malignant compared to benign disease (e.g., IPMN or chronic pancreatitis), whereas 30-day and in-hospital mortality was not related to pathological diagnoses.[4,7,27] In this study, patients with IPMN had an acceptable major morbidity of 21.0% and in-hospital mortality of 3.1%. In multivariable analysis, patients with periampullary cancer had significant higher odds for major morbidity when compared to pancreatic ductal adenocarcinoma, but histopathological diagnosis was not a predictor for in-hospital mortality. Considering these results the indication for TP should be well-considered in all patients, but a shared-decision making program is feasible for patients with a benign disease. For example, the PROPAN program for patients with a very high risk on developing pancreatic cancer (i.e., main-duct IPMN).[28]

Another significant difference among the countries was the rate of reoperation. Similar to our analyses of patients who underwent PD, Germany had the highest reoperation rate.[8] The high reoperation rate

was surprising given the fact that no pancreatic fistula would have been present after surgery and it is common practice to use a step-up approach before performing a reoperation. Other complications such as post-pancreatectomy hemorrhage, bile leak, organ space surgical site infections are potential indications for reoperation. This possibility is supported by a report from a very high-volume German center in which the relaparotomy rate in 434 consecutive TPs was 17.1%.[4]

The readmission rate was the highest in the USA. In the literature, increasing age, comorbidity, preoperative therapy, extensive surgery, and complications were described as predictors for readmission in pancreatic surgery.[29–32] These predictors do not completely explain our results. For example, median age in the USA was lower than in the other countries, and the major morbidity rate in the USA was lower than in Germany. Likely, the shorter length of stay observed in the USA cohort contributed to readmission rates. In addition, readmission and length of hospital stay might also be largely influenced by cultural differences, for example by temporary housing with family or referral to a nursing home.

The present study has several limitations that must be considered when interpreting the results. First, baseline characteristics differed among countries. These differences may not explain the findings since the differences do not seem to benefit countries with good outcomes (e.g., high BMI, ASA in the USA). Second, the exact use of TP could not be calculated for each of the four countries since only the registries of the Netherlands and Sweden include all procedures nationwide. However, the ratio TP to PD is expected to give a rather good insight in the relative use of TP per country. Third, information about center volume of pancreatic resections was not available for the USA and Sweden. Therefore, outcomes could not be related to center volume, which could have been a partial and potentially large explanation for differences among countries.

In conclusion, this transatlantic cohort study showed that one-stage TP is associated with substantial major morbidity and in-hospital mortality. Use of TP widely varied among countries. Although this analysis is one of the largest cohorts over a relatively short time period, overall results of this contemporary experience were not improved compared to earlier reports. Outcomes were better in the USA and Sweden, but the comparison between countries remains difficult due to differences in use of TP and designs of the registries. One of the main challenges of the GAPASURG study group will be to harmonize the key parameters registered. Taken together, the results suggest that center volume might be responsible for improved postoperative outcomes. The observed differences among countries require further research to ultimately improve patient outcome.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1. Sensitivity analysis of centers performing ≥40 pancreatoduodenectomies annually in Germany and the Netherlands.

	High-volume StuDoQ, Germany n = 246	Low-volume StuDoQ, Germany n = 292	p-value	High-volume DPCA, The Netherlands n = 81	Low-volume DPCA, The Netherlands n = 39	p-value
Clavien Dindo classification			0.537			0.095
No complications or Clavien Dindo <3	156 (63.4%)	190 (65.1%)		46 (56.8%)	18 (46.2%)	
Clavien Dindo ≥3	90 (36.6%)	98 (33.6%)		26 (32.1%)	20 (51.3%)	
Missing		4 (1.4%)		9 (11.1%)	1 (2.6%)	
In-hospital mortality	24 (9.8%)	31 (10.6%)	0.733	4 (4.9%)	9 (23.1%)	**0.002**
Missing		1 (0.3%)			1 (2.6%)	

Bold numbers indicate statistical significance (p<0.05). StuDoQ: Studien-, Dokumentations- und Qualitätszentrum; DPCA: Dutch Pancreatic Cancer Audit.

PART III

SURVIVAL

CHAPTER 12

Conditional survival after resection for pancreatic cancer: a population-based study and prediction model

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Annals of Surgical Oncology. 2020 Jul;27(7):2516-2524.

ABSTRACT

Background: Conditional survival is the survival probability after already surviving a predefined time period. This may be informative during follow-up, especially when adjusted for tumor characteristics. Such prediction models for patients with resected pancreatic cancer are lacking and therefore conditional survival was assessed and a nomogram predicting 5-year survival at a predefined period after resection of pancreatic cancer was developed.

Methods: This population-based study included patients with resected pancreatic ductal adenocarcinoma from the Netherlands Cancer Registry (2005-2016). Conditional survival was calculated as the median and the probability of surviving up to 8 years in patients who already survived 0-5 years after resection using the Kaplan-Meier method. A prediction model was constructed.

Results: Overall, 3,082 patients were included with a median age of 67 years. Median overall survival was 18 months (95%CI 17-18 months) with a 5-year survival of 15%. The 1-year conditional survival (i.e. probability to survive the next year) increased from 55 to 74 to 86% at 1, 3, and 5 years after surgery, respectively, while the median overall survival increased from 15 to 40 to 64 months at 1, 3, and 5 years after surgery, respectively. The prediction model demonstrated that the probability to achieve 5-year survival at 1 year after surgery varied from 1-58% depending on patient- and tumor characteristics.

Conclusions: This population-based study showed that 1-year conditional survival was 55% 1 year after resection and 74% 3 years after resection in patients with pancreatic cancer. The prediction model is available via www.pancreascalculator.com to inform patients and caregivers.

INTRODUCTION

Pancreatic ductal adenocarcinoma (hereafter called pancreatic cancer) is one of the most lethal cancers. In Europe and the US, approximately 18 per 100.000 persons and 13 per 100.000 persons, respectively, are diagnosed with this disease annually.[1,2] Approximately 16% of all patients will undergo surgical resection with a 5-year survival of 15-20%.[3–5] Survival following resection of pancreatic cancer has improved because of better adjuvant treatment strategies.[6,7] Therefore, increasing numbers of patients with pancreatic cancer will survive the first year following surgery and these patients might want to be informed about accurate data on survival estimates during follow-up.

Survival estimates are traditionally calculated from the time of diagnosis or from the time of surgery. However, in patients who underwent pancreatic resection for pancreatic cancer, predicted survival changes considerably during follow-up.[8,9,10] Conditional survival (CS), defined as the survival probability and calculated in the subgroup of patients who have survived a predefined period, may therefore provide better insight. This could for instance be relevant when patients in follow-up after resection of pancreatic cancer are faced with important decisions regarding work and personal life with impact on both themselves and their next of kin. CS may also facilitate appropriate risk-stratification of patients, e.g. regarding the frequency and timing of follow-up.[8–13] For optimal risk-stratification, calculation of the CS probability should also take other predictors of overall survival into account. Multiple prediction models have been developed for survival after surgery for pancreatic cancer, however, prediction models for CS in pancreatic cancer are lacking.[14,15]

The Netherlands Cancer Registry (NCR) contains patient, tumor, and treatment characteristics of all patients with pancreatic cancer, as well as corresponding survival data. The objective of this study was to assess CS using nationwide NCR data for patients who underwent resection of pancreatic cancer and to develop a nomogram to predict CS probabilities, with the possibility to adjust survival estimates for a certain period already survived after surgery.

METHODS

Study design

This cohort study used nationwide data from the NCR, a prospective population-based database, that covers all Dutch hospitals (i.e. a population of 16.8 million). Information on patient, tumor, and treatment characteristics from patients with a newly diagnosed malignancy are routinely collected from medical records by trained NCR administrators. Patients were queried from the national pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. This study was reported in

accordance with the STROBE guidelines.[16] No informed consent was required as anonymized data were used.

Study population

Patients who underwent resection of pancreatic ductal adenocarcinoma during the period 2005-2016 were extracted from the NCR database (International Classification of Diseases for Oncology, Third Revision [ICD-O-3] morphology codes are shown in electronic supplementary Text 1). Pancreatic resection was defined as pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy. Patients younger than 18 years of age at the time of diagnosis, patients with neuroendocrine tumors, and patients with distant metastases were excluded. In addition, patients, who died within 30 days after surgery, were excluded since our aim was to develop a nomogram for postoperative use in the outpatient clinic.

Data collection

Primary tumor location was classified as pancreatic head, body, tail or other/not otherwise specified (NOS), according to the ICD-O-3. Staging was based on the pathological classification according to the TNM classification at the time of registration (6th edition of the Union for International Cancer Control [UICC] TNM staging during 2005–2009; 7th edition of the UICC TNM staging during 2010–2016).[17,18] In case of neoadjuvant treatment or missing pathological TNM stage, clinical TNM classification was used. Adjuvant chemotherapy has been recommended since 2008 after judgement of a national commission (Commissie BOM), and was, according to the guidelines, almost universally gemcitabine only. Survival data were obtained by an annual cross-check with the Municipal Personal Records Database, which contains the vital status of all Dutch inhabitants. Survival was calculated as the time between the date of surgery (or date of histological diagnosis when date of surgery was unknown, n=3) and date of death, or censored when alive at the last check of the patient's vital status (1 February 2018).

Statistical analysis

Patient, tumor, and treatment characteristics were presented using descriptive statistics. Overall survival was calculated using the Kaplan-Meier method. CS was defined as the probability of surviving an additional number of 'y' years given that a patient had already survived for 'x' years, and was calculated as $CS_{(x|y)} = S_{(x+y)}/S_{(x)}$, with $S_{(x)}$ representing the overall survival at x years estimated using the Kaplan-Meier method.[12] For example, to estimate the CS for surviving 2 more years for patients who already have survived 3 years after surgery, $CS_{(3|2)}$ is calculated by dividing the 5-year Kaplan–Meier survival estimate $S_{(5)}$ by the 3-year Kaplan–Meier survival estimate $S_{(3)}$.[8,19–21] Median CS was also

determined at specific times and was derived from Kaplan-Meier estimates by discarding the patients who died before that time.

To develop a nomogram predicting 5-year survival, the predictors of the previously published and externally validated Amsterdam model were used.[14,22] This model was used because of its simplicity and methodological quality according to a recent systematic review and to maintain consistency with previous studies.[14,23] The Amsterdam model uses adjuvant chemotherapy, margin status, tumor differentiation, and lymph node ratio to predict overall survival for patients who underwent pancreatoduodenectomy for pancreatic cancer.[14] Moreover, age was also incorporated in the prediction model, because of its relation with CS. In the current study, multiple imputation was used to impute missing data by creating 10 datasets, using the *mice* package in R. Variables of the Amsterdam model were included in a multivariable Cox proportional hazards model. A penalized LASSO model (Least Absolute Shrinkage and Selector Operator) was used in order to enhance prediction accuracy and reduce overfitting.[24] Results were presented as hazard ratios (HR) with 95% confidence intervals (CIs). A nomogram was created and the C-statistic was presented, with optimism adjusted for by bootstrapping (B=200). Nomogram-predicted CS rates to reach 5-year survival were presented directly after surgery and given 1, 2, 3, and 4 years survival after surgery (for use in the outpatient clinic during follow-up). Of note, CS predictions 'directly after surgery' are actually the predictions at 30 days post-surgery (since 30-day mortality was excluded), but was described as 'directly after surgery' to enhance readability. All p-values were based on a 2-sided test and p-values of <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, N.Y., USA) and R version 3.4.3 (cran.r-project.org).

RESULTS

In total, 3204 patients underwent resection of pancreatic cancer between 2005 and 2016. Patients who died within 30 days after surgery were excluded (4%, n=122). The final cohort consisted of 3,082 patients; median age was 67 years (IQR 60-73) and 1,630 patients (53%) were male. All baseline characteristics are shown in Table 1.

Overall and conditional survival

Median overall survival was 18 months (95%CI 17-18 months) with a 5-year survival of 15% (Figure 1). The survival probability increased per year already survived relative to the total survival time. The probability of achieving 5-year survival after resection increased from 15% directly after surgery to 23%, 42%, 61%, and 82% per additional year survived (i.e. 1, 2, 3, and 4 years after resection, respectively). The 1-year CS (i.e. probability to survive the next year) decreased from 67% directly after surgery to 55%

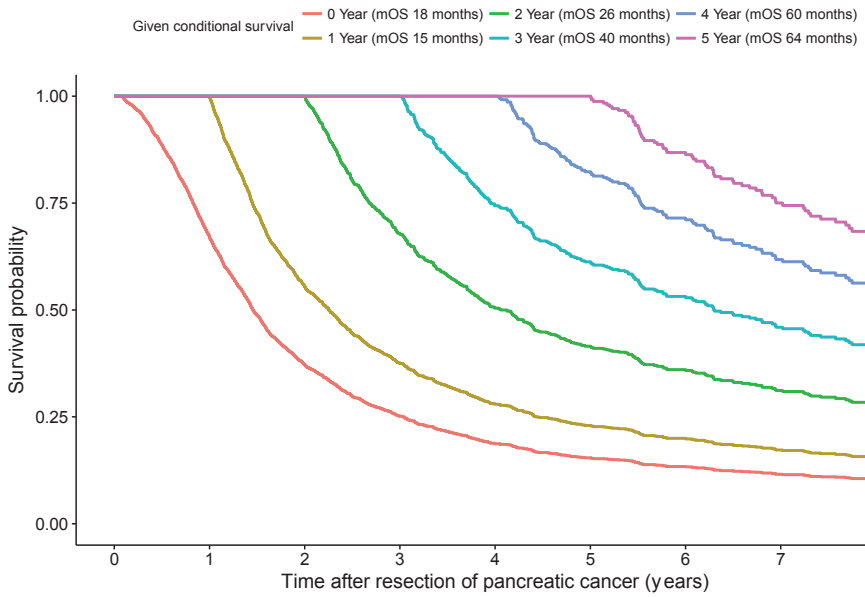
at 1 year after surgery, and then increased to 74% and 86% at 3 and 5 years after surgery, respectively (Figure 1). The median CS decreased from 18 months (95%CI 17-18) directly after surgery to 15 months (95%CI 14-16) at 1 year after surgery and then increased to 40 (95%CI 32-52) and 64 months (95%CI 54 to not reached) at 3 and 5 years after surgery, respectively.

TABLE 1. Baseline characteristics of 3,082 patients with resected pancreatic cancer diagnosed between 2005-2016.

Clinicopathological parameter	Total cohort, No. (%)[a] n = 3,082
Male	1,630 (53%)
Age, median (IQR)	67 (60-73)
< 70 years	1,892 (61%)
≥ 70 years	1,190 (39%)
Primary tumor location	
Head of pancreas	2,509 (81%)
Corpus of pancreas	110 (3.6%)
Tail of pancreas	235 (7.6%)
Pancreas, NOS	228 (7.4%)
Type of operation	
Pancreatoduodenectomy	2,686 (87%)
Distal pancreatectomy	333 (11%)
Total pancreatectomy	47 (1.5%)
Other/NOS	16 (0.5%)
Tumor differentiation grade	
Well differentiated (grade I)	360 (12%)
Moderately differentiated (grade II)	1,626 (53%)
Poorly- or undifferentiated (grade III)	1,096 (36%)
Missing	484 (16%)
Pathological T stage[b]	
T1	222 (7.2%)
T2	555 (18%)
T3	2,167 (70%)
T4	138 (4.5%)
Pathological N stage[c]	
N0	1,000 (32%)
N1	2,082 (68%)
Resection margin status	
R0	2,065 (67%)
R1	966 (31%)
R2	51 (1.6%)
Missing	132 (4.3%)
Neoadjuvant chemo(radio)therapy	140 (4.5%)
Adjuvant chemotherapy	1,492 (48%)

[a] Imputed data is presented. Percentages are separately calculated for the group of missing values, explaining the cumulative exceeding 100% for tumor grade and resection margin status. [b] Clinical T stage was used in case of missing pathological T stage (n = 26, 0.8%). [c] Clinical N stage was used in case of missing pathological N stage (n = 49, 1.6%). NOS, not otherwise specified.

FIGURE 1. Kaplan-Meier estimates for conditional survival up to 8 years in 3,082 patients given 0 to 5 years' survival after resection of pancreatic cancer.



Given years of survival	Survival probability to reach X years								
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
0	*100 %*	*67 %*	*37 %*	*25 %*	*18 %*	*15 %*	*13 %*	*12 %*	*10 %*
1		*100 %*	*55 %*	*38 %*	*28 %*	*23 %*	*20 %*	*17 %*	*15 %*
2			*100 %*	*68 %*	*50 %*	*42 %*	*36 %*	*31 %*	*28 %*
3				*100 %*	*74 %*	*61 %*	*53 %*	*46 %*	*41 %*
4					*100 %*	*82 %*	*71 %*	*62 %*	*55 %*
5						*100 %*	*86 %*	*75 %*	*67 %*
Number at risk	*3,082*	*2,054*	*1,001*	*585*	*367*	*246*	*176*	*125*	*88*

Each column represents the years survived from surgery and each row represents the percentage to reach a certain total survival time from that point of survived years. For example, if a patient has survived 2 years after surgery, the probability to be alive at 3 years after surgery is 68% and to achieve 5-year survival after surgery is 42%.

Multivariable analysis of survival

In our cohort, all four variables of the Amsterdam model (i.e. adjuvant chemotherapy, margin status, tumor differentiation, and lymph node ratio), as well as age, were independent predictors of survival in a multivariable Cox analysis (Table 2). Moderately and poorly differentiated tumors were associated with worse survival compared with well differentiated tumors (HR 1.27 [95% CI 1.11-1.46] for moderately differentiated tumors, and HR 1.74 [95% CI 1.51-2.00] for poorly/undifferentiated tumors). In addition, higher lymph node ratio and a R1/R2 resection margin were independently associated with decreased survival, as was the absence of use of adjuvant chemotherapy (HR 1.64 [95% CI 1.51-1.79]).

TABLE 2. Univariable and multivariable Cox regression analyses according to the Amsterdam model in patients with resected pancreatic cancer diagnosed between 2005-2016.

Clinicopathological parameter	Median OS, months	5-year survival	Univariable analysis HR (95% CI)	Multivariable analysis HR (95% CI)[b]	P value[c]
Age (each incremental year)	-	-	1.01 (1.00-1.01)	1.00 (1.00-1.01)	0.04
Tumor differentiation grade					
Well differentiated	27	27%	1.00 (reference)	1.00 (reference)	
Moderately differentiated	19	16%	1.41 (1.21-1.65)	1.27 (1.11-1.46)	0.001
Poorly- or undifferentiated	14	12%	1.94 (1.66-2.28)	1.74 (1.51-2.00)	<0.001
Lymph node ratio[a]					
0 (lymph node negative)	25	28%	1.00 reference	1.00 (reference)	
>0 and ≤0.18	18	13%	1.44 (1.27-1.63)	1.47 (1.31-1.64)	<0.001
>0.18	15	8%	1.86 (1.67-2.07)	1.94 (1.76-2.14)	<0.001
Resection margin					
R0	20	19%	1.00 (reference)	1.00 (reference)	
R1/R2	14	8%	1.57 (1.44-1.70)	1.44 (1.33-1.57)	<0.001
Adjuvant chemotherapy					
Yes	21	20%	1.00 (reference)	1.00 (reference)	
No	14	11%	1.52 (1.41-1.65)	1.64 (1.51-1.79)	<0.001

Data after multiple imputation were used. [a] Lymph node ratio is the number of positive lymph nodes divided by the total number of lymph nodes harvested. [b] Hazard ratios and 95% confidence intervals from the Cox LASSO model are presented. [c] P values of multivariable analyses are shown.

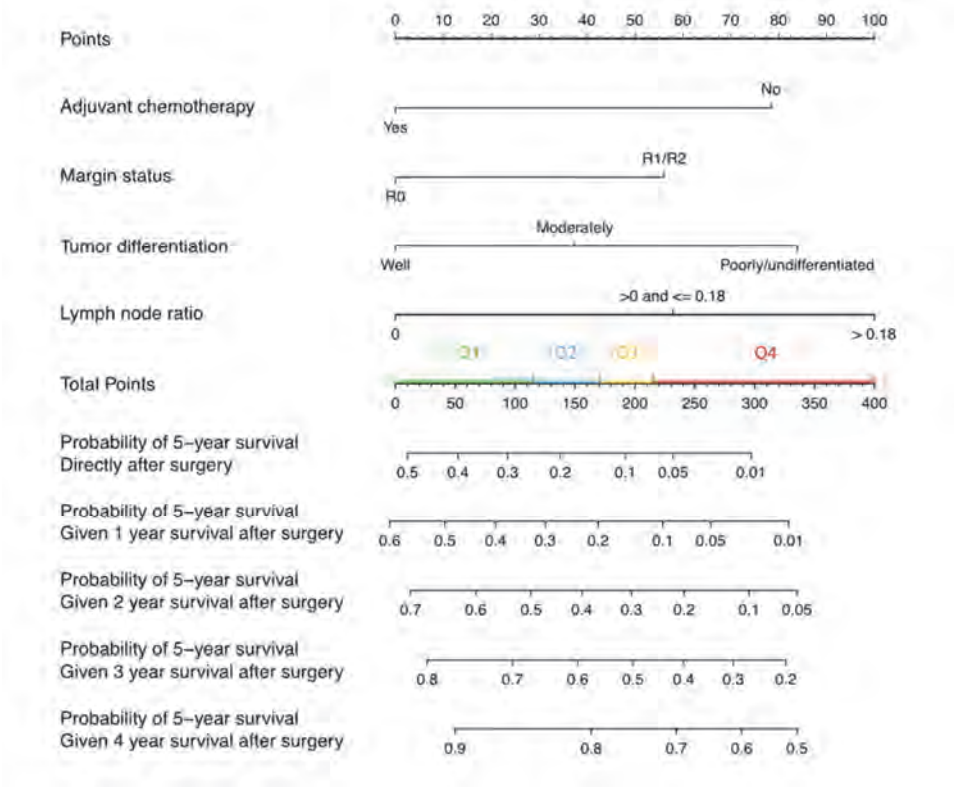
Prediction nomogram for conditional survival

In Figure 2, a nomogram was created based on the predictors of the multivariable Cox model. The prediction model had a calibration slope of 1.1 (Supplementary Figure 1) and an optimism-adjusted C-statistic of 0.65 (95% CI 0.64-0.66). The nomogram predicts the probability of reaching 5-year survival directly after surgery and after surviving 1-4 years after surgery. Quartiles of the nomogram score are indicated in the nomogram to show the distribution of the current cohort. The probability of achieving 5-year survival, measured 1 year after surgery, varied from 1 to 58% depending on patient and tumor characteristics. For example, a 60-year old patient with a moderately differentiated tumor and a lymph

node ratio of <0.18 who underwent an R1 resection without adjuvant chemotherapy would have a total nomogram score of 249 (24+37+58+55+75). The probability of being alive 5 years after surgery is 10% after surviving the first year for this particular patient, $CS_{(5|1)}$, increasing to 45% when surviving the first 3 years after surgery, $CS_{(5|3)}$. If this patient had received adjuvant chemotherapy, the total nomogram score would have been 174 points (24+37+58+55) and the probability of 5-year survival would have been 25% after surviving the first year, rising to 61% after surviving the first 3 years after surgery, $CS_{(5|3)}$.

A calculator to estimate the probability to achieve 5-year survival, calculated from the time of surgery, given 'x' years of survival after surgery, has been made available at www.pancreascalculator.com.

FIGURE 2. Nomogram for the prediction of overall and conditional survival to achieve 5-year survival after resection.



DISCUSSION

This nationwide study, in 3,082 patients who underwent resection of pancreatic cancer is the first to present a prediction model for CS. The probability of achieving 5-year survival after pancreatic resection increased from 15% directly after surgery to 61% after surviving the first 3 years. A prediction model was created, using easily accessible predictors, and made available at www.pancreascalculator.com to estimate patient-specific CS probabilities for 5-year survival after surgery.

CS is especially of interest in cancers with a poor survival prognosis as the survival estimates change considerably after surviving the first year. In the current study, the 1-year CS (i.e. the probability of surviving another year) decreased the first year after surgery (67% directly after surgery vs. 55% at 1 year after surgery). This indicates that relatively more patients die in the second year after surgery than in the first year after surgery. After this initial decrease, the 1-year CS estimates gradually increase. The large decline in survival in the second year after surgery is merely a reflection of the non-linear death rate in patients diagnosed with pancreatic cancer. In other large series, disease recurrence also typically occurs after a median of 12 months.[25] Patients who have survived the first years after surgery, probably have less aggressive cancers. This is also confirmed by the different shapes of the CS curves in Figure 1 (the concave becoming more linear over time). Another explanation might be extensive patient care with optimization of the physical condition perioperatively and during the first year postoperatively. After the first year, oncological treatments are typically completed and the intensity of supportive care potentially decreases. However, the exact reason of the biggest decline in the second year after surgery remains unknown.

The increase of the CS after these first years is probably because only patients who had a tumor with favorable biological behavior remain. These patients survive until late tumor recurrence or other causes of death, leading to an increased CS as patients have accrued a longer postoperative survival. Moreover, distinction between pancreatic, ampullary and distal bile duct cancer remains challenging, while these cancers carry different prognoses.[26] Tumors might be misclassified as pancreatic ductal adenocarcinoma and patients could therefore have a better survival than expected, being translated in increasing CS over time.

The survival in this study is lower compared with other large, monocenter series.[27,28] However, this is a population-based study and the results are therefore more representative than studies with selected cohorts, for example from single, high-volume centers. Compared with the population based Surveillance, Epidemiology, and End Results (SEER) database our results are similar.[29]

The current CS estimates are developed for the outpatient clinic after full recovery from surgery and when patients would like to discuss their prognosis and future perspectives. Our nomogram uses readily available and widely recognized predictors of survival in pancreatic cancer. Although some might argue that a C-statistic of 0.65 is relatively low, it is in line with previous prediction models in pancreatic cancer.[23] The difficulty in accurately predicting survival after resected pancreatic cancer is partly related to the narrow-banded survival distribution (poor prognosis for the vast majority of patients with very few long-term survivors), which complicates accurate discrimination in terms of clinical outcome.

Recently, other studies reported on CS in colorectal liver metastases, hepatocellular carcinoma, non-small lung cancer, and malignant brain tumors.[20,21,30,31] However, in pancreatic cancer, only a few, mostly single-center studies have assessed CS without taking other prognostic factors into account.[8–11,13,32,33] One European study analyzed CS among all stages of pancreatic cancer, stratified for age and sex, but presented only limited information on CS.[32] Another recent study combined data from Verona and Boston and stratified for TNM stage, tumor grade, resection margin, and adjuvant therapy.[33] This study separated patients with and without tumor recurrence. Unfortunately, this was not possible in our cohort since this information was not yet available in the NCR during 2005-2016. Comparison of the overall population analysis from that study with our results showed that 1-year CS was slightly higher in their study, but this effect diminished over time.[33] Moreover, a recent study including five national cancer registries developed a survival-predicting model for 1-, 2-, 3-, and 5-year survival probabilities.[34] CS was not calculated in this large cohort. However, none of the previously mentioned series proposed a way to calculate CS with adjustment for known clinicopathological predictors. As known from previous studies, not only time since resection affected overall survival but obviously also patient, tumor, and treatment characteristics.[27,35,36] In studies on CS for gastric cancer a nomogram to adjust for covariates was created and consequently increased accuracy of CS estimates.[37,38]

Patients might be unable to adequately interpret traditional 3- and 5-year survival estimates, potentially leading to rigorous decisions. The nomogram created in the current study will potentially add to traditional survival estimates in counselling patients and surveillance during follow-up. Moreover, patients prefer explicit information about prognosis.[39] Some patients might experience anxiety as 3 years after surgery is approaching, while this study demonstrates that CS rates are actually improving over time. These psychological consequences, such as fear of cancer recurrence or death, become more important due to novel and improved treatment possibilities that increase survival.[40] Personalized survival estimates will potentially aid to deal with these psychological factors and will pave the way for personalized follow-up schedules. Furthermore, as can be calculated with the prediction model, patients with adjuvant chemotherapy have higher CS estimates compared with patients without

chemotherapy. These estimates might increase the patients' visualization of the impact of adjuvant chemotherapy on survival. Based on these estimates, one might also cautiously advocate for treatment of oligometastatic disease after 2-3 years progression-free survival as CS probabilities are improving over time.

This study has some limitations. First, the retrospective design could have caused bias because surgical and pathological procedures were not standardized among centers. For example, the pathological assessment of pancreatic resection specimens improved considerably during these years (2005-2016), which we were not able to adjust for retrospectively and might have influenced our results. Second, one of the strengths of this study, the long study period, also represents one of its limitations. Surgical outcomes improved due to increased centralization and new (neo)adjuvant chemotherapy regimens were introduced.[6,41–44] It is likely that the majority of patients received adjuvant gemcitabine monotherapy, whereas now most patients receive (neo)adjuvant FOLFIRINOX resulting in an improved survival.[6] Unfortunately, in our cohort only a small proportion of patients was treated neoadjuvantly as this was only done in randomized trials during these years. With new insights available and treatment shifting rapidly towards neoadjuvant therapy, the current CS estimates are probably an underestimation of the actual prognosis. An update of the nomogram would be appropriate in a few years due to these improvements, perhaps including type of chemotherapy and completeness of chemotherapy regimens. Third, no data were available on tumor recurrence and cancer antigen (CA) 19-9. Recurrence has a considerable prognostic impact, as was shown in the study from Verona and Boston.[33] The NCR database is currently expanded with recurrence data, and, subsequently, further research should incorporate these data to improve patient tailored calculations. CA19-9 is a tumor marker that was shown to be of prognostic value but was not yet registered in a considerable proportion of the patient included in our cohort and could therefore not be considered in our analysis.[26] Fourth, it should be noted that the number of patients at risk in the CS analysis substantially decreased over time. Smaller groups obviously result in wider CIs, especially longer after surgery, which should be taken into account. Due to the statistical challenges to calculate CIs of the CS Kaplan-Meier estimates, the number of patients at risk is presented instead.

CONCLUSION

This nationwide study describes CS following resection of pancreatic cancer. A nomogram and online calculator based on national data may be useful for counselling patients during follow-up. External validation of the nomogram and CS estimates in other cohorts of patients with pancreatic cancer would be recommended.

ACKNOWLEDGEMENTS

The Dutch Pancreatic Cancer Project, including the Netherlands Cancer Registry, received funding from the Dutch Cancer Society (KWF Kankerbestrijding; grant no. UVA2013-5842). The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TEXT 1

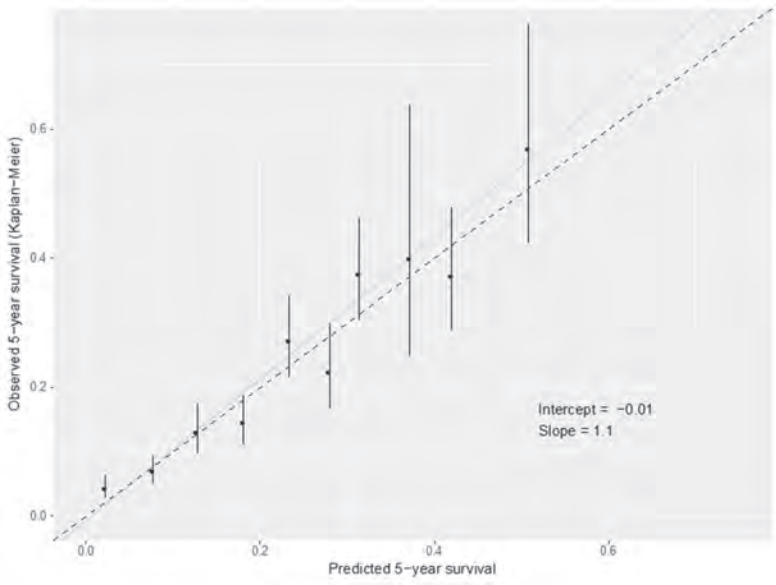
Patients were included based on the ICD-O-3 morphology codes below. One patient, who underwent pancreatic resection, was coded with code 8010. This patient was also included.

8012 Large cell carcinoma, NOS
8020 Carcinoma, undifferentiated, NOS
8021 Carcinoma, anaplastic, NOS
8022 Pleomorphic carcinoma
8031 Giant cell carcinoma
8032 Spindle cell carcinoma, NOS
8033 Pseudosarcomatous carcinoma
8035 Carcinoma with osteoclast-like giant cells
8046 Non-small cell carcinoma
8070 Squamous cell carcinoma, NOS
8071 Squamous cell carcinoma, keratinizing, NOS
8072 Squamous cell carcinoma, large cell, nonkeratinizing, NOS
8140 Adenocarcinoma, NOS
8141 Scirrhous adenocarcinoma
8143 Superficial spreading adenocarcinoma
8144 Adenocarinoma, intestinal type
8145 Carcinoma, diffuse type
8163 Pancreatobiliary-type carcinoma
8201 Cribiform carcinoma, NOS
8211 Tubular adenocarcinoma
8255 Adenocarcinoma with mixed subtypes
8310 Clear cell adenocarcinoma, NOS
8480 Mucinous adenocarcinoma
8481 Mucin-producing adenocarcinoma
8490 Signet ring cell carcinoma
8500 Ductal carcinoma, NOS
8510 Medullary carcinoma, NOS
8521 Infiltrating ductular carcinoma
8523 Infiltrating duct mixed with other types of carcinoma
8560 Adenosquamous carcinoma
8570 Adenocarcinoma with squamous metaplasia
8572 Adenocarcinoma with spindle cell metaplasia

8575 Metaplastic carcinoma

8576 Hepatoid adenocarcinoma

SUPPLEMENTARY FIGURE 1. The calibration plot for prediction of 5-year survival.



CHAPTER 13

Relationship between quality of life and survival in patients with pancreatic and periampullary cancer: a multicenter cohort analysis

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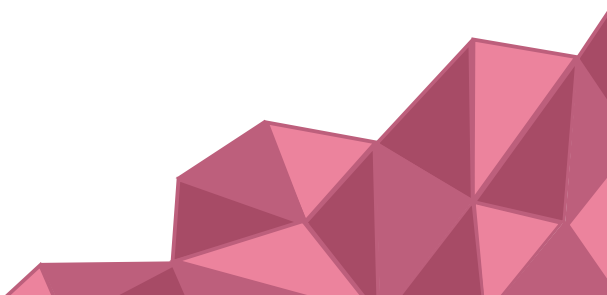
Journal of the National Comprehensive Cancer Network. 2020 Oct 1;18(10):1354-1363.



ABSTRACT

Background: A relation between quality of life (QoL) and survival has been demonstrated for several types of cancer, mostly in clinical trials with highly selected patient groups. The relation between QoL and survival for patients with pancreatic or periampullary cancer patients is unclear.

Methods: Analysis of QoL data from a prospective multicenter patient reported outcome registry in patients with pancreatic or periampullary carcinoma registered in the nationwide Netherlands Cancer Registry (2015-2018). Baseline and delta QoL, between baseline and three months follow-up, was assessed with the Happiness, EORTC QLQ-C30 and QLQ-PAN26 questionnaires. The relation between QoL and survival was assessed with Cox regression models and additional prognostic value of separate items with Nagelkerke's R2 (explained variance).

Results: For the baseline and delta analyses, 233 and 148 patients were available. The majority had pancreatic adenocarcinoma (n=194, 83.3%), stage III disease (n=77, 33.0%), with a median overall survival of 13.6 months. Multivariate analysis using baseline scores, indicated several scales to be of prognostic value for the total cohort (i.e. happiness today, role functioning, diarrhea, pancreatic pain, and body image, hazard ratios all $p<0.05$) and for patients without resection (i.e. overall satisfaction with life, physical and cognitive functioning, QLQ-C30 summary score, fatigue, pain, constipation, diarrhea, and body image, hazard ratios all $p<0.05$). Except for diarrhea, all QoL items accounted for >5% of the additional explained variance and were of added prognostic value. Multivariate analysis using delta QoL revealed that only constipation was of prognostic value for the total cohort, while no association with survival was found for subgroups with or without resection.

Conclusion: In a multicenter cohort of patients with patients with pancreatic or periampullary carcinoma, QoL scores predicted survival, regardless of patient, tumor and treatment characteristics. QoL scores may thus be used for shared decision making regarding disease management and choice of treatment.

INTRODUCTION

Patient reported outcome measures (PROMs) are increasingly used in clinical practice to assess patients' quality of life (QoL). Addressing QoL is important for patients with a short life expectancy such as patients with pancreatic and periampullary carcinoma with a median overall survival of 4-6 months[1]. Different types of treatment that may improve survival of pancreatic cancer may also impact QoL. Pancreatic resection has been found to be associated with a temporary deterioration in QoL after which it usually returns to baseline values after 3-6 months[2, 3]. Moreover, chemotherapy has been found to improve QoL in randomized studies in the adjuvant and palliative setting[4, 5].

QoL may also be used to predict survival. Previous studies with other types of cancer (e.g., breast, lung, oesophageal, or liver cancer) consistently found a correlation between QoL and survival[6-11]. Previous studies combined patients with different types of cancer, including a limited number (approximately 6%) of patients with pancreatic cancer[9, 10]. Most of the data were acquired from randomized trials that included patients who were relatively fit. Only one case series of 55 patients with advanced pancreatic cancer suggested a prognostic relation between the physical functioning scale scores of the EORTC QLQ-C30 and survival[12].

In the Netherlands, the Dutch Pancreatic Cancer Project (PACAP) was established in 2013. This is a multicenter cohort of patients with pancreatic and periampullary carcinoma of whom clinical data and PROMs are collected[13]. We used this cohort to investigate the relation between QoL and survival in daily clinical practice. The aim of this study was to examine which domains of QoL are predictive of survival in patients with pancreatic and periampullary cancer.

METHODS

Study design

This is a post-hoc analysis of a prospective multicenter cohort of PROMs in patients with pancreatic and periampullary cancer. Currently, 48 centers in the Netherlands participate in the PACAP PROMs. Clinical data were included from the nationwide population-based Netherlands Cancer Registry (NCR). Both registries are incorporated within PACAP[13]. Patients provided written informed consent for participation and linkage of their data between the registries. This study was designed in accordance with the STROBE guidelines[14].

Study population

Adult patients diagnosed with pancreatic and periampullary cancer between January 2015 and February 2018 who were registered in the NCR and participated in PACAP PROMs were included. Patients were

excluded if they completed the baseline questionnaire after start of cancer treatment (n=143 of the total cohort).

Data collection

The NCR data include patient, tumor, and treatment characteristics (i.e. date of diagnosis, age at diagnosis, sex, BMI, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, pathological diagnosis, tumor location, tumor stage (according to American Joint Committee on Cancer 7th edition), tumor size, tumor differentiation grade, date of initial treatment, type of pancreatic resection, margin status (microscopically radical (R0) and irradical resection (R1)), (neo)adjuvant/palliative chemo(radio)therapy, biliary drainage, and survival data[15]. PROMs at baseline and three months follow-up were used. Baseline measurement was defined as a measurement between date of diagnosis and date of start of first cancer treatment (e.g., chemo(radio)therapy, resection or local ablative therapy). Overall survival was defined as time between date of diagnosis and date of death.

QoL assessment

The QoL data include data derived from the Happiness[16], EORTC QLQ-C30[17], and EORTC QLQ-PAN26[18] questionnaires[19, 20]. The Happiness questionnaire consists of four items, including satisfaction with one's life as a whole, happiness today, happiness during the last month, and at which level one feels to personally stand at present on a ladder from worst to best possible life. All items employ a 0 (worst) to 10 (best) scale[16].

The cancer-specific EORTC QLQ-C30 questionnaire encompasses global health status, five functioning scales (i.e. physical, role, emotional, cognitive, and social functioning) and eight symptom scales/items (i.e. fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea), and financial difficulties. The pancreatic-specific EORTC QLQ-PAN26 questionnaire includes nine disease and treatment-related symptoms (pain, eating-related items, cachexia, hepatic symptoms, side-effects, altered bowel habit, ascites, indigestion and flatulence) and five emotional domains specific to pancreatic cancer (body image, healthcare satisfaction, sexuality, fear of future health and ability to plan future). The items of the EORTC questionnaires employ four response categories, which after linear transformation, form a scale ranging from 0 to 100. A higher score on the functional and global scales indicate better QoL, whereas for problems and symptoms higher scores indicate poorer QoL. In addition, a summary score was obtained from the EORTC QLQ-C30 questionnaire[21], based on the mean of all scale and item scores with the exclusion of global QoL and financial impact, and after reversing the scores of the symptom scales.

The relation between baseline QoL and delta QoL (between baseline and three months follow-up), and survival was assessed with the scales/items of the three questionnaires. Secondary analyses addressed the relation between QoL and survival for patients 1) undergoing pancreatic resection and 2) not undergoing pancreatic resection (with or without metastases).

Statistical analysis

Descriptive statistics were used for analysis of baseline, tumor, and treatment characteristics, and QoL scores. They were reported as proportions for binary or categorical variables, and as mean with standard deviation (SD) or as median with interquartile range (IQR) for continuous variables as appropriate. Missing data from clinical variables (0.9-13.7%) were imputed by multiple imputation using predictive mean matching in which 20 dummy sets were created. Primary and secondary analyses were performed with baseline QoL and delta QoL (three months follow-up minus baseline) scores. Survival analyses were performed with Cox regression models. QoL variables with $P<0.20$ in univariable analysis were selected for inclusion in multivariable analysis with backward stepwise selection and reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Analyses were adjusted for patient, tumor, and treatment characteristics as well as other known predictors for survival. Delta analyses were additionally adjusted for baseline scores. The covariates are presented in the footnotes of the tables. The prognostic value of baseline QoL predictors was assessed with Nagelkerke's R^2 (i.e. explained variance) in univariable analysis, multivariable analysis with adjustment for clinical variables (i.e. sex, age, BMI, ECOG performance status, tumor topography, tumor stage, and type of chemotherapy), and multivariable analysis with adjustment clinical variables and other predictive QoL items from the same questionnaire. An increase in explained variance in analyses with adjustment for clinical variables of 5% was considered clinically relevant. These analyses were performed according to the previously described method for estimation of R^2 after multiple imputation.[22] The survival analyses were repeated for the resected and non-resected subgroups. Two-sided $P<0.05$ were considered statistically significant after adjustment for multiple testing by Benjamini-Hochberg procedure.

RESULTS

Population

For baseline analyses, 376 patients were included. After exclusion of 143 patient who completed the baseline questionnaire after start of treatment, 233 patients remained. Similarly for delta analyses, 256 patients were included, and after exclusion of 108 patients, 148 patients remained. Overall response rate to the questionnaires during the study period was 60%. The majority of patients were diagnosed with pancreatic adenocarcinoma (n=194, 83.3%) and had stage III (n=77, 33.0%) or IV (n=61, 26.2%) disease. Overall, 141 patients (60.5%) received chemotherapy. Of all patients, 103 (44.2%) underwent

a pancreatic resection and 130 (55.8%) did not. During the study period, 159 patients (68.2%) of the cohort died. Median follow-up of patients was 13.1 months (IQR 7.4-17.5). Median overall survival was 13.6 months (95% CI 11.6-15.6) for the total cohort, 20.7 months (95% CI 14.9-26.5) for patients after resection, and 9.3 months (95% CI 7.7-11.2) for patients without resection. Table 1 provides an overview of patient, tumor, and treatment characteristics. Most QoL scores changed over time, see Table 2 for QoL scores of all items and Figure 1A and 1B for a radar chart of the EORTC QLQ-C30 and -PAN26 scores.

TABLE 1. Characteristics of 233 patients with pancreatic and periampullary adenocarcinoma in the Netherlands.

Clinical characteristics	Total cohort (n=233)
Male (n, %)	126 (54.1)
Age at diagnosis (mean, SD)	66.6 (9.1)
BMI (median, IQR)	23.9 (21.4-26.7)
Comorbidities (n, %)	
Previous cancer	36 (15.5)
Pulmonary	26 (11.2)
Cardiovascular	70 (30.0)
Diabetes mellitus	70 (30.0)
ECOG performance status (n, %)	
0-1	195 (83.7)
2-4	38 (16.3)
Year of diagnosis (n, %)	
2015	47 (20.2)
2016	14 (6.0)
2017	157 (67.4)
2018	15 (6.4)
Follow-up in months (median, IQR)	13.1 (7.4-17.5)
No surgery	9.1 (5.7-13.6)
Surgery	16.4 (12.1-19.5)
Tumor characteristics	
Location (n, %)	
Pancreas	194 (83.3)
Periampullary	39 (16.7)
Stage (n, %)	
IA	11 (4.7)
IB	20 (8.6)
IIA	16 (6.9)
IIB	48 (20.6)
III	77 (33.0)
IV	61 (26.2)
Treatment characteristics	
Surgical intervention (n, %)	109 (46.8)
Pancreatoduodenectomy	91 (39.1)[$]
Other pancreatectomy	12 (5.2)[$]
IRE / RFA	6 (2.6)[$]

Resection margin (n, %)	
R0	70 (68.0)^
R1	33 (32.0)^
Radiotherapy (n, %)	16 (6.9)
Chemotherapy (n, %)	141 (60.5)
Neo-adjuvant only	4 (2.8)#
Adjuvant only	45 (31.9)#
Neo-adjuvant and adjuvant	9 (6.4)#
Chemotherapy, no resection	83 (58.9)#
Type of first chemotherapy (n, %)	
Gemcitabine only	31 (22.0)#
Gemcitabine in combination*	33 (23.4)#
FOLFIRINOX	68 (48.2)#
Other	9 (6.4)#
Chemotherapy courses (n, %)	
1-4	50 (35.5)#
5-8	69 (48.9)#
≥9	22 (15.6)#
Adjustment of chemotherapy (n, %)	36 (25.5)#
Biliary drainage (n, %)	101 (43.3)

BMI = Body Mass Index, ECOG = Eastern Cooperative Oncology Group, IRE = irreversible electroporation, RFA = radiofrequent ablation. $ Proportion of patients who underwent surgical intervention. ^ Proportion of patients who underwent resection. # Proportion of patients who underwent chemotherapy. * Gemcitabine + nab-paclitaxel and gemcitabine + capecitabine.

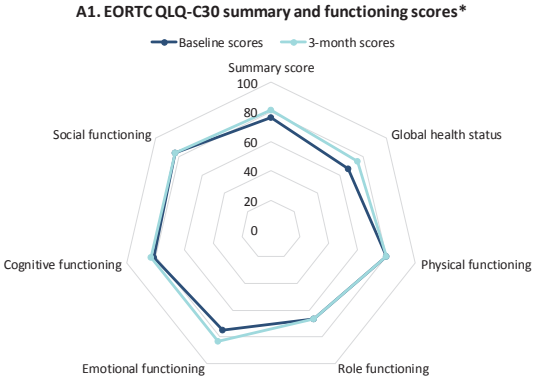
Baseline QoL and survival

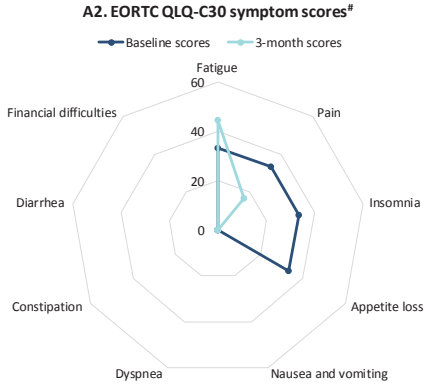
For the total cohort, independent baseline QoL predictors based on multivariable analyses for reduced survival were overall happiness today (HR per step on 0-10 scale 0.92 (95% CI 0.84-0.92, *P* = 0.046)), role functioning (HR per step on 0-100 scale 0.99 (95% CI 0.99-1.00, *P* = 0.007)), diarrhea (HR per step on 0-100 scale 1.01 (95% CI 1.00-1.01, *P* = 0.018)), pancreatic pain (HR per step on 0-100 scale 1.01 (95% CI 1.00-1.02, *P* = 0.009)), and body image (HR per step on 0-100 scale 1.01 (95% CI 1.00-1.01, *P* = 0.035), Table 3).

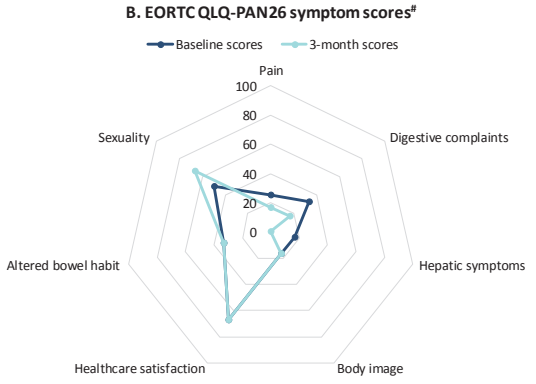
For patients who had undergone resection, no independent baseline QoL score predicted survival (Supplementary Table S1).

For patients without resection, lower overall satisfaction with life, and physical and cognitive functioning, and higher QLQ-C30 summary, fatigue, (pancreatic) pain, constipation, diarrhea, and body image scores were independent predictors for reduced survival in multivariable analysis (Table 4).

FIGURE 1A and 1B. Baseline and 3-month quality of life scores from the EORTC QLQ-C30 (A1: summary and functioning scores, A2: symptom scores) and -PAN26 (B: symptom scores) items for the total cohort.







* Higher scores represent better quality of life; # Higher scores represent worse quality of life

Delta QoL and survival

For the total cohort in multivariable analysis, the only independent predictor for reduced survival was more constipation at three months compared to baseline (HR per step on 0-100 scale 1.02 (95% CI 1.01-1.03, *P* = 0.006), Supplementary Table S2). For patients with or without resection, no independent delta QoL score predicted survival (Supplementary Table S3 and S4).

The small HRs from baseline and delta multivariable analyses from the EORTC QLQ-C30 and -PAN26 scales (e.g. HR 1.02) represent the risk of mortality per 1 point change in score on a 0-100 scale (e.g. from 66 to 67). This HR of 1.02 corresponds to a HR of 1.22 per 10 points change in score (e.g. from 66 to 76; HR 1.02^10 = 1.22).

TABLE 2. Median QoL scores with IQR on all items of three questionnaires at baseline and after three months.

	Baseline (n=233)	Three months (n=148)
Happiness		
Item one*	7.0 (5.0-8.0)	7.0 (6.0-8.0)
Item two*	7.0 (5.0-8.0)	7.0 (6.0-8.0)
Item three*	5.0 (4.0-7.0)	7.0 (5.0-8.0)
Item four*	6.0 (4.0-7.0)	7.0 (5.0-8.0)
EORTC QLQ-C30		
Summary score*	76.4 (64.7-85.1)	81.0 (71.3-89.1)
Global health status*	66.7 (50.0-83.3)	75.0 (58.3-83.3)
Physical functioning*	80.0 (61.7-93.3)	80.0 (63.3-86.7)
Role functioning*	66.7 (37.5-100.0)	66.7 (50.0-100.0)
Emotional functioning*	75.0 (58.3-91.7)	83.3 (70.8-100.0)
Cognitive functioning*	81.7 (66.7-100.0)	83.3 (66.7-100.0)
Social functioning*	83.3 (66.7-100.0)	83.3 (66.7-100.0)
Fatigue#	33.3 (22.2-66.7)	44.4 (22.2-55.6)
Nausea and vomiting#	0.0 (0.0-33.3)	0.0 (0.0-16.7)
Pain#	33.3 (0.0-50.0)	16.7 (0.0-33.3)
Dyspnea#	0.0 (0.0-33.3)	0.0 (0.0-33.3)
Insomnia#	33.3 (0.0-66.7)	0.0 (0.0-33.3)
Appetite loss#	33.3 (0.0-66.7)	0.0 (0.0-33.3)
Constipation#	0.0 (0.0-33.3)	0.0 (0.0-0.0)
Diarrhea#	0.0 (0.0-33.3)	0.0 (0.0-33.3)
Financial difficulties#	0.0 (0.0-0.0)	0.0 (0.0-0.0)
EORTC QLQ-PAN26		
Pain#	25.0 (8.3-50.0)	16.7 (8.3-25.0)
Digestive complaints#	33.3 (0.0-50.0)	16.7 (0.0-33.3)
Hepatic symptoms#	16.7 (0.0-33.3)	0.0 (0.0-4.2)
Body image#	16.7 (0.0-33.3)	16.7 (0.0-33.3)
Healthcare satisfaction#	66.7 (50.0-83.3)	66.7 (33.3-83.3)
Altered bowel habit#	33.3 (16.7-50.0)	33.3 (12.5-50.0)
Sexuality#	50.0 (0.0-100.0)	66.7 (33.3-83.3)

QoL = quality of life. IQR = interquartile ranges. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. * Higher scores represent better QoL. # Higher scores represent worse QoL.

TABLE 3. Uni- and multivariable analysis of the relation between baseline QoL scores with overall mortality of patients with pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	HR (95% CI)	P value	Adjusted P value	HR (95% CI)	P value	Adjusted P value
Happiness						
Item one	**0.92 (0.85-1.01)**	**0.068**	**0.131**			
Item two	**0.92 (0.84-0.92)**	**0.035**	**0.086**	**0.92 (0.84-0.92)**	**0.035**	**0.035**
Item three	0.96 (0.89-1.04)	0.357	0.482			
Item four	**0.91 (0.83-0.99)**	**0.020**	**0.060**			
EORTC QLQ-C30						
Summary score	**0.98 (0.97-0.99)**	**0.001**	**0.027**			
Global health status	**0.99 (0.99-1.00)**	**0.082**	**0.148**			
Physical functioning	**0.99 (0.98-1.00)**	**0.008**	**0.043**			
Role functioning	**0.99 (0.99-1.00)**	**0.005**	**0.034**	**0.99 (0.99-1.00)**	**0.007**	**0.023**
Emotional functioning	**0.99 (0.99-1.00)**	**0.106**	**0.179**			
Cognitive functioning	**0.99 (0.98-1.00)**	**0.018**	**0.060**			
Social functioning	**0.99 (0.99-1.00)**	**0.059**	**0.122**			
Fatigue	**1.01 (1.00-1.02)**	**0.002**	**0.027**			
Nausea and vomiting	**1.01 (1.00-1.01)**	**0.124**	0.792			
Pain	**1.01 (1.00-1.01)**	**0.015**	**0.058**			
Dyspnea	1.00 (1.00-1.01)	0.530	0.622			
Insomnia	1.00 (1.00-1.01)	0.631	0.710			
Appetite loss	**1.01 (1.00-1.01)**	**0.040**	**0.090**			
Constipation	**1.01 (1.00-1.01)**	**0.035**	**0.086**			
Diarrhea	**1.01 (1.00-1.01)**	**0.128**	**0.192**	**1.01 (1.00-1.01)**	**0.018**	**0.030**
Financial difficulties	1.00 (1.00-1.01)	0.463	0.572			
EORTC QLQ-PAN26						
Pancreatic pain	**1.01 (1.00-1.02)**	**0.003**	**0.027**	**1.01 (1.00-1.02)**	**0.009**	**0.023**
Digestive complaints	1.00 (1.00-1.01)	0.288	0.409			
Hepatic symptoms	1.00 (1.00-1.00)	0.466	0.572			
Body image	**1.01 (1.00-1.01)**	**0.012**	**0.054**	**1.01 (1.00-1.01)**	**0.035**	**0.035**
Healthcare satisfaction	1.00 (1.00-1.01)	0.761	0.822			
Altered bowel habit	1.00 (1.00-1.01)	0.934	0.934			
Sexuality	1.00 (1.00-1.01)	0.876	0.910			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for sex, age, BMI, ECOG performance status, tumor topography, tumor stage, surgical intervention, type of chemotherapy, and number of chemotherapy courses. # Not adjusted for QoL scores from the other two other questionnaires.

Explained variance baseline without resection

Together, the clinical variables (i.e. sex, age, BMI, ECOG, tumor topography, tumor stage, and type of chemotherapy) in this subgroup model explained 20% of the outcome variance (blue bars, Figure 2). Figure 2 shows what percentage of the outcome is explained additionally by the various independent QoL predictors individually (orange bars). When for example the item physical functioning was added,

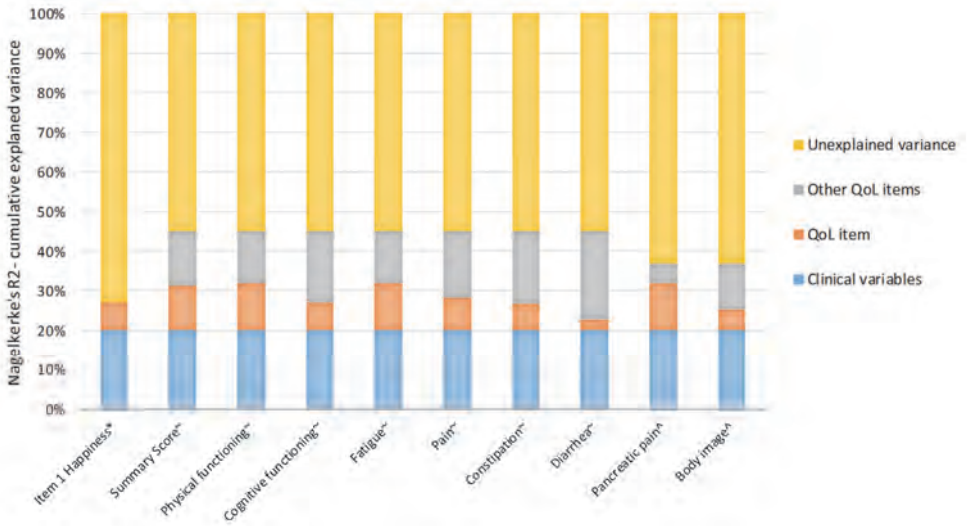
32% of variance of the outcome was explained (12% increase by adding this to the model; blue plus orange bar for physical functioning). All baseline QoL items but diarrhea accounted for >5% of the additional explained variance and were therefore considered to be of additional prognostic value. A similar effect was seen after adding the other QoL items from the same questionnaire to the model (grey bars, Figure 2).

TABLE 4. Uni- and multivariable analysis of the relation between baseline QoL scores with overall mortality of patients without resection for pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	**HR (95% CI)**	**P value**	**Adjusted P value**	**HR (95% CI)**	**P value**	**Adjusted P value**
Happiness						
Item one	**0.86 (0.77-0.95)**	**0.004**	**0.010**	**0.86 (0.77-0.95)**	**0.004**	**0.006**
Item two	**0.89 (0.81-0.99)**	**0.006**	**0.014**			
Item three	0.94 (0.85-1.01)	0.293	0.360			
Item four	**0.89 (0.80-0.99)**	**0.035**	**0.056**			
EORTC QLQ-C30						
Summary score	**0.97 (0.95-0.98)**	**<0.001**	**<0.001**	**1.07 (1.02-1.11)**	**0.004**	**0.006**
Global health status	**0.98 (0.97-0.99)**	**0.001**	**0.003**			
Physical functioning	**0.98 (0.97-0.99)**	**<0.001**	**<0.001**	**0.98 (0.96-0.99)**	**0.003**	**0.006**
Role functioning	**0.99 (0.98-1.00)**	**0.004**	**0.010**			
Emotional functioning	**0.99 (0.98-1.00)**	**0.068**	**0.097**			
Cognitive functioning	**0.98 (0.98-0.99)**	**<0.001**	**<0.001**	**0.99 (0.97-0.99)**	**0.029**	**0.029**
Social functioning	**0.99 (0.98-1.00)**	**0.020**	**0.039**			
Fatigue	**1.02 (1.01-1.03)**	**<0.001**	**<0.001**	**1.02 (1.01-1.04)**	**0.004**	**0.006**
Nausea and vomiting	**1.01 (1.00-1.02)**	**0.052**	**0.078**			
Pain	**1.02 (1.01-1.02)**	**<0.001**	**<0.001**	**1.01 (1.00-1.02)**	**0.018**	**0.020**
Dyspnea	1.00 (0.99-1.01)	0.715	0.715			
Insomnia	1.00 (0.99-1.01)	0.710	0.715			
Appetite loss	**1.01 (1.00-1.01)**	**0.097**	**0.131**			
Constipation	**1.01 (1.01-1.02)**	**0.001**	**0.003**	**1.02 (1.01-1.03)**	**<0.001**	**<0.001**
Diarrhea	**1.01 (1.00-1.02)**	**0.024**	**0.043**	**1.01 (1.00-1.02)**	**0.015**	**0.019**
Financial difficulties	1.00 (0.99-1.01)	0.671	0.715			
EORTC QLQ-PAN26						
Pancreatic pain	**1.02 (1.01-1.03)**	**<0.001**	**<0.001**	**1.02 (1.01-1.03)**	**<0.001**	**<0.001**
Digestive complaints	**1.01 (1.00-1.02)**	**0.012**	**0.025**			
Hepatic symptoms	1.00 (0.99-1.01)	0.398	0.467			
Body image	**1.01 (1.00-1.02)**	**0.004**	**0.010**	**1.01 (1.00-1.02)**	**0.002**	**0.006**
Healthcare satisfaction	1.00 (1.00-1.01)	0.540	0.608			
Altered bowel habit	**1.01 (1.00-1.02)**	**0.035**	**0.056**			
Sexuality	1.00 (0.99-1.01)	0.233	0.300			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for sex, age, BMI, ECOG performance status, tumor topography, tumor stage, and type of chemotherapy. # Not adjusted for QoL scores from the other two other questionnaires.

FIGURE 2. Additional prognostic value of independent baseline quality of life (QoL) predictors for overall mortality of patients without resection for pancreatic and periampullary adenocarcinoma expressed as Nagelkerke's R^2



Blue bars: the clinical variables include sex, age, BMI, ECOG performance status, tumor topography, tumor stage, and type of chemotherapy. Orange bars: additional explained variance of the QoL item. Grey bars: additional explained variance of the other QoL items from the same questionnaire. Yellow bars: unexplained variance.
*Item one (i.e. satisfaction with one's life as a whole) from the Happiness questionnaire. In grey, not adjusted for other QoL items from the Happiness questionnaire. ~Items from the EORTC QLQ-C30 questionnaire. In grey, adjusted for the other predictive QoL items from the EORTC QLQ-C30 questionnaire (i.e. summary score, physical functioning, cognitive functioning, fatigue, pain, constipation, diarrhea). ;;FIGURE ^Items from the EORTC QLQ-PAN26 questionnaire. In grey, adjusted for the other predictive QoL items from the EORTC QLQ-PAN26 questionnaire (i.e. pancreatic pain, body image).

DISCUSSION

This multicenter study including patients with pancreatic and periampullary cancer in daily clinical practice showed that several QoL domains measured at baseline and follow-up predict survival, even when adjusting for well-known clinical prognostic parameters such as ECOG performance status[15]. Since QoL questionnaires measure patients' perspective on their functioning and symptoms, they may provide a more sensitive and comprehensive picture of patients' health status that may be missed by traditional clinical measures (e.g., tumor stage or performance status)[6, 23].

We found lower happiness, a worse body image, and a lower summary score to predict reduced survival of patients with pancreatic and periampullary cancer. With the used questionnaire, happiness is measured as life satisfaction, hedonic level of affect, and contentment[16]. Taking this into account, the happiness items could cover more QoL aspects than for example the global health status item only, and

therefore come forth as predictor, while global health status does not. Previous studies found that satisfaction with life of cancer patients is correlated with clinical (e.g., times of admission, surgical treatment, postoperative complications, length of hospital stay), psychosocial (e.g., depressive symptoms, stress, social support, self-esteem), and sociodemographic (e.g., marital status, occupation) factors[24-26]. Several of these factors have been associated with survival, such as postoperative complications, depressive symptoms, and marital status[27-29]. This could also be a reason why life satisfaction or happiness is associated with survival in our population. In addition, it was suggested that socioeconomic status (e.g., marital status, occupation) of cancer patients is a survival predictor[23]. Unfortunately, because socioeconomic status is not registered accurately in the NCR, we could not investigate this in more detail.

Body image is often negatively influenced in cancer patients by physical changes due to the disease or treatment, for example after surgery for breast- or colorectal cancer (e.g., mastectomy, colostomy)[30, 31]. Specifically for patients with pancreatic and periampullary cancer, body image may be affected by the occurrence of cachexia[32]. The incidence of cachexia in patients with pancreatic cancer is high, cachexia related complications occur often, and cachexia has been associated with reduced survival[33-35]. A part from obstructive jaundice, which often is the presenting symptom of pancreatic and periampullary cancer patients, other mechanisms leading to cachexia are still not completely clear and evaluation of this multifactorial syndrome is not straightforward[35]. For this reason, this easy to measure QoL item - body image - could be representative of cachexia, which is an important prognostic factor for patients with cancer, especially in combination with other factors of cachexia (e.g., weight loss, anorexia).

The summary score combines 13 of the 15 EORTC QLQ-C30 scales and was amongst other things developed to reduce the risk of type-I-errors due to multiple testing. The score was found to have equal or superior known-groups validity and responsiveness to change over time as compared to the separate scales[21]. Although many of these individual scales were shown to have predictive value in other cancers[7, 23, 36, 37], this was not yet the case for patients with pancreatic and periampullary cancer, nor for the relatively new summary score. This score uses the information of the individual scales, while maintaining a broad QoL scope. In addition, it is measured with a widely implemented and validated questionnaire. Therefore, it can be investigated with comparison of data of other pancreatic or periampullary cancer populations whether this item is not only efficient (i.e. single vs. multiple testing), but also effective for measuring a predictive relation to survival (i.e. robust single higher order factor model)[21].

We found that baseline QoL scores were specifically predictive of survival for the subgroup of patients who did not undergo pancreatic resection. In contrast, baseline scores were not predictors of mortality in the resected subgroup. This might be due to the longer survival times after resection and thus other factors that may come into play in the course time that could also influence survival. In other patient groups, for example patients with colorectal cancer, baseline QoL has been associated with survival after resection[38]. However, the disease course of patients with pancreatic cancer is fairly different from other types of cancer, for example regarding morbidities, treatment, disease recurrence, and survival. Of the baseline symptoms that we found to be predictive of survival for patients who did not undergo a resection, diarrhea as a symptom deserves special attention. Diarrhea can be treatment related, or a symptom of exocrine pancreatic insufficiency, which occurs in up to 92% in patients with unresectable pancreatic or periampullary tumors within six months from diagnosis[39]. Unfortunately, often only a small proportion of patients in the palliative setting receive pancreatic enzyme replacement therapy[40]. Recent studies have suggested that this therapy may independently improve survival[41]. Therefore, this is an important and potentially modifiable risk factor that can be identified through PROMs.

For delta QoL, we found that constipation was predictive of mortality for the total cohort. Some studies, for example in lung and oesophageal cancer patients, demonstrated that deterioration of QoL scores was predictive of shorter survival times[37, 42], whereas delta scores for head-neck cancer patients were not related to survival[43]. It may be hypothesized that the patients with more constipation were patients with progressive disease and more pain, and therefore received more opioids, leading to obstipation. Unfortunately, due to a limited number of events in the subgroups of our dataset, we could not test this hypothesis and could only adjust for a limited number of confounding factors.

Our results have important implications for daily practice and research. In the explained variance analysis (Nagelkerke's R^2), we found that the QoL items were of additional prognostic value on top of the clinical variables. Given the prognostic value of QoL parameters, these parameters may be used during shared decision making on disease management and treatment in the (outpatient) clinic. Ideally, patients should complete questionnaires before meeting their clinician so that QoL can be discussed during the subsequent appointment. The summary score could be easily used for evaluation of overall QoL, as it is one seemingly valid score compared to the 15 individual scale scores. When specific symptoms are present, such as diarrhea, these could be acted upon immediately. Predictive QoL parameters may be added to prediction models for survival[44, 45], in addition to patient, tumor, and treatment characteristics to improve their predictive outcome. Finally, QoL parameters may be considered as a stratification factor in clinical trials and should be included in the core set of mandatory baseline measurements[15, 20].

Some limitations of our study should be taken into account. First, median overall survival of our cohort is relatively high compared to other population-based studies[46-48]. Although the NCR covers all patients with cancer in the Netherlands, selection bias has probably occurred in the PROMs registry. Almost half of this study population underwent resection, while usually this is approximately 20% in the Netherlands[47]. Second, almost 60% of patients without surgery received chemotherapy, while this is approximately 30% in an unselected subgroup[47]. Presumably, fit patients are more willing to participate in QoL questionnaire studies, or clinicians are more likely to include fit patients. Third, approximately 40% of patients were excluded because baseline questionnaires were not filled out before start of cancer treatment. Fourth, although the association model remained stable, due to limitations in the sample size, multiple testing and some statistical uncertainty were introduced. To reduce this, the Benjamini-Hochberg procedure was used. Fifth, adjustment for chemotherapy duration or change of treatment was not feasible in delta subgroup analyses, as the number of patients and non-events (i.e. non-death) decreased in the subgroups compared to the total cohort. Future studies with a larger sample size are needed to investigate this newly found relation between QoL and survival more clearly.

In conclusion, in daily clinical practice for patients with pancreatic and periampullary carcinoma, QoL is related to survival regardless of patient, tumor, and treatment characteristics. Overall happiness (Happiness), summary score (EORTC QLQ-C30), and several functioning and symptom scale item scores (EORTC QLQ-C30 and -PAN26) were predictive of survival. Baseline QoL scores were of prognostic value for patients without resection, whereas delta QoL scores were predictive for the total cohort. Given their additional prognostic value, PROMs may be used for different reasons in the clinical setting (i.e. shared decision making, disease management/treatment, clinical prediction models, or stratification in trials).

ACKNOWLEDGEMENTS

The authors thank the registration team of the Netherlands Cancer Registry for their dedicated data collection.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Uni- and multivariable analysis of the relation between baseline QoL scores with overall mortality of patients who underwent resection for pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	**HR (95% CI)**	**P value**	**Adjusted P value**	**HR (95% CI)**	**P value**	**Adjusted P value**
Happiness						
Item one	0.99 (0.81-1.22)	0.945	0.973			
Item two	1.01 (0.87-1.16)	0.932	0.973			
Item three	0.99 (0.87-1.13)	0.858	0.965			
Item four	0.92 (0.79-1.06)	0.249	0.932			
EORTC QLQ-C30						
Summary score	1.00 (0.98-1.03)	0.843	0.965			
Global health status	1.01 (0.99-1.03)	0.203	0.914			
Physical functioning	**1.01 (1.00-1.03)**	**0.132**	0.713			
Role functioning	1.00 (0.98-1.01)	0.491	0.932			
Emotional functioning	1.00 (0.98-1.01)	0.656	0.932			
Cognitive functioning	1.00 (0.98-1.01)	0.646	0.932			
Social functioning	1.00 (0.99-1.02)	0.714	0.964			
Fatigue	1.00 (0.99-1.02)	0.634	0.932			
Nausea and vomiting	0.99 (0.97-1.01)	0.412	0.932			
Pain	1.00 (0.98-1.01)	0.412	0.932			
Dyspnea	1.00 (0.99-1.02)	0.973	0.973			
Insomnia	1.00 (0.99-1.01)	0.811	0.965			
Appetite loss	1.00 (0.99-1.01)	0.627	0.932			
Constipation	**0.99 (0.98-1.00)**	**0.118**	0.713			
Diarrhea	1.00 (0.98-1.01)	0.574	0.932			
Financial difficulties	1.01 (0.99-1.04)	0.309	0.932			
EORTC QLQ-PAN26						
Pancreatic pain	1.00 (0.98-1.01)	0.607	0.932			
Digestive complaints	**0.99 (0.97-1.00)**	**0.051**	0.713			
Hepatic symptoms	1.00 (0.99-1.01)	0.494	0.932			
Body image	**0.99 (0.97-1.00)**	**0.119**	0.713			
Healthcare satisfaction	1.00 (0.99-1.01)	0.540	0.932			
Altered bowel habit	**0.99 (0.98-1.00)**	**0.084**	0.713			
Sexuality	1.00 (0.99-1.01)	0.788	0.965			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for sex, age, BMI, ECOG performance status, tumor topography, tumor stage, and type of chemotherapy. # Not adjusted for QoL scores from the other two other questionnaires.

SUPPLEMENTARY TBALE S2. Uni- and multivariable analysis of the relation between delta QoL scores with overall mortality of patients with pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	**HR (95% CI)**	**P value**	**Adjusted P value**	**HR (95% CI)**	**P value**	**Adjusted P value**
Happiness						
Item one	1.04 (0.82-1.30)	0.772	0.940			
Item two	0.95 (0.80-1.14)	0.584	0.907			
Item three	0.98 (0.82-1.18)	0.852	0.940			
Item four	1.12 (0.92-1.35)	0.257	0.861			
EORTC QLQ-C30						
Summary score	1.01 (0.98-1.04)	0.575	0.907			
Global health status	0.99 (0.98-1.01)	0.455	0.907			
Physical functioning	1.00 (0.99-1.02)	0.782	0.940			
Role functioning	**1.01 (1.00-1.02)**	**0.173**	0.861			
Emotional functioning	1.01 (0.99-1.03)	0.499	0.907			
Cognitive functioning	0.99 (0.97-1.01)	0.224	0.861			
Social functioning	1.00 (0.99-1.02)	0.938	0.940			
Fatigue	1.00 (0.99-1.01)	0.940	0.940			
Nausea and vomiting	1.00 (0.98-1.02)	0.850	0.940			
Pain	1.00 (0.99-1.02)	0.564	0.907			
Dyspnea	0.99 (0.98-1.02)	0.807	0.940			
Insomnia	0.99 (0.98-1.01)	0.329	0.874			
Appetite loss	0.99 (0.98-1.01)	0.215	0.861			
Constipation	**1.02 (1.01-1.03)**	**0.006**	**0.162**	**1.02 (1.01-1.03)**	**0.006**	**0.006**
Diarrhea	0.99 (0.98-1.01)	0.638	0.907			
Financial difficulties	0.99 (0.96-1.01)	0.287	0.861			
EORTC QLQ-PAN26						
Pancreatic pain	1.00 (0.99-1.02)	0.631	0.907			
Digestive complaints	1.00 (0.99-1.02)	0.538	0.907			
Hepatic symptoms	1.01 (0.99-1.03)	0.356	0.873			
Body image	**1.01 (1.00-1.03)**	**0.097**	0.861			
Healthcare satisfaction	0.99 (0.98-1.00)	0.263	0.861			
Altered bowel habit	1.00 (0.99-1.00)	0.897	0.940			
Sexuality	**1.01 (1.00-1.03)**	**0.041**	0.554			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for baseline score, sex, age, BMI, ECOG performance status, tumor topography, tumor stage, surgical intervention, type of chemotherapy, and number of chemotherapy courses. # Not adjusted for QoL scores from the other two other questionnaires.

SUPPLEMENTARY TBALE S3. Uni- and multivariable analysis of the relation between delta QoL scores with overall mortality of patients who underwent resection for pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	**HR (95% CI)**	**P value**	**Adjusted P value**	**HR (95% CI)**	**P value**	**Adjusted P value**
Happiness						
Item one	0.94 (0.75-1.17)	0.563	0.813			
Item two	0.97 (0.76-1.25)	0.815	0.842			
Item three	0.98 (0.80-1.20)	0.835	0.842			
Item four	1.10 (0.91-1.33)	0.333	0.692			
EORTC QLQ-C30						
Summary score	1.02 (0.98-1.06)	0.299	0.680			
Global health status	1.00 (0.98-1.02)	0.647	0.813			
Physical functioning	**0.98 (0.96-1.01)**	**0.141**	0.476			
Role functioning	0.99 (0.97-1.01)	0.302	0.680			
Emotional functioning	**1.02 (1.00-1.05)**	**0.062**	0.476			
Cognitive functioning	**0.98 (0.96-1.01)**	**0.168**	0.504			
Social functioning	1.00 (0.99-1.02)	0.666	0.813			
Fatigue	1.00 (0.98-1.02)	0.723	0.813			
Nausea and vomiting	**0.97 (0.94-1.00)**	**0.071**	0.476			
Pain	1.00 (0.99-1.02)	0.707	0.813			
Dyspnea	**0.97 (0.95-1.00)**	**0.092**	0.476			
Insomnia	0.99 (0.97-1.01)	0.478	0.807			
Appetite loss	**0.99 (0.97-1.00)**	**0.073**	0.476			
Constipation	0.99 (0.98-1.01)	0.508	0.807			
Diarrhea	**0.99 (0.97-1.00)**	**0.121**	0.476			
Financial difficulties	0.99 (0.96-1.02)	0.467	0.807			
EORTC QLQ-PAN26						
Pancreatic pain	1.00 (0.97-1.02)	0.663	0.813			
Digestive complaints	1.01 (0.99-1.03)	0.273	0.680			
Hepatic symptoms	**0.98 (0.95-1.01)**	**0.138**	0.476			
Body image	1.01 (0.99-1.02)	0.466	0.807			
Healthcare satisfaction	**0.99 (0.97-1.00)**	**0.111**	0.476			
Altered bowel habit	1.00 (0.99-1.02)	0.702	0.813			
Sexuality	1.00 (0.99-1.01)	0.842	0.842			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for baseline score, sex, age, BMI, tumor topography, tumor stage, and type of chemotherapy; not for ECOG performance status as 96.2% of patients had ECOG I-II. # Not adjusted for QoL scores from the other two other questionnaires.

SUPPLEMENTARY TBALE S4. Uni- and multivariable analysis of the relation between delta QoL scores with overall mortality of patients without resection for pancreatic and periampullary adenocarcinoma.

	Univariable*			Multivariable*#		
QoL scores	**HR (95% CI)**	**P value**	**Adjusted P value**	**HR (95% CI)**	**P value**	**Adjusted P value**
Happiness						
Item one	0.92 (0.78-1.08)	0.311	0.881			
Item two	0.96 (0.80-1.15)	0.684	0.924			
Item three	0.95 (0.78-1.15)	0.570	0.924			
Item four	1.00 (0.84-1.20)	0.960	0.974			
EORTC QLQ-C30						
Summary score	1.01 (0.98-1.04)	0.684	0.924			
Global health status	0.99 (0.97-1.01)	0.230	0.881			
Physical functioning	1.01 (0.99-1.03)	0.591	0.924			
Role functioning	1.01 (0.98-1.02)	0.359	0.881			
Emotional functioning	1.01 (0.99-1.03)	0.345	0.881			
Cognitive functioning	1.00 (0.98-1.02)	0.974	0.974			
Social functioning	1.01 (0.99-1.03)	0.336	0.881			
Fatigue	1.00 (0.98-1.02)	0.941	0.974			
Nausea and vomiting	1.01 (0.99-1.03)	0.309	0.881			
Pain	**1.01 (1.00-1.02)**	**0.107**	0.772			
Dyspnea	1.00 (0.98-1.02)	0.725	0.924			
Insomnia	1.00 (0.98-1.01)	0.535	0.924			
Appetite loss	1.00 (0.99-1.01)	0.819	0.933			
Constipation	**1.02 (1.00-1.03)**	**0.013**	0.351			
Diarrhea	1.00 (0.99-1.01)	0.829	0.932			
Financial difficulties	**0.98 (0.96-1.00)**	**0.079**	0.711			
EORTC QLQ-PAN26						
Pancreatic pain	1.01 (0.99-1.03)	0.333	0.881			
Digestive complaints	1.01 (0.99-1.02)	0.552	0.924			
Hepatic symptoms	1.00 (0.98-1.03)	0.753	0.924			
Body image	1.00 (0.98-1.01)	0.554	0.924			
Healthcare satisfaction	1.00 (0.99-1.01)	0.600	0.924			
Altered bowel habit	1.00 (0.99-1.01)	0.740	0.924			
Sexuality	**1.01 (1.00-1.02)**	**0.063**	0.711			

HR = hazard ratio, CI = confidence interval, QoL = quality of life, EORTC = European Organization for Research and Treatment of Cancer, QLQ = quality of life questionnaire. Item one = satisfaction with one's life as a whole. Item two = happiness today. Item three = happiness during the last month. Item four = where one feels to personally stand at present on a ladder from worst to best possible life. Bold in univariable analysis indicates use of variable in multivariable analysis. Bold in multivariable analysis indicates statistical significance after backward step selection. * Adjusted for baseline score, sex, age, BMI, tumor topography, tumor stage, and type of chemotherapy; not for ECOG performance status as 87.7% of patients had ECOG I-II. # Not adjusted for QoL scores from the other two other questionnaires.

CHAPTER 14

Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: a multicenter cohort study

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Cancer Medicine. 2020 Dec;9(24):9385-9395.

ABSTRACT

Background: It is unclear to what extent patients with pancreatic cancer have cachexia and had a dietetic consult for nutritional support. The aim was to assess the prevalence of cachexia, dietitian consultation, and overall survival in these patients.

Methods: This prospective multicenter cohort study included patients with pancreatic cancer, who participated in the Dutch Pancreatic Cancer Project and completed patient reported outcome measures (2015-2018). Additional data were obtained from the Netherlands Cancer Registry. Cachexia was defined as self-reported >5% body weight loss, or >2% in patients with a BMI <20 kg/m^2 over the past half year. The Kaplan-Meier method was used to analyze overall survival.

Results: In total, 202 patients were included from 18 centers. Cachexia was present in 144 patients (71%) and 81 of those patients (56%) had dietetic consultation. Cachexia was present in 63% of 94 patients who underwent surgery, 77% of 70 patients who received palliative chemotherapy and 82% of 38 patients who had best supportive care. Dietitian consultation was reported in 53%, 52% and 71% respectively. Median overall survival did not differ between patients with and without cachexia, but decreased in those with severe weight loss (12 months (IQR 7-20) vs. 16 months (IQR 8-31), p=0.02), as compared to those with <10% weight loss during the past half year.

Conclusion: Two-thirds of patients with pancreatic cancer present with cachexia of which nearly half had no dietetic consultation. Survival was comparable in patients with and without cachexia, but decreased in patients with more severe weight loss.

INTRODUCTION

Patients with pancreatic ductal adenocarcinoma and periampullary carcinoma (hereafter: pancreatic cancer) frequently present with malnutrition.[1] Weight loss or even cachexia is reported in up to 80% of patients with pancreatic cancer.[2–4] Weight loss could be caused by reduced dietary intake due to anorexia, abdominal pain, nausea, diarrhea, catabolic effects of the tumor, exocrine and endocrine pancreatic insufficiency, and duodenal obstruction.[5,6] Cachexia is defined as weight loss greater than 5%, or weight loss greater than 2% in individuals with a low body mass index (BMI, <20 kg/m²) or low skeletal muscle mass (sarcopenia) during the past six months.[7] Cachexia is nowadays regarded to as the ultimate form of disease related malnutrition, whereby, severe malnutrition is defined as a weight loss of 10% or more.[8,9] In pancreatic cancer, severe weight loss is associated with reduced survival, progressive disease, reduced treatment tolerance, and a decrease in quality of life.[2,7] In patients with resectable cancer it was shown that preoperative weight loss was associated with a shorter survival.[10] This emphasizes the need for early screening (the risk of) for malnutrition and to start nutritional interventions, preferably before start of anti-cancer treatment, such as surgery.[8,11–16] Dietitians can create an individualized treatment plan based on patients' specific needs, for example in the context of exocrine and/or endocrine insufficiency or nutritional impact symptoms. Currently, it is unclear to what extent patients with pancreatic cancer in a real-world setting have cachexia and had a dietetic consult for nutritional assessment and support. Therefore, the aims were to assess the prevalence of cachexia, dietetic consultation, and overall survival in these patients.

METHODS

Study design

This prospective multicenter cohort study included patients with pancreatic cancer who participated in the Dutch Pancreatic Cancer Project (PACAP).[17] PACAP was established in 2013 and includes a collection of clinical and patient reported outcome measures (PROMs, questionnaires) data. Currently, 48 centers participate in this nationwide project (www.pacap.nl). The PROMs data included self-reported nutritional parameters and body weight. Patient, tumor, and treatment data were retrieved from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry in which all patients with a newly diagnosed malignancy are identified by automatic notifications of the national pathological archive (PALGA) and the National Hospital Discharge Register. Data within the NCR were collected from medical records by trained NCR administrators. The data from the PROMs and NCR were linked as all patients provided written informed consent for participation and linkage of data. This study was performed in accordance with the STROBE guidelines.[18]

Study population

All patients with pancreatic and periampullary cancer who participated in the PACAP PROMs registry between January 2015 and February 2018 were included. Patients were excluded if the questionnaire was not completed at baseline or if data on weight loss were lacking in any questionnaire.

Data collection

The NCR includes clinical data, specifically sex, age, World Health Organization (WHO) performance status, comorbidities, tumor location, tumor stage, and treatment details regarding resection and chemotherapy. Tumor stage was classified according to TNM 7 for patients diagnosed in 2015-2016 and TNM 8 if diagnosed in 2017-2018.[19,20] Tumor stage was based on the pathological TNM stage. If patients received neoadjuvant therapy or if pathological TNM stage was not available, clinical TNM stage was used. Patients were categorized into three groups based on treatment (a) patients who underwent surgery (pancreatoduodenectomy, other pancreatectomy, or irreversible electroporation or radiofrequency ablation) and regardless of receiving or completing (neo)adjuvant chemotherapy; (b) patients who started palliative chemotherapy (patients who started neoadjuvant chemotherapy but did not undergo surgery were also included) and; (c) patients who received best supportive care. PROMs were collected at baseline and at 3, 6, 9, 12, 18, and 24 months after baseline, and yearly thereafter, until death or dropout. Results from baseline, 3, and 9 months were used, because dietary intake measurements (by the Dutch Healthy Diet Food Frequency Questionnaire (DHD-FFQ)) were available at these time points. A questionnaire was considered a baseline measurement if the first questionnaire was completed (best supportive care group) or if it was completed between the date of diagnosis and (a) date of surgery or (b) date of start of neoadjuvant or palliative chemotherapy or within one week after start of chemotherapy (i.e. considering that this would not influence the results, because most questions were about a longer retrospective period). Survival data were obtained by linkage with the Municipal Personal Records Database which contains the vital status of all Dutch inhabitants. Overall survival time was defined as the time between date of diagnosis and date of death or censoring (1 February 2020).

Nutritional status

The PROMs contained questions on the following domains with respect to nutritional status and interventions: height, current weight, weight loss, dietetic consultation (including both intramural and extramural health care), self-reported reduced food intake, appetite, use of oral nutritional supplements or parenteral nutrition, and tube feeding. BMI (kg/m^2) was calculated from reported weight and height. A dietetic consultation is designed in accordance the Dutch Guidelines on malnutrition.[21] A consult starts with screening of and diagnosing malnutrition and, in case of malnutrition, an extensive nutritional

assessment will be performed. Based on these results an appropriate and individualized treatment plan will be made. Cachexia was defined as >5% body weight loss, or >2% with a BMI of <20 kg/m^2 according to the international consensus criteria of Fearon et al. (2011).[7] Severe weight loss (≥10%) was calculated from the reported body weight and weight loss over the past half year before diagnosis in the PROMs. The DHD-FFQ was completed by patients who consumed food orally. This is a validated questionnaire based on national dietary guidelines including questions about portion sizes of bread, dairy, meat, fish, vegetables and candy, and alcohol consumption.[22,23] Based on previously described methods, a protein score was calculated from the results of the DHD-FFQ ranging from 0 to 10 and categorized into two categories: 0-9.9 or 10.[22,24] A score <10 corresponds with a protein intake that provides room for improvement by increasing the consumption of protein sources that were included in the DHD-FFQ for the general healthy population.[23] Patients with cancer have higher protein requirements than healthy persons and therefore, a protein intake assessed as needed to be improved for a healthy person could be interpreted as needed for dietetic consultation and/or oral nutritional supplements for cancer patients.

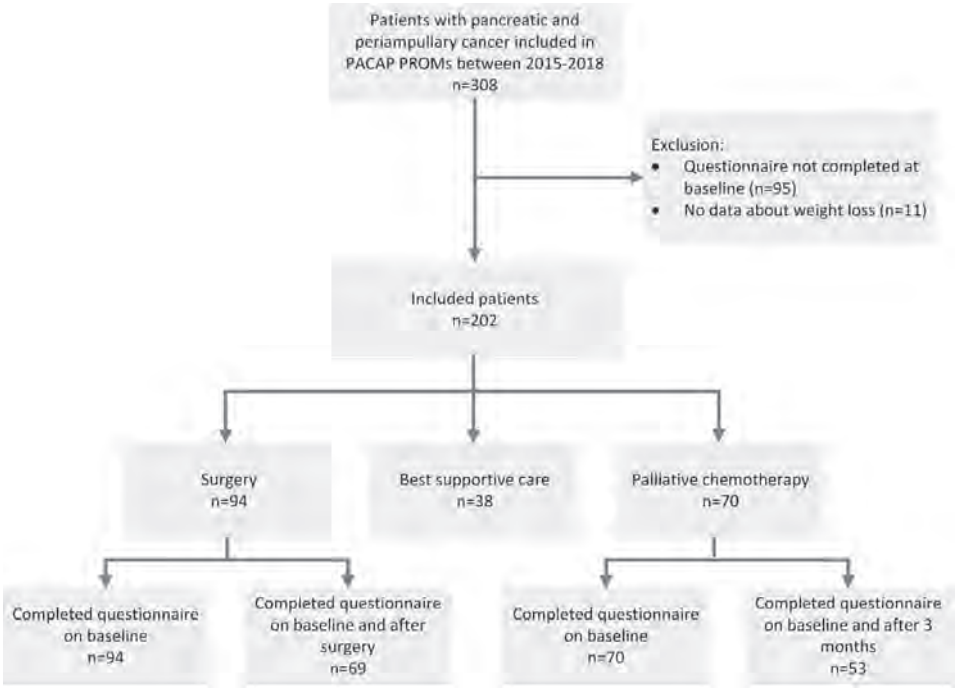
Statistical analysis

Baseline characteristics and nutritional parameters were presented using descriptive statistics. Normally distributed continuous data were presented as means with standard deviations (SD). Non-normally distributed continuous data were presented as medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages. Median overall survival was calculated using the Kaplan-Meier method in patients with and without cachexia, and with <10% and ≥10% weight loss at baseline. Overall survival was compared using the log-rank test. P-values <0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute).

RESULTS

In total, 308 patients with pancreatic cancer from 18 centers were included in the PACAP cohort between 2015 and 2018 (Figure 1). Of these patients, 95 were excluded because the first questionnaire was not completed at baseline and 11 because data about weight loss were lacking. Of the remaining 202 patients, 94 (47%) were female and the median age was 68 years (IQR 62-73, Table 1). The majority of patients (n=132, 65%) had a WHO performance status of 0 or 1. Of the 94 patients (47%) with surgery, 79 (84%) underwent a pancreatoduodenectomy and 57 (61%) received neoadjuvant and/or adjuvant chemotherapy. Neoadjuvant therapy had a median duration of 50 days (IQR 43-91). Seventy out of the 202 patients (35%) received palliative chemotherapy, and 38 patients (19%) received best supportive care.

FIGURE 1. Flow diagram of patient inclusion



Nutritional status

At diagnosis, cachexia was present in 144 patients (71%). In 81 of these cachectic patients (56%), dietetic consultation was reported at baseline, compared to 7 patients in the group without cachexia (12%). At baseline, 40% of all included patients (n=81) presented with ≥10% weight loss during the past 6 months and 52 of these patients (64%) had dietetic consultation. The protein score (<10) was insufficient in 147 patients (78%), of whom 58 patients (39%) were seen by a dietician.

Of all 94 patients who underwent surgery, 59 patients (63%) had cachexia at baseline of whom 31 (53%) had a dietetic consultation (Table 2, Figure 2). The presence of cachexia did not differ between patients with a BMI <25 compared to those with a BMI ≥25 (35 patients (69%) vs. 29 patients (69%), respectively, p=0.965), as accounted for weight loss ≥10% (17 patients (33%) vs. 11 patients (26%), respectively, p=0.455). At baseline, 4 patients (4%) received tube feeding,28 patients (30%) used oral nutritional supplements, and none used parenteral nutrition. The protein score was insufficient at baseline in 62 patients (66%), 23 of these patients (37%) had dietetic consultation, and 21 patients (34%) received oral

nutritional supplements. Pancreatic enzyme supplementation was given to 13 patients (19%) at baseline and to 44 patients (64%) after surgery.

TABLE 1. Baseline characteristics of all patients and stratified per type of treatment.

	All patients (n=202)	Surgery (n=94)	Palliative chemotherapy (n=70)	Best supportive care (n=38)
Female, No. (%)	94 (47%)	42 (45%)	35 (50%)	17 (45%)
Age, years, median (IQR)	68 (62-73)	70 (62-74)	65 (60-70)	72 (62-77)
<55	17 (8%)	8 (9%)	6 (9%)	3 (8%)
55-64	60 (30%)	25 (27%)	25 (36%)	10 (26%)
65-74	83 (41%)	40 (43%)	33 (47%)	10 (26%)
≥75	42 (21%)	21 (22%)	6 (9%)	15 (39%)
Performance status, No. (%)				
0 or 1	132 (65%)	60 (64%)	52 (74%)	20 (53%)
≥ 2	21 (10%)	4 (4%)	7 (10%)	10 (26%)
Missing	49 (24%)	30 (32%)	11 (16%)	8 (21%)
Comorbidities, No. (%)				
0	45 (22%)	19 (20%)	17 (24%)	9 (24%)
1	66 (33%)	35 (37%)	22 (31%)	9 (24%)
≥2	70 (35%)	30 (32%)	24 (34%)	16 (42%)
Missing	21 (10%)	10 (11%)	7 (10%)	4 (11%)
Tumor location, No. (%)				
Pancreas	163 (81%)	63 (67%)	64 (91%)	36 (95%)
Periampullary	39 (19%)	31 (33%)	6 (9%)	2 (5%)
Clinical stage, No. (%)				
I	27 (13%)	14 (15%)	6 (9%)	7 (18%)
II	46 (23%)	32 (34%)	11 (16%)	3 (8%)
III	72 (36%)	43 (46%)	19 (27%)	10 (26%)
IV	55 (27%)	3 (3%)	34 (49%)	18 (47%)
Missing	2 (1%)	2 (2%)	0 (0%)	0 (0%)
Surgery, No. (%)				
Pancreatoduodenectomy	79 (39%)	79 (84%)	NA	NA
Other pancreatectomy	11 (5%)	11 (12%)	NA	NA
IRE/RFA	4 (2%)	4 (4%)	NA	NA
Chemotherapy, No. (%)				
Neoadjuvant only	5 (2%)	5 (5%)	NA	NA
Adjuvant only	42 (21%)	42 (45%)	NA	NA
Neo-adjuvant and adjuvant	10 (5%)	10 (11%)	NA	NA
Palliative	70 (35%)	NA	70 (100%)	NA

Abbreviations: IQR = interquartile range, BMI = body mass index, IRE = irreversible electroporation, RFA = radiofrequency ablation, NA = not applicable.

Of all 70 patients who received palliative chemotherapy, 54 patients (77%) had cachexia at baseline (Table 3, Figure 2). Dietitian consultation was offered in 28 of these cachectic patients (52%). In patients with a BMI ≥25, both cachexia (33 patients (80%) vs. 21 patients (72%), respectively, p=0.428) and weight loss ≥10% (21 patients (51%) vs. 10 patients (34%), respectively, p=0.164) were not different compared to patients with a BMI <25. Of all 53 patients (76%) with an insufficient protein score at baseline, 17 (32%) had a dietetic consultation and 17 (32%) received oral nutritional supplements. Pancreatic enzymes were supplemented in 12 patients (23%) at baseline and this increased to 17 patients (32%) after 3 months.

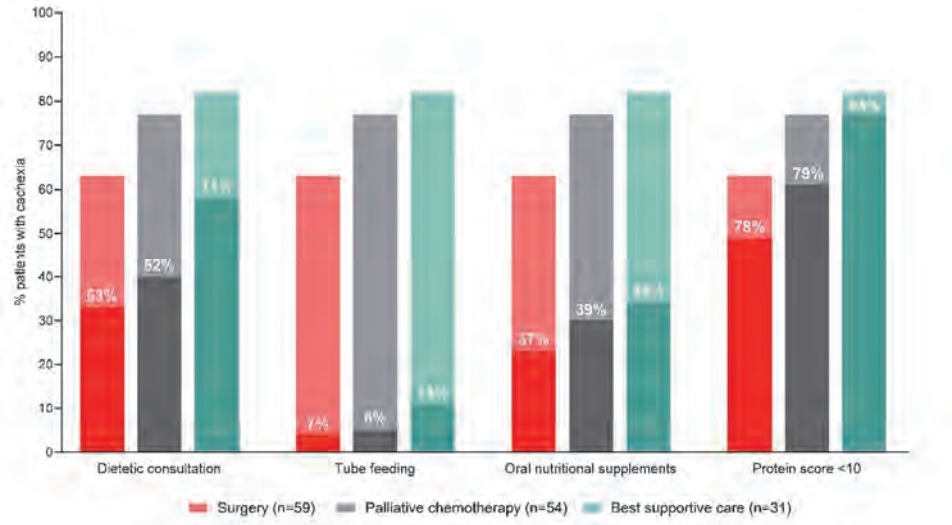
Of all 38 patients with best supportive care 31 patients (82%) had cachexia of whom 22 had a dietetic consultation (71%) (Figure 2). Tube feeding and oral nutritional supplements were used in 5 patients (13%) and 16 patients (42%), respectively. None used parenteral nutrition.

TABLE 2. Nutritional and weight parameters in patients who underwent surgery.

	Patients who completed the questionnaire at baseline* (n=94)	Patients who completed a questionnaire at baseline and after surgery^ (n=69)	
	Baseline	Baseline	After 3 months
Dietitian consultation, No. (%)	36 (38%)	24 (35%)	40 (58%)
Missing	1 (1%)	1 (1%)	1 (1%)
Oral tube feeding, No. (%)	4 (4%)	4 (6%)	2 (3%)
Missing	1 (1%)	0 (0%)	2 (3%)
Oral nutritional supplements, No. (%)	28 (30%)	18 (26%)	26 (38%)
Reduced food intake, No. (%)	50 (53%)	35 (51%)	49 (71%)
Missing	1 (1%)	1 (1%)	0 (0%)
Self-reported BMI, kg/m^2, median (IQR)	25 (22, 27)	25 (21, 28)	23 (21, 27)
<18.5 (underweight)	6 (6%)	5 (7%)	8 (12%)
18.5-25 (normal weight)	45 (48%)	32 (46%)	35 (51%)
≥25 (overweight)	42 (45%)	31 (45%)	26 (38%)
Missing	1 (1%)	1 (1%)	0 (0.0%)
Weight loss at baseline[&], No. (%)		NA	NA
<10%	66 (70%)		
≥10%	28 (30%)		
Cachexia, No. (%)	59 (63%)	41 (59%)	NA
Pancreatic enzyme supplementation, No. (%)	19 (20%)	13 (19%)	44 (64%)
Missing	2 (2%)	1 (1%)	5 (7%)
Protein score, No. (%)			
<10	62 (66%)	44 (64%)	47 (68%)
10	26 (28%)	20 (29%)	17 (25%)
Missing (did not complete DHD-FFQ)	6 (6%)	5 (7%)	5 (7%)

Abbreviations: BMI = body mass index, NA = not applicable. *Baseline is before or within one week after start neoadjuvant chemotherapy.^ After surgery is based on the 3 or 9 month questionnaire, depending on time of surgery. [&] Reported half year weight loss in baseline questionnaire.

FIGURE 2. Nutritional parameters in patients with cachexia at baseline.



Percentages within the bars reflect the proportion of cachectic patients that had a dietitian consultation, received a nutritional intervention, or had a protein score <10.

TABLE 3. Nutritional and weight parameters in patients who received palliative chemotherapy.

	Patients who completed the questionnaire at baseline* (n=70)	Patients who completed the baseline and 3 month questionnaires (n=53)	
	Baseline	Baseline	After 3 months
Dietitian consultation, No. (%)	29 (41%)	21 (40%)	21 (40%)
Missing	0 (0%)	0 (0%)	0 (0%)
Oral tube feeding, No. (%)	3 (4%)	2 (4%)	2 (4%)
Oral nutritional supplements, No. (%)	22 (31%)	15 (28%)	22 (42%)
Reduced food intake, No. (%)	55 (79%)	42 (79%)	33 (62%)
Self-reported BMI, kg/m^2, median (IQR)	25 (22, 26)	24 (22, 26)	23 (21, 25)
<18.5 (underweight)	1 (1%)	1 (2%)	3 (6%)
18.5-25 (normal weight)	40 (57%)	32 (60%)	36 (68%)
≥25 (overweight)	29 (41%)	20 (38%)	12 (23%)
Missing	0 (0%)	0 (0%)	2 (4%)
Weight loss at baseline&, No. (%)		N/A	N/A
<10%	39 (56%)		
≥10%	31 (44%)		
Cachexia, No. (%)	54 (77%)		N/A
Pancreatic enzyme supplementation, No. (%)	16 (23%)	12 (23%)	17 (32%)
Missing	4 (6%)	4 (8%)	5 (9%)
Protein score, No. (%)			
<10	53 (76%)	40 (75%)	37 (70%)
10	13 (19%)	10 (19%)	12 (23%)
Missing (did not complete DHD-FFQ)	4 (6%)	3 (6%)	4 (8%)

Abbreviations: BMI = body mass index, N/A = not applicable. *Baseline is in patients who received palliative chemotherapy: before or within one week after start palliative chemotherapy. & Reported half year weight loss in baseline questionnaire.

Survival

Median overall survival in patients with cachexia was 13 months (IQR 11-16), which was not significantly different to patients without cachexia (17 months, IQR 11-23, p=0.18, Figure 3A), although patients with cachexia tended to have a poorer survival. In patients with ≥10% weight loss median overall survival was significantly lower, as compared to those with <10% weight loss (12 months (IQR 7-20) vs. 16 months (IQR 8-31), p=0.02, Figure 3B). Analyses in the subgroups based on treatment showed no differences in survival in patients with and without cachexia, and with <10% or ≥10% weight loss.

FIGURE 3. Kaplan Meier curves showing overall survival for all patients.

FIGURE 3A. Kaplan Meier curves stratified by cachexia at baseline.

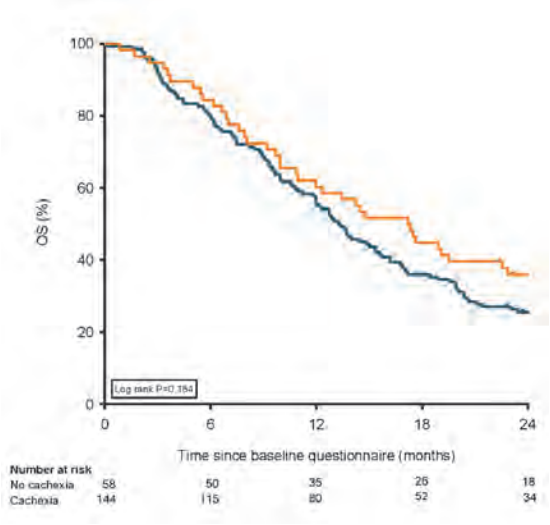
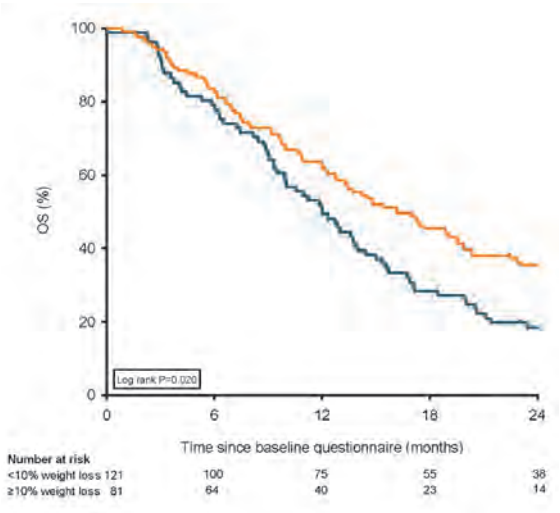


FIGURE 3B. Kaplan Meier curves stratified by weight loss (<10 or ≥10%) at baseline.



DISCUSSION

This prospective multicenter cohort study showed that 71% ofpatients with pancreatic cancer presented with cachexia at diagnosis of whom almost half had no dietetic consultation. Survival did not differ in patients with and without cachexia at diagnosis, but was shorter in patients with more severe weight loss (≥10%).

This is the first multicenter study to investigate the real-life situation regarding cachexia and dietetic consultation in pancreatic cancer. In previous studies, cachexia was diagnosed in 31-41% of patients

with resectable pancreatic cancer, which is lower than in our study.[4,10] This could be explained by different definitions. In our study, BMI was also taken into account, whereas in previous studies cachexia was defined as weight loss >10%.[4,7,10] We therefore also assessed weight loss ≥10%, which was 40% and thus in line with previous studies. The high prevalence of cachexia underscores that physicians should be aware of cachexia in patients with pancreatic cancer.

In the three subgroups based on treatment for pancreatic cancer, patients undergoing best supportive care most often received dietitian support. In general, these patients were in their end-of-life and therefore, the rate of dietetic consultation was higher than expected on forehand, while the low percentage of dietetic consultation in patients who underwent surgery is surprising. It could be speculated that this difference occurred because dietitian consultation is one of the few things that can be offered to patients with best supportive care. In addition, it should be noted that patients with best supportive care group are a selection of a relatively fit subgroup, since in general patients with a relatively good performance status are included in PACAP PROMs. It is possible that in these relatively fit patients, physicians may be more likely to start an intervention, including dietetic consultation.[25] However, in these patients in the end-of-life stage, dietitian support is not focusing on improving nutritional status anymore, but is tailored to the patients' needs and wishes enhancing comfort and support quality of life.[26] In contrast, in patients with anti-cancer treatment, dietitian support may be considered less important by physicians compared to the impact of surgery or chemotherapy on survival. Another explanation could be under reportation by the patient, or nutritional support given by an experienced nurse practitioner. Dietitian counseling, however, could support the effects of anti-cancer treatments and might diminish complications by optimizing nutritional status.[14,27] To optimize dietetic consultation, all patients with pancreatic cancer planned for life enhancing treatment should be screened for malnutrition.[28] Screening could be performed according to the GLIM criteria, which present a consensus scheme for diagnosing malnutrition in adults in clinical settings.[8] Based on our results, it could be advised to include the screening for malnutrition in standard operating procedures, because the referral rate could be greatly improved.

It was expected that cachexia would negatively affect overall survival, but patients with and without cachexia at baseline did not show differences in overall survival. Nevertheless, patients with more severe weight loss (≥10%) had a decreased survival compared to those with <10% weight loss. This is also shown in previous studies.[29,30] A higher percentage of weight loss, especially in combination with a lower BMI, independently decreases survival.[30] This could partially explain the difference in results between cachexia and severe weight loss. Moreover, the study might be underpowered for demonstrating a significant effect in patients with cachexia, because both in patients with cachexia as

well as in those with severe weight loss, survival is decreased by 4 months. It could be suggested that an early start of nutritional interventions in patients with cachexia could prevent the development of severe weight loss and consequently improve survival. It should be mentioned that survival is also affected by other factors, such as tumor location, tumor stage, postoperative complications, use of (adjuvant) chemotherapy, and disease recurrence.[31,32] Prevention of weight loss only will probably not result in a clinically relevant improvement of survival.

In more than half of patients who underwent surgery and who received palliative chemotherapy, the protein score was <10. This already indicates that protein intake should be improved because the score for protein intake has been based on cut-offs for the general healthy population. Since this study is focusing on pancreatic cancer patients, in whom it is even recommended to use a high protein diet, all patients with a score <10 should have a dietetic consultation.[28] In our cohort, 39% of the patients with a protein score <10 had a dietetic consultation and around one third used oral nutritional supplements. This demonstrates that there is room for improvement. After referral, a dietitian will devise a patient tailored nutritional support plan based on the patient's nutritional intake to improve nutritional status in patients undergoing surgery or palliative chemotherapy. In patients receiving best supportive care, dietary support should be focused at comfort and increasing quality of life and should not be based on improving protein intake.

Another important aspect of malnutrition is exocrine pancreatic insufficiency.[33–36] In patients with pancreatic cancer, exocrine insufficiency is highly prevalent, but currently underdiagnosed and undertreated.[33,34,37] Enzyme supplementation was not reported in more than a quarter of the patients that received palliative chemotherapy, which is low compared to the prevalence of exocrine insufficiency at diagnosis (66%).[34] Nearly two-thirds of patients who underwent surgery, however, received enzyme supplementation after surgery, probably because it was included in hospitals' postoperative protocols.[11] This could also be increased as the incidence of exocrine insufficiency in these patients is 74% at 6 months postoperatively.[33] Enzyme supplementation requires more attention and also support from a dietitian or nurse practitioner to provide patient education on proper use of enzymes.[37,38]

The strength of this prospective multicenter study is the real-life overview of the proportion of patients with cachexia and the current situation regarding dietetic consultation. The study also had some limitations. First, selection bias may be present towards a relatively high proportion of patients who underwent resection and/or received adjuvant or palliative chemotherapy.[31] Possibly, fitter patients were more keen on being included, which might have led to an underestimation of malnutrition in our

cohort. This emphasizes the need for proper identification and treatment of malnutrition even more. Second, nutritional support based on dietetic consultation could be underestimated, because of an under reportation of patients or support by a nurse practitioner. In large and specialized pancreatic surgery centers, an important role is often reserved for nurse practitioner or physician assistants experienced within pancreatic cancer to consult patients on their nutritional status and pancreatic enzyme supplementation. Third, the DHD-FFQ was included in the PROMs to assess the diet quality according (and derived protein score) to the national dietary guideline, but was only a qualitative measure and not quantitative. Fourth, patients, especially those who underwent surgery, frequently did not complete the baseline questionnaire before start of treatment which unfortunately resulted in exclusion of these patients and might be prevented by improved logistics within PACAP. Fifth, the criterion for cachexia that included the presence of sarcopenia was not used, because this data was not available in the NCR or PROMs.[7] The loss of skeletal muscle mass depletion is the main aspect of malnutrition that predicts the risk of physical impairment, complications and mortality, and probably led to an underestimation of patients with cachexia.[28,39,40] However, some advocate to focus on cachexia rather than sarcopenia in pancreatic cancer, because cachexia is the main problem.[41]

In conclusion, this study showed that over two-thirds of patients with pancreatic cancer present with cachexia of which nearly half had no dietetic consultation. Only 39% of patients with a protein score <10 had a dietetic consultation and pancreatic enzyme supplementation could be increased. Survival was comparable in patients with and without cachexia, but significantly decreased in patients with severe weight loss (≥10%) suggesting the importance of preventing further weight loss. Increased awareness of cachexia and severe weight loss, screening on (the risk) of malnutrition based on the GLIM criteria, and dietetic consultation to improve protein intake could be helpful improving treatment outcomes.

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SUMMARY AND DISCUSSION

SUMMARY

This thesis aimed to evaluate the nationwide practice in the treatment of pancreatic and periampullary cancer and outcomes after pancreatic surgery. Nationwide practice and survival were assessed in population-based studies with data derived from the Dutch Pancreatic Cancer Project (PACAP) which resulted in a more accurate reflection of current practice compared to studies with selected populations. Two retrospective studies were performed to assess endocrine and exocrine pancreatic insufficiency and micronutrient deficiencies in patients after pancreatic resection. International outcomes and differences after total pancreatectomy were analyzed with data from four western registries and data gathered with a pan-European snapshot study.

Part I Nationwide practice

The incidence of pancreatic ductal adenocarcinoma increased over the years due to better diagnostic modalities and more exposure to risk factors, such as obesity, alcohol, and diabetes. **Chapter 1** showed that in the Netherlands the age-standardized incidence of pancreatic cancer increased from 12.1 to 15.3 per 100,000 persons from 1997 to 2016 based on data of 36,453 patients. In addition, 23% more patients were treated with resection and/or systemic treatment. The resection rate doubled (8.3% to 16.6%), more patients received adjuvant chemotherapy (3.0% to 56.2%), and three-year overall survival following resection increased (16.9% to 25.4%). Overall survival improved only by three weeks which is disappointing and emphasizes the urgent need for further developments in diagnostics and effective treatment of pancreatic cancer.

The national multidisciplinary guideline on pancreatic cancer was published in 2011 and guideline compliance one year later was shown to be poor. In 2019, an update of the guideline was published. To investigate whether implementation is necessary or guideline compliance improves naturally over the years, compliance to the 2011 guideline was assessed up to six years after its introduction (**Chapter 2**). Five selected quality indicators were evaluated in 14,491 patients: discussion in a multidisciplinary team meeting, treatment within a maximum 3-week interval between final multidisciplinary team meeting and start of treatment, preoperative biliary drainage (if bilirubin >250 µmol/L), use of adjuvant chemotherapy, and chemotherapy for inoperable (i.e., non-metastatic and metastatic) pancreatic cancer. Very few improvements were shown in three subsequent time periods (2012-2013 vs. 2014-2015 vs. 2016-2017). The sole indicator that improved over time was the proportion of patients with non-metastatic, non-resected disease who received chemotherapy (23.4% vs. 25.6% vs. 29.7%, p-

trend=0.001). These results highlight the importance of a structured implementation program for the new 2019 guideline to enhance compliance in order to improve patients' outcomes.

Chapter 3 assessed the implementation of new more effective chemotherapies in 8,726 patients with metastatic pancreatic ductal adenocarcinoma. In 2012 to 2016, after the advent of FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine with nab-paclitaxel, nationwide variation in the use of chemotherapy decreased compared with 2007 to 2011. Only one-third of patients received chemotherapy in 2012 to 2016. For patients who received chemotherapy, overall survival increased from 5.6 to 6.4 months ($p<0.001$). For all included patients, overall survival barely increased, from 3.3 to 3.4 months ($p<0.001$). FOLFIRINOX was widely implemented in 2015 to 2016, but its use varied between hospitals. Moreover, a considerable proportion of patients still received gemcitabine monotherapy (25%) with a disappointing survival benefit. This chapter clearly shows that the implementation of using more effective chemotherapeutic regimens was difficult and did not translate directly into a clinically relevant improvement in overall survival. These results also support the need for a structured implementation program.

In patients with pancreatic head and periampullary cancer who undergo pancreatoduodenectomy endoscopic biliary drainage may be indicated due to an extrahepatic bile duct obstruction. Chapter 4 described that endoscopic biliary drainage was required in 62% of the 1,056 included patients from the Dutch Pancreatic Cancer Audit (DPCA) in 2017 and 2018. Although the European Society of Gastrointestinal Endoscopy Clinical Guideline advised to use metal stents, still 57% of this cohort received a plastic stent. The rate of overall endoscopic biliary drainage-related complications was similar between metal stents and plastic stents. Metal stents were not associated with a higher post-endoscopic retrograde cholangiopancreatography pancreatitis rate. In addition, patients receiving metal stents had lower odds of cholangitis, less postoperative pancreatic fistula, and a shorter postoperative hospital stay. Again, it is demonstrated that guideline implementation should be improved.

A step towards improvement of pancreatic cancer care might be obtained via the nationwide PACAP-1 trial. In Chapter 5, the study protocol of this nationwide multicenter stepped-wedge cluster randomized controlled trial explicates a structured enhanced implementation program for three best practices to improve overall survival and quality of life. These best practices were identified from the national guideline, outcomes from PACAP data, and current literature. They include optimal use of chemotherapy, increased awareness for exocrine insufficiency and subsequent treatment, and metal stent placement for endoscopic biliary drainage. From May 2018 to July 2020 a stepwise

implementation of these best practice was performed in 17 regions (based on the 17 pancreatic surgery centers and their referral centers), covering all of the Netherlands. Within these regions, collaboration was enhanced and a local 'pancreatic cancer expert team' was appointed to stimulate accessible communication and improve referral patterns. The primary outcome is one-year overall survival and therefore results are not expected before July 2021.

Part II Quality of life and clinical outcomes after pancreatic surgery

Over the years, centralization within pancreatic surgery developed and improved. It was hypothesized that this would equalize resection rates for all patients diagnosed with non-metastatic pancreatic head or periampullary carcinoma regardless of diagnosis in a pancreatic surgery or non-pancreatic surgery center. This hypothesis was tested in a population-based database including 10,079 patients in **Chapter 6**. In 2015 to 2017, the period after implementation of centralization, the resection rate became similar for patients diagnosed in pancreatic surgery and non-pancreatic surgery centers (OR 1.08, 95% CI 0.90-1.28, p=0.422). Overall survival remained higher in pancreatic surgery centers (HR 0.92, 95% CI 0.85-0.99, p=0.047). These findings suggest that centralization improved care and further development of existing regional networks is essential as this could increasingly optimize patient outcomes.

Quality of life and exocrine and endocrine insufficiency were retrospectively studied in 234 patients who underwent pancreatic surgery for premalignant or benign (non-pancreatitis) disease (**Chapter 7**). Long-term generic quality of life was similar to the general population and diabetes related distress was low, but nearly half of all patients reported surgery related complaints and 8% would, in retrospect, not undergo pancreatic surgery again. The current treatment of EPI needs further attention, potentially by personalized treatment schemes given by dieticians or nurse practitioners. The current results should be used in the shared-decision making process in case surgery is considered for benign (non-pancreatitis) or premalignant pancreatic diseases.

The nutritional status of patients is also related to quality of life and exocrine insufficiency. **Chapter 8** showed that in patients at least four months after pancreatoduodenectomy most serum values of micronutrients were sufficient. However, deficiencies of iron, ferritin, vitamin A, and vitamin D and anemia were common. Prospective studies should determine whether standardized laboratory assessments and supplementation of deficiencies would improve patients' outcomes. Moreover, adequate supplementation of pancreatic enzymes is expected to contribute to an optimal micronutrient status as there were deficiencies in vitamin A and D, which were probably related to exocrine insufficiency.

Total pancreatectomy is typically performed for diseases involving the entire pancreas, such as some types of pancreatic cancer, main-duct intraductal papillary mucinous neoplasm, or chronic pancreatitis. In general, there is reluctance to perform a total pancreatectomy, because of high postoperative major complication and mortality rates, and especially the life-long endocrine and exocrine insufficiency with considerable impact on quality of life. In **Chapter 9**, the Dutch nationwide PANORAMA cohort was presented including 148 patients after total pancreatectomy between 2006 to 2016. The major complication and 90-day mortality rate were high with 32% and 8%, respectively. Long-term survivors after total pancreatectomy scored their self-rated global health status, which was worse compared to the healthy population, involving more symptoms and functional complaints. The differences, though, were small and the clinical relevance was unknown. Patients were satisfied with their diabetes mellitus treatment and experienced similar distress compared to type 1 diabetes mellitus patients. This data should be taken into account in shared-decision making when faced with the decision to undergo total pancreatectomy.

The inclusion period of the PANORAMA cohort was rather long and for accurate short-term postoperative outcomes a more representative reflection of clinical practice was desirable. Using the relatively new snapshot design in **Chapter 10**, the aim was to create generalizable data regarding postoperative outcomes after total pancreatectomy. In this prospective pan-European cohort, 277 patients who underwent total pancreatectomy were included from 16 countries between 2017 and 2018. The major complication rate was 25% and the in-hospital mortality was 5%. In-hospital mortality was lower in patients operated in centers with an annual center volume for pancreatoduodenectomies of ≥60 compared <60 (4% vs. 10%, p=0.046). In multivariable analysis, several risk factors for major complications and mortality were identified which may be used to improve outcomes by better patient selection or selective patient referral.

Data from four Western registries (i.e., the United States of America, Germany, the Netherlands, and Sweden) also enabled evaluation of postoperative outcomes after total pancreatectomy in a large cohort during a relatively short time span (2014 to 2018). **Chapter 11** demonstrated that in 1,579 patients, major complications were found in 26.8% and in-hospital mortality was 5.4%. The postoperative outcomes were considerably different between the four countries, but this was difficult to compare due to differences in use of TP and designs of the registries. One of the main challenges of the GAPASURG study group will be to harmonize the key parameters registered. The observed differences among countries require further research to ultimately improve patient outcome.

Part III Survival

Chapter 12 presented the first prediction model for conditional survival in pancreatic cancer. Condition survival is the probability of surviving an additional number of years after already surviving a predefined period. In this nationwide study, including 3,082 patients, the probability of achieving 5-year survival after a pancreatic resection increased from 15% directly after surgery to 61% after surviving the first three years. An online calculator was made available to estimate personalized conditional survival probabilities for 5-year survival after pancreatic resection.

Whether quality of life or cachexia were related to survival was investigated in the following chapters. Chapter 13 demonstrated that overall happiness, a quality of life summary score, and several functioning and symptom scale item scores were predictive of survival in 376 patients with pancreatic and periampullary cancer. Several baseline quality of life scores were of prognostic value for patients without resection, whereas the delta quality of life constipation score (i.e., between baseline and three months follow-up) was predictive of survival in the total cohort. Quality of life scores are therefore of value for usage in the clinical setting, i.e., shared decision making, disease management/treatment, clinical prediction models, or stratification in trials.

Another variable that was closely related to survival in previous literature is cachexia. This relation was investigated in 202 patients with pancreatic cancer in a prospective multicenter cohort study (Chapter 14). Survival did not differ in patients with and without cachexia at diagnosis (13 vs. 17 months, p=0.18). In patients with severe weight loss (≥10%) during the half year before their cancer diagnosis, survival was shorter as compared to those with <10% weight loss (12 vs. 16 months, p=0.02). It was remarkable that 71% of all 202 patients presented with cachexia at diagnosis and surprisingly, less than half of them had a dietetic consultation. Based on these results it is suggested to increase awareness of cachexia and severe weight loss, screen for malnutrition, and improve dietetic referral.

SUMMARY OF RESEARCH QUESTIONS AND MAIN FINDINGS

Chapter	Research question
1	**What are the trends in incidence, treatment, and survival for patients with all stages of pancreatic ductal adenocarcinoma in the Netherlands between 1997 and 2016?** The incidence of pancreatic ductal adenocarcinoma increased over the last two decades, while median overall survival only improved marginally (from 3.1 months in 1997-2000 to 3.8 months in 2013-2016, p<0.001) despite an increase of patients receiving treatment (16% to 39%, p-trend<0.001).
2	**Did compliance to selected quality indicators of the 2011 Dutch guideline on pancreatic cancer improve in the six years after introduction?** Nationwide compliance to quality indicators hardly improved over the six year period after release of the guideline. Five indicators did not improve and solely the proportion of patients with non-metastatic, non-resected disease who received chemotherapy improved from 23% to 26% and 30% in the three periods from 2012 to 2017 (p-trend<0.001).
3	**How does the implementation of new more effective chemotherapy regimens (FOLFIRINOX and gemcitabine with nab-paclitaxel) for patients with metastatic pancreatic ductal adenocarcinoma affect nationwide clinical practice and overall survival?** After implementation of FOLFIRINOX and gemcitabine with nab-paclitaxel, the nationwide use of chemotherapy increased and variation in the use of chemotherapy decreased. However, a considerable proportion of patients still received gemcitabine with a disappointing survival benefit. Overall survival only increased from 3.3 to 3.4 months (p<0.001) for all patients, but for patients with chemotherapy overall survival increased from 5.6 to 6.4 months (p<0.001).
4	**What is the current nationwide practice of using self-expanding metal stents in preoperative endoscopic biliary drainage for resectable pancreatic head and periampullary cancer and what are the outcomes?** Preoperative endoscopic biliary drainage only involved self-expanding metal stents in 43%. Compared to plastic stents, metal stents were associated with lower odds of cholangitis and postoperative pancreatic fistula, and hospital stay was shorter. In addition, no relation with post-endoscopic retrograde cholangiopancreatography pancreatitis was found.
5	**Is nationwide implementation of best practices by a multicenter stepped-wedge cluster randomized controlled trial (PACAP-1) effective to improve survival and quality of life for patients with pancreatic cancer?** The nationwide implementation of best practices in the PACAP-1 trial was completed in July 2020. The results of this study, i.e., the effect on survival and quality of life, will become available in 2021 after completion of the one-year follow-up.
6	**Did the resection rate in patients with non-metastatic pancreatic head and periampullary carcinoma who were diagnosed in pancreatic surgery compared to non-pancreatic surgery centers change between 2009 and 2017 and did this influence survival patterns?** In the period 2015-2017, after centralization, the resection rate became similar for patients diagnosed in pancreatic surgery and non-pancreatic surgery centers. Overall survival remained higher in pancreatic surgery centers.

7	**What is the long-term quality of life and status of exocrine and endocrine insufficiency in patients after pancreatic surgery for benign non-pancreatitis or premalignant disease?** Long-term generic quality of life was similar to the general population. Almost half of all patients reported surgery related complaints and 8% would, in retrospect, not undergo pancreatic surgery again. Diabetes related distress was low, but the current treatment of exocrine pancreatic insufficiency requires further attention.
8	**Which micronutrients are deficient in patients during the follow-up after pancreatoduodenectomy?** Most serum values of micronutrients in patients during follow-up were sufficient, but deficiencies of iron, ferritin, vitamin A, and vitamin D, and anaemia were common. This emphasizes that more attention for a standardized assessment of micronutrients during follow-up is required and deficiencies should be supplemented.
9	**What are the short-term postoperative outcomes and long-term quality of life outcomes in patients after total pancreatectomy?** The 90-day mortality after total pancreatectomy in the Netherlands was high with 8%. Compared to the healthy population, patients after total pancreatectomy had a worse, self-rated global health status, involving more symptoms and functional complaints. Patients were, however, satisfied with their diabetes mellitus therapy and had similar diabetes-related distress as patients with type 1 diabetes mellitus.
10	**What are the short-term postoperative outcomes after elective total pancreatectomy in a multicenter pan-European snapshot cohort?** In patients after total pancreatectomy across Europe, a 25% major complication and an 5% in-hospital mortality rate were found. In-hospital mortality was lower in patients operated in centers with an annual center volume of ≥60 pancreatoduodenectomies compared <60 (4% vs. 10%, p=0.046). Risk factors were identified in in multivariable analysis. In-hospital mortality was related to an annual volume of <60 pancreatoduodenectomies, age, and estimated blood loss ≥2L. American Society of Anesthesiologists (ASA) score ≥3 and estimated blood loss ≥2L were associated with major complications.
11	**What are the short-term postoperative outcomes after one-stage total pancreatectomy in patients from four Western registries and do outcomes differ between countries?** The major complication rate after total pancreatectomy in four Western registries was 26.8% and in-hospital mortality was 5.4%. Outcomes were better in the USA and Sweden, but the comparison between countries was difficult due to differences in use of TP and designs of the registries. The observed differences among countries require further research to ultimately improve patient outcome.
12	**What is the personalized conditional survival of patients after resection of pancreatic cancer?** A prediction model was created and transformed into an online calculator to inform caregivers and patients about personalized survival probabilities after resection for pancreatic cancer. This model showed that the probability of achieving 5-year survival increased from 15% directly after surgery to 61% after surviving the first three years.

13	**Is quality of life related to survival in patients with pancreatic and periampullary cancer?** In daily clinical practice, quality of life is related to survival regardless of patient, tumor, and treatment characteristics. Several baseline quality of life scores were of prognostic value for patients without resection, whereas in the total cohort the delta quality of life constipation score (i.e., between baseline and three months follow-up) was predictive for survival.
14	**To what extent is cachexia present in the real-world setting in patient with pancreatic cancer and how is this associated with dietetic consultation and survival?** Two-thirds of patients with pancreatic cancer presented with cachexia of which nearly half had no dietetic consultation. Survival was comparable in patients with and without cachexia but decreased in patients with more severe weight loss (≥10%) over the past half year before diagnosis compared to those with <10% weight loss.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis sheds light on several topics within pancreatic and periampullary cancer and outcomes after pancreatic surgery. Nationwide practice (variation), short-term and long-term postoperative outcomes, and survival were described. Within this chapter, the insights and results from this thesis are discussed and future perspectives are considered.

Nationwide practice variation and guideline implementation

Over the past two decades, many aspects of pancreatic cancer care have improved. Besides surgical innovations and improved chemotherapy regimens, also new regional networks were established. As described in this thesis, increased centralization equalized resection rates for patients with non-metastatic pancreatic head or periampullary carcinoma regardless of their center of diagnosis (**Chapter 6**). This indicated improved patient selection and efficient referral patterns. It was expected that these improved referral patterns would also shorten the maximum transit time between the final multidisciplinary team meeting and start of treatment, but **Chapter 2** (i.e. guideline compliance) showed no improvement of this quality indicator over time. Probably, patient and hospital factors might have been of greater influence than logistical factors. These factors also affected other quality indicators, such as the percentage of patients that received chemotherapy. For example, patients in academic hospitals more often received adjuvant chemotherapy compared to those in non-academic hospitals. On the other hand, for patients with metastatic disease, it was demonstrated that type of hospital did not affect the likelihood of receiving chemotherapy (**Chapter 3**). Moreover, it was shown that a remarkable number of patients did not receive improved chemotherapy regimens, but gemcitabine monotherapy. However, both studies were limited by the fact that performance status was not available, which complicated adequate selection of patients eligible for chemotherapy. Currently, this variable is included in the Netherlands Cancer Registry (NCR). Another quality indicator from **Chapter 2** with low compliance was the performance of preoperative biliary drainage in patients with a bilirubin >250 µmol/L. In addition, **Chapter 4** showed that the use of self-expandable metal stents was insufficient in patients who underwent preoperative biliary drainage. Since the use of neoadjuvant chemotherapy is rapidly increasing, it is expected that preoperative biliary drainage will increase and more self-expandable metal stents will be used as this is strictly recommended in the trial protocol (i.e. PREOPANC-2 trial) and new guideline.[1] Taken together, this existing practice variation shows that guideline compliance should be further improved.

Guideline utilization depends on the quality of the guideline, characteristics of physicians and the practice setting, the implementation strategy, and cultural factors.[2,3] An enhanced implementation of selected best practices in pancreatic cancer care was performed in the nationwide PACAP-1 trial (Chapter 5). Many lessons were learned during this stepped-wedge cluster randomized controlled trial, especially regarding differences in multidisciplinary communication and regional networks. Changing current practice was found to be extremely challenging and required approaches adapted to the specific region and physicians. The results of the trial are awaited in 2021 and will show whether the active, time-consuming implementation strategy with hospital visits and build-in reminders was effective and improved one-year survival.

Exocrine pancreatic insufficiency and nutritional status

One of the best practices of the PACAP-1 trial was improvement of exocrine insufficiency treatment. Patients with pancreatic cancer often suffer from exocrine insufficiency. This is associated with increased morbidity and mortality and currently underdiagnosed and inadequately treated.[4,5] Chapter 7 showed that after pancreatic resection for premalignant or benign diseases patients registered complaints pointing towards exocrine insufficiency. Proper enzyme supplementation will increase quality of life and it was also suggested that it could lead to improved survival.[6–9] Increased attention for enzyme supplementation should be twofold: increased awareness and improved guidance of supplementation with individualized treatment schemes. Guidance should preferably be given by nurse practitioners or dieticians, because of their experience and time. Moreover, in the coming years new insights will probably occur in the ideal diagnostic tool and the optimal dosage of enzymes. The most accurate test for diagnosing exocrine insufficiency is the three-day fecal fat quantification and determination of coefficient of fat absorption.[10] This test is cumbersome and invasive for both patient and laboratory personnel. Other tests have been described, such as the fecal elastase-1 test, but literature is controversial about its accuracy.[11–14] In clinical practice, exocrine insufficiency is often diagnosed based on complaints (i.e., steatorrhea), but diagnosing remains difficult.[5,15] The ongoing OPPERT study (Netherlands Trial Register NL8038) investigates the most accurate diagnostic tool which will lead to better identification of patients with exocrine insufficiency. Optimal dosing of pancreatic enzymes is the second challenge and the general thought is that patients often receive too low a dose.[4,5] In current practice, uncertainty about correct enzyme supplementation exists and education of physicians, nurse practitioners, and dieticians is necessary.

In the evidence-based European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines the following statement is made: “All cancer patients should be screened regularly for the risk or the presence of malnutrition”.[16] Therefore, it seems as if nutritional aspects gained attention over the past

years. However, in Chapter 14 it was shown that over two-thirds of patients with pancreatic cancer presented with cachexia of which nearly half had no dietetic consultation. Chapter 8 demonstrated that in patients at least four months after pancreatoduodenectomy (mostly performed for pancreatic or periampullary cancer) most serum values of micronutrients were sufficient, but deficiencies of iron, ferritin, vitamin A, and vitamin D were common and anemia developed regularly. These results emphasize that increased attention for the nutritional status is desirable. Assessing the nutritional status and referral to a dietician might be undervalued compared to anti-cancer treatment. During the implementation of the PACAP-1 best practices, it was noted that processes regarding dietician referral were very different between hospitals. Maybe, a solution is to refer all patients with pancreatic cancer to a dietician for screening on (the risk) of malnutrition and the presence of micronutrient deficiencies. This idea should be elaborated in one hospital to assess cost and time effectiveness. If proven effective, it should be enrolled on a nationwide scale. In patients with esophagus cancer receiving chemoradiotherapy a similar process has been studied. A nutritional pathway was developed based on the principles of nutritional support in cancer patients.[17,18] This pathway promoted a proactive approach of assessing malnutrition and nutritional interventions. It was shown to be effective in terms of decreased weight loss, improved clinical outcomes and less hospital admission compared to patients not included in the pathway. However, in this study the assessment was not performed by a dietician, whereas this seems the only feasible method in real-life practice, because an earlier study showed that mandatory nutritional screening by treating physicians was poorly performed.[19] The nutritional status of patients with pancreatic cancer has to be improved and we have to join forces to implement this in standard care for all patients.

Total pancreatectomy

This thesis also focused on the short-term and long-term outcomes after total pancreatectomy. Reported short-term postoperative outcomes after total pancreatectomy are concerning, but often not reflect current practice as study results are very heterogeneous.[20] Our nationwide series including all 17 Dutch centers (2006-2016) in Chapter 9 also showed a high 90-day mortality (8%). To gain an actual reflection of recent outcomes a prospective, multicenter pan-European snapshot study (2018-2019, Chapter 10) and an assessment of four transatlantic registries (multicenter or nationwide, 2014-2018, Chapter 11) were performed. Both studies demonstrated substantial major morbidity and mortality in patients after total pancreatectomy. Risk factors (e.g., age, vascular resection, and American Society of Anesthesiologists (ASA) score) were identified and should be used for patient identification. Moreover, intercountry and hospital-volume differences were found. The indication for total pancreatectomy should be carefully considered and it could be proposed to increase centralization of pancreatic surgery to improve future outcomes.

As described in **Chapter 9**, long-term survivors after total pancreatectomy had a slightly lower quality of life compared to the general population, but the clinical relevance was unknown. Endocrine insufficiency was similar to type I diabetes mellitus patients. Two promising developments (i.e., islet autotransplantation and the artificial pancreas) will further improve the treatment of endocrine insufficiency. Islet autotransplantation is mainly indicated in patients with hereditary or chronic pancreatitis after total pancreatectomy. Pancreatic islets are isolated from the pancreas, purificated, and infused in the liver via the portal vein.[21] This method offers sustained insulin independence or a more stable glycemic control.[22,23] A future alternative will be the artificial pancreas, a bihormonal closed loop system which comprises continuous subcutaneous insulin and glucagon infusion with continuous glucose monitoring.[24] Feasibility studies have been extensively performed in patients with type I diabetes mellitus and showed safety and better glucose control.[25–28] After improving the prototype, the device was studied in an open-loop crossover randomized controlled trial in patients with type I diabetes mellitus at the home-setting for three weeks (NCT03858062). The artificial pancreas was found to be effective as an increased duration of normal glucose values was demonstrated compared to the standard therapy. A randomized controlled trial, based on the same design and methods, will demonstrate whether the artificial pancreas is also safe and effective in patients after total pancreatectomy (Netherlands Trials Register NL8871). Both methods are expected to undergo extensive progress in the coming years and hopefully become widely available. Better glucose control will decrease long-term diabetes mellitus complications and allow patients to optimally participate in society by alleviating their treatment burden and increasing quality of life.

Although outcomes after total pancreatectomy are still raising concerns, for some patients with a high lifetime risk of developing pancreatic ductal adenocarcinoma (i.e., hereditary pancreatitis or main-duct of mixed type intraductal papillary mucinous neoplasm) a prophylactic total pancreatectomy could be considered. Such preference-sensitive treatment decisions should be taken by the physician and a well-informed patient after careful consideration by a multidisciplinary team of experts. This was organized within the shared decision-making program for prophylactic total pancreatectomy (PROPAN) using decision tables.[29] Currently, the first patients are enrolled within the PROPAN program and their experiences and outcomes should be prospectively monitored to assess postoperative outcomes and patient satisfaction. If the program seems feasible and safe, indications might be expanded to Peutz-Jeghers syndrome and p16-Leiden (CDKN2A mutation).

Future of the Dutch Pancreatic Cancer Project

Many studies within this thesis were performed with data from the Dutch Pancreatic Cancer Project (PACAP). PACAP was established in 2013 and until now improvements of this project mainly included

increasing efficiency, optimizing the patient inclusion rate, combining registries, completing legal documents due to the new privacy legislation, and searching for new funding. Time has come to take PACAP to a higher level which hopefully increases survival probabilities during the coming decade, in contrast to the disappointing outcomes over the past two decades as described in **Chapter 1**.

Computer technology is one of the main aspects that should be adopted in PACAP and three innovations may be interesting in the near future. First, patients who are eligible for patient reported outcomes measures (PROMs) are currently contacted and included via central coordination of research nurses. This is a time-consuming job and should be replaced by an automatic system based on the patients' diagnosis as registered in the patient chart. However, the General Data Protection Regulation complicates automatic patient registration and inclusion. Methods to overcome this problem should be created and might be based on a 'general informed consent' for contacting patients and using patient chart data for all related issues of that particular hospital visit. Second, a mobile application could be developed in which questionnaires can be completed and which contains build-in notifications for new questionnaires and reminders for old questionnaires. Third, automatic data transfer from patient charts to the registries should be established. One of the barriers is that registration of patient data is not standardized yet and registries cannot be completely uploaded from the patient chart. Standardization of data is increasingly obtained by clinical building blocks.[30] In the Netherlands, a large initiative from Citrien and 'Registratie aan de Bron' aims to decrease registration burdens by supporting standardization and usage of clinical building blocks.[31] This will eventually enhance data transfer into registries without interference of data administrators which additionally increases data quality.

One of the achieved milestones during this thesis was the linkage between the NCR and the PROMs, which resulted in the first manuscript of combined data (**Chapter 13**). The next step is to additionally link the surgical registry (the Dutch Pancreatic Cancer Audit (DPCA)) to the NCR and PROMs. Combining short-term postoperative outcomes with quality of life, oncological, and survival data would enable extended population-based data analyses, for example about the relation between postoperative outcomes, eligibility for adjuvant chemotherapy, and long-term (survival) outcomes. Overlapping variables in the registries can be reduced after linkage and therefore further decrease the registration burden. Unfortunately, the DPCA and NCR with PROMs cannot be combined yet due to legal and logistical problems. These problems should be solved in the near future.

Future of treatment and research

The nationwide collaboration in the DPCG has shown to be effective, because this study group was the first world-wide to complete a randomized controlled trial investigating neoadjuvant therapy (PREOPANC-1 trial).[32] However, it has to be mentioned that an earlier study was terminated early because of oncological benefits of neoadjuvant therapy in patients with borderline resectable pancreatic cancer.[33] Many lessons were learned from the PREOPANC-1 trial, which took over four years due to a slow inclusion of patients. The study was extensively evaluated and points of improvement were established. This resulted in a high inclusion rate for the currently ongoing PREOPANC-2 trial and shows strengths of the DPCG. A new challenge for the DPCG is the performance of a cohort multiple randomized controlled trial (cmRCT), also known as Trials within Cohorts (TwiCs) design.[34,35] In the cmRCT design, the trial intervention is offered to a randomly selected subset of eligible patients from a large, prospective observational cohort of patients with the condition of interest.[35] Outcomes are compared in the randomly selected subset and patients who were not selected (i.e., receiving usual care). If used properly, the cmRCT approach is efficient, especially for expensive or high risk interventions. Patients who participate in PACAP have given their consent for participation in cmRCTs and a short-term aim is to perform the first cmRCT. Currently, trial protocols about the effect of additional treatment (e.g. stereotactic radiotherapy) for locally recurrence of primary resected pancreatic cancer are written.

Another aspect of future research could be machine learning, which is increasingly adopted by researchers within medicine. Machine learning is a method of artificial intelligence which can discover and identify logical patterns from mass data and construct predictive models.[36,37] Pancreatic cancer is difficult to predict and patients are often diagnosed at late stages. Developing effective prediction models might facilitate earlier diagnosis of primary tumors or recurrence, but could also improve models for personalized survival estimates as outlined in **Chapter 12** (based on traditional prediction model techniques).[36–38] PACAP offers access to large datasets of clinical data and samples from the Dutch Pancreas Biobank which are suitable for artificial intelligence purposes.[39] Until now, machine learning within pancreatic cancer care is mainly based on clinical data to develop prediction models for cancer diagnosis or recurrence.[40–42] Although promising, artificial intelligence is not yet at the stage for clinical implementation. Large databases are available, but still challenges arise regarding bias, missing data, and the distinction between correlation and causation.[43,44] Integration of expert knowledge in machine learning could improve outcomes. Multidisciplinary teams should therefore be expanded with data scientist and future research within this field should be stimulated. Machine learning should be seen as a supportive tool and not as a replacement of traditional clinical decision-making.[43,44]

As illustrated, PACAP provides an important backbone for registries and trials. To continue current and new initiatives, PACAP requires funding. The construction and first years of PACAP were funded by a grant of the Dutch Cancer Society, but this source is limited. Grants are often only available for new trials or the development of projects/platforms. This is problematic, because these projects require a structural funding for continuation. New ways to support these ongoing projects should be initiated and could include expanded criteria for grant proposals, but also standard governmental support for projects that have proven to have structural added value. The Dutch Pancreatic Cancer Group (DPCG) together with the Maag Lever Darm Stichting (MLDS) and Living with Hope (patient organization) initiated Deltaplan Alvleesklierkanker (www.deltaplanalvleesklierkanker.nl) to guarantee finance for the essentials of PACAP. The objective of Deltaplan Alvleesklierkanker is to accelerate research, to ensure availability of the best treatment for all patients, and to work towards a better quality of life. This fund is a unique national commitment and widely supported by health care professionals, patients, and the Dutch population. Deltaplan Alvleesklierkanker is determined to raise sufficient funds to secure the PACAP future by partnerships with governmental funding bodies, private or industrial corporations, and health care insurances, or by organizing events.

International collaboration

PACAP and the DPCG bring together data, new techniques or treatments, and experience and consequently form an effective basis for international collaboration. Such collaboration is important because pancreatic cancer is relatively rare and exchanging knowledge might accelerate the development of new treatments or insights. However, populations, health care, cultural and geographical factors, and (research) legislation differ among countries. This complicates intercountry collaboration and decreases generalizability of research results. In Chapter 11, a transatlantic comparison of multicenter or national registries on the outcomes after total pancreatectomy was performed based on data collected in the Global Audits on Pancreatic Surgery Group (GAPASURG). Although this resulted in a large dataset, comparisons were complex due to differences in use of total pancreatectomy and designs of the registries. International collaboration has also proven to be convenient for large prospective (randomized) studies, for example the pan-European snapshot study (Chapter 10) within the European-African Hepato-Pancreato-Biliary Association (E-AHPBA). Randomized controlled trials on an international scale could profit a high inclusion rate, such as the DIPLOMA trial which compares open or minimally invasive distal pancreatectomy for malignancies (ISRCTN44897265) within the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS). Further improvement of international collaboration should focus on standardizing pancreatic cancer care and registrations. A first step towards improvement would be to uniform registries based on suggested core

outcome parameters.[45] Hereafter, the registries can be used to identify points of improvement. Ultimately, increased collaboration will result in improved patient outcomes.

In conclusion, over the last years multiple milestones have been reached within PACAP, but great challenges still await this project. Results from registries and patient reported outcomes measures demonstrated that practice variation is present. The PACAP-1 trial aimed to decrease this variation and improve care by enhanced implementation of best practices, regarding chemotherapy, biliary stenting, and exocrine insufficiency. Future initiatives to decrease practice variation should be encouraged and may have an international character. For total pancreatectomy, short-term postoperative outcomes are still relatively concerning and require further research, but might be improved by increased centralization. Long-term consequences will improve due to new treatment modalities for endocrine insufficiency and more attention and guidance for pancreatic enzyme supplementation. The collaboration within the Dutch Pancreatic Cancer Group (DPCG) and development of the Dutch Pancreatic Cancer Project (PACAP) will be cornerstones to reach future improvements in daily clinical practice and could help to increase the life expectancy of pancreatic cancer patients.

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APPENDICES

NEDERLANDSE SAMENVATTING

In dit proefschrift wordt de landelijke praktijkvoering van de behandeling van pancreas- en periampullaire carcinomen beschreven en worden de uitkomsten na pancreaschirurgie uiteengezet. Landelijke praktijkvariatie en overleving werden geanalyseerd in 'population-based' studies met gegevens van het Dutch Pancreatic Cancer Project (PACAP). Deze studies geven een accuratere reflectie van de huidige praktijk dan studies met een geselecteerde populatie. Endocrine- en exocrine pancreasinsufficiëntie en deficiënties van micronutriënten bij patiënten na een pancreasresectie werden onderzocht in twee retrospectieve studies. Daarnaast werden internationale uitkomsten na een totale pancreatectomie geanalyseerd. Deze studies waren gebaseerd op gegevens uit vier registraties en op de resultaten van een pan-Europese snapshot studie.

Deel I De huidige praktijk op landelijk niveau

De incidentie van pancreas ductaal adenocarcinoom is de afgelopen jaren toegenomen door betere diagnostische methoden en doordat de populatie meer is blootgesteld aan risicofactoren, zoals obesitas, alcohol en diabetes. In hoofdstuk 1 wordt op basis van de gegevens van 36.453 patiënten aangetoond dat in Nederland de voor leeftijd gestandaardiseerde incidentie van pancreascarcinoom toenam van 12,1 tot 15,3 per 100.000 personen van 1997 tot 2016. Het aantal patiënten met een resectie of systemische behandeling steeg met 23%. Het resectiepercentage verdubbelde (8,3% naar 16,6%), meer patiënten kregen adjuvante chemotherapie (3,0% naar 56,2%) en de drie-jaar overleving na resectie verbeterde (16,9% naar 25,4%). In het gehele cohort verbeterde de overleving slechts drie weken. Dit is teleurstellend en benadrukt dat verdere ontwikkeling van diagnostiek en effectieve behandeling van het pancreascarcinoom noodzakelijk is.

De landelijke, multidisciplinaire richtlijn over pancreascarcinoom is in 2011 gepubliceerd en in 2012 bleek de compliance aan deze richtlijn slecht te zijn. In 2019 is de richtlijn vernieuwd en om te bepalen of actieve richtlijnimplementatie noodzakelijk is of dat compliance over de jaren is toegenomen, is in hoofdstuk 2 de compliance aan de richtlijn van 2011 onderzocht tot zes jaar na introductie. In 14.491 patiënten zijn vijf geselecteerde kwaliteitsindicatoren geëvalueerd: bespreking in een multidisciplinair overleg, start van behandeling binnen drie weken na het multidisciplinaire overleg, verrichten van preoperatieve biliaire drainage indien bilirubine >250 µmol/L, gebruik van adjuvante chemotherapie en gebruik van chemotherapie voor patiënten met een inoperabel pancreascarcinoom (zowel niet-gemetastaseerd als gemetastaseerd). In drie opeenvolgende tijdsperioden (2012-2013 versus 2014-2015 versus 2016-2017) werd geen tot minimale verbetering gezien. De enige kwaliteitsindicator die

verbeterde, was het percentage patiënten met niet-gemetastaseerde, niet-gereseceerde ziekte die behandeld werden met chemotherapie (23,4% versus 25,6% versus 29,7%, p-trend=0,001). Deze resultaten laten zien dat een gestructureerde implementatie van de nieuwe richtlijn uit 2019 essentieel is voor goede compliance en uiteindelijk voor verbetering van patiëntuitkomsten.

In **hoofdstuk 3** is de implementatie van nieuwe, effectievere chemotherapieën onderzocht bij 8.726 patiënten met een gemetastaseerd pancreas ductaal adenocarcinoom. In de periode van 2012 t/m 2016, na de introductie van FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan en oxaliplatin) en gemcitabine gecombineerd met nab-paclitaxel, had slechts een derde van de patiënten een chemotherapiebehandeling. De landelijke variatie in het voorschrijven van chemotherapie lag lager dan in 2007 t/m 2011. Bij patiënten met chemotherapie steeg de overleving van 5,6 naar 6,4 maanden (p<0,001), terwijl bij alle patiënten tezamen de overleving toenam van 3,3 naar 3,4 maanden (p<0,001). In 2015 en 2016 was het voorschrijven van FOLFIRINOX op brede schaal geïmplementeerd, maar het gebruik tussen ziekenhuizen varieerde. Bovendien kreeg een aanzienlijk deel van de patiënten gemcitabine monotherapie (25%) met een betreurenswaardig overlevingsvoordeel. Dit hoofdstuk toont duidelijk dat de implementatie van gebruik van effectievere chemotherapieën moeilijk is en zich niet direct vertaalt in een klinisch relevante overlevingswinst. De resultaten ondersteunen dat een gestructureerd implementatieprogramma nodig is.

Bij patiënten met een pancreaskop- en periampullair carcinoom die een pancreatoduodenectomie ondergaan, kan endoscopische biliaire drainage geïndiceerd zijn vanwege een extrahepatische galwegobstructie. In 2017 en 2018 onderging 62% van 1.056 patiënten uit de Dutch Pancreatic Cancer Audit (DPCA) endoscopische biliaire drainage (**hoofdstuk 4**). Van deze patiënten kreeg 57% een plastic stent ondanks het feit dat het in de European Society of Gastrointestinal Endoscopy Clinical Guideline geadviseerd wordt om metalen stents te gebruiken. Het voorkomen van een complicatie gerelateerd aan endoscopische biliaire drainage was vergelijkbaar bij patiënten met metalen en plastic stents. Metalen stents waren niet gerelateerd aan een hogere kans op post-endoscopische retrograde cholangiopancreatografie pancreatitis vergeleken met plastic stents. Bovendien waren metalen stents geassocieerd met een lagere kans op cholangitis, minder postoperatieve pancreasfistels en een kortere postoperatieve ziekenhuisopname. In dit hoofdstuk komt opnieuw naar voren dat richtlijnimplementatie (ten aanzien van het gebruik van metalen stents) verbeterd moet worden.

In de landelijke PACAP-1 trial wordt mogelijk een belangrijke stap gezet richting verbetering van de pancreascarcinoomzorg. Het studieprotocol van deze landelijke, multicenter, stapsgewijze, cluster gerandomiseerde trial wordt beschreven in **hoofdstuk 5**. De trial omvat een gestructureerd

verbeterprogramma voor drie zogenaamde 'best practices' om overleving en kwaliteit van leven te verbeteren. Deze best practices werden geïdentificeerd in de landelijke richtlijn, de huidige literatuur en in uitkomsten van de PACAP registraties. De best practices bestonden uit optimaal gebruik van chemotherapie, meer bewustzijn voor (de behandeling van) exocriene insufficiëntie en het gebruik van metalen stents voor endoscopische biliaire drainage. Nederland werd verdeeld in zeventien regio's gebaseerd op de zeventien pancreaschirurgie centra en de naar hen verwijzende centra. Vervolgens werden de best practices stapsgewijs geïmplementeerd van mei 2018 t/m juli 2020. Binnen de regio's werd een lokaal 'pancreascarcinoom expertteam' aangewezen voor laagdrempelige communicatie en verbetering van verwijslijnen. De primaire uitkomst is één-jaar overleving en de studieresultaten worden daarom verwacht in juli 2021.

Deel II Kwaliteit van leven en klinische uitkomsten na pancreaschirurgie

Gedurende de afgelopen jaren heeft de centralisatie van pancreaschirurgie zich ontwikkeld en verbeterd. Een hypothese is dat hierdoor de kans op resectie gelijk zou zijn geworden voor alle patiënten met een niet-gemetastaseerd pancreaskop- en periampullair carcinoom, onafhankelijk van het ziekenhuis van diagnose (een pancreaschirurgie versus niet-pancreaschirurgie centrum). Deze hypothese is getoetst in een 'population-based' studie met 10.079 patiënten (hoofdstuk 6). In 2015 t/m 2017, de periode na centralisatie, was het resectiepercentage gelijk voor patiënten gediagnosticeerd in pancreaschirurgie en niet-pancreaschirurgie centra (OR 1,08, 95% betrouwbaarheidsinterval 0,90-1,28, p=0,422). De overleving was hoger in pancreaschirurgie centra (HR 0,92, 95% betrouwbaarheidsinterval 0,85-0,99, p=0,047). Deze bevindingen suggereren dat centralisatie de zorg heeft verbeterd en dat verdere ontwikkeling van de bestaande regionale netwerken patiëntuitkomsten kan verbeteren.

Kwaliteit van leven en exocriene en endocriene insufficiëntie zijn retrospectief onderzocht bij 234 patiënten die pancreaschirurgie ondergingen voor premaligne of benigne (niet-pancreatitis) ziekte (hoofdstuk 7). De lange-termijn kwaliteit van leven was vergelijkbaar met de algemene populatie en diabetes gerelateerde stress was laag. Bijna de helft van de patiënten had klachten gerelateerd aan de operatie en 8% zou de operatie niet opnieuw ondergaan. De huidige behandeling van exocriene insufficiëntie behoeft meer aandacht, bijvoorbeeld het opzetten van persoonlijke behandelschema's door diëtisten of verpleegkundig specialisten. De resultaten kunnen gebruikt worden in gezamenlijke besluitvorming indien chirurgie overwogen wordt bij patiënten met benigne of premaligne pancreasziekten.

De voedingsstatus van patiënten is ook gerelateerd aan de kwaliteit van leven en exocriene insufficiëntie. Hoofdstuk 8 beschrijft dat de meeste micronutriënten bij patiënten minimaal vier

maanden na een pancreatoduodenectomie binnen de referentiewaarden vallen. Er waren echter deficiënties aanwezig van ijzer, ferritine, vitamine A en vitamine D en ook een anemie kwam regelmatig voor. Prospectieve studies moeten worden opgezet om te bepalen of gestandaardiseerde laboratoriumafnames en het suppleren van deficiënties patiëntuitkomsten verbeteren. Bovendien zal de suppletie van pancreasenzymen ook bijdragen aan een optimale voedingsstatus, omdat de deficiënties van vitamine A en D mogelijk gerelateerd zijn aan exocriene insufficiëntie.

Een totale pancreatectomie wordt voornamelijk uitgevoerd bij patiënten met een ziekte van de gehele pancreas, zoals een pancreascarcinoom, main-duct intraductaal papillair mucineus neoplasma of chronische pancreatitis. Over het algemeen heerst er een relatief hoge drempel voor het uitvoeren van een totale pancreatectomie vanwege een hoog postoperatief complicatie- en overlijdensrisico en levenslange endocriene- en exocriene insufficiëntie. **Hoofdstuk 9** beschrijft de uitkomsten van de Nederlandse, landelijke PANORAMA studie. Deze studie omvatte 148 patiënten die een totale pancreatectomie ondergingen tussen 2006 t/m 2016. Het majeure complicatie- en 90-dagen mortaliteitspercentage waren hoog met respectievelijk 32% en 8%. Lange termijn overlevers scoorden een slechtere, zelf gerapporteerde, globale gezondheidsstatus dan de gezonde populatie, met name door meer symptomen en functionele klachten. De verschillen waren echter klein en de klinische relevantie is onduidelijk. Patiënten waren tevreden met hun diabetes mellitus behandeling en ervaarden dezelfde diabetes-gerelateerde stress als type 1 diabetes mellitus patiënten. Deze uitkomsten zijn belangrijk voor gezamenlijke besluitvorming ten aanzien van de beslissing over het uitvoeren van een totale pancreatectomie.

De inclusieperiode van de PANORAMA studie was relatief lang en voor accurate postoperatieve uitkomsten is een representatievere reflectie van de huidige praktijk wenselijk. Met het gebruik van het relatief nieuwe snapshot studiedesign is het doel van **hoofdstuk 10** om generaliseerbare gegevens over postoperatieve uitkomsten na een totale pancreatectomie te creëren. In dit prospectieve pan-Europese cohort werden tussen 2017 en 2018 in totaal 277 patiënten, die een totale pancreatectomie ondergingen, uit zestien landen geïncludeerd. Majeure complicaties ontstonden in 25% en de ziekenhuismortaliteit was 5%. De ziekenhuismortaliteit van patiënten die geopereerd waren in een centrum met een jaarlijks pancreatoduodenectomie volume van ≥60 lag lager dan in centra met een volume <60 (4% versus 10%, p=0,046). In een multivariabele analyse werden risicofactoren geïdentificeerd voor majeure complicaties en mortaliteit. Deze risicofactoren kunnen gebruikt worden voor patiëntselectie en het verwijzen van patiënten, zodat mogelijk de uitkomsten verbeteren.
In vier registraties uit de Verenigde Staten, Duitsland, Nederland en Zweden zijn ook de postoperatieve uitkomsten na een totale pancreatectomie geanalyseerd (**hoofdstuk 11**). Deze analyse bevatte 1.579

patiënten die gedurende een relatief korte periode geopereerd waren (2014 t/m 2018). Het majeure complicatierisico was 26,8% en de ziekhuismortaliteit was 5,4%. De postoperatieve uitkomsten waren verschillend tussen de vier landen, maar dit was lastig te vergelijken door verschillen in de indicatiestelling voor een totale pancreatectomie en de verschillen in de opzet van de registraties. Het harmoniseren van de belangrijkste parameters uit de registraties zal één van de uitdagingen zijn van de GAPASURG studiegroep. De gevonden verschillen behoeven verder onderzoek, zodat uiteindelijk patiëntuitkomsten verbeterd worden.

Deel III Overleving

In **hoofdstuk 12** is het eerste predictiemodel voor conditionele overleving bij patiënten met een pancreascarcinoom gepresenteerd. De conditionele overleving is de overlevingskans nadat reeds een bepaalde periode is overleefd, dus bijvoorbeeld de kans om twee jaar meer te overleven, nadat drie jaar na de operatie overleefd zijn (vijf-jaar overleving). In een landelijke studie met 3.082 patiënten bleek dat de kans op het bereiken van vijf-jaar overleving na een pancreasresectie toenam van 15% direct na de resectie tot 61% als reeds drie jaar na de resectie waren overleefd. Een online calculator is ontwikkeld voor gebruik gedurende de postoperatieve follow-up. Met deze calculator kunnen geïndividualiseerde conditionele overlevingskansen voor vijf-jaar overleving na een pancreasresectie worden berekend.

Mogelijke relaties tussen kwaliteit van leven en cachexie of overleving zijn onderzocht in de volgende hoofdstukken. **Hoofdstuk 13** laat zien dat bij 376 patiënten met een pancreas- en periampullair carcinoom, de algemene gelukscore, een samenvattende score van kwaliteit van leven, evenals enkele functionerings- en symptoomscores voorspellend waren voor overleving. Verscheidene kwaliteit van leven scores, die gemeten werden bij diagnose, hadden een prognostische waarde bij patiënten zonder resectie en de delta van de obstipatiescore (tussen diagnose en drie maanden follow-up) was voorspellend voor overleving van het gehele cohort. Kwaliteit van leven scores blijken dus nuttig voor gebruik in de klinische praktijk, bijvoorbeeld bij gezamenlijke besluitvorming, ziektemanagement en -behandeling, klinische predictiemodellen of stratificatie in trials.

Een andere factor die in eerdere literatuur gerelateerd was aan overleving is cachexie. In **hoofdstuk 14** is deze relatie onderzocht in een prospectieve multicenter cohort studie met 202 patiënten met een pancreascarcinoom. Overleving was niet verschillend bij patiënten met en zonder cachexie (13 versus 17 maanden, p=0,18). Bij patiënten met ernstig gewichtsverlies (≥10%) in het half jaar voor diagnose was overleving echter korter ten opzichte van patiënten met <10% gewichtsverlies (12 versus 16 maanden, p=0,02). Het was opvallend dat 71% van de 202 patiënten zich presenteerde met cachexie bij diagnose en dat minder dan de helft van hen verwezen was naar een diëtist. Op basis van deze

resultaten kan gesuggereerd worden dat meer aandacht nodig is voor de aanwezigheid van cachexie en ernstig gewichtsverlies bij diagnose, de screening op malnutritie en de verwijzing naar de diëtist.

SAMENVATTING VAN DE ONDERZOEKSVRAGEN EN BELANGRIJKSTE BEVINDINGEN

Hoofdstuk	Onderzoeksvraag
1	**Wat zijn de trends van de incidentie, behandeling en overleving van patiënten met pancreas ductaal adenocarcinoom (alle stadia) in Nederland tussen 1997 en 2016?** De incidentie van het pancreas ductaal adenocarcinoom steeg de afgelopen twintig jaar. De mediane overleving verbeterde slechts marginaal (van 3,1 maanden in 1997-2000 naar 3,8 maanden in 2013-2016, p<0,001), ondanks het feit dat meer patiënten een behandeling kregen (van 16% naar 39%, p-trend<0,001).
2	**Is de compliance aan geselecteerde kwaliteitsindicatoren van de Nederlandse richtlijn uit 2011 verbeterd over de zes jaar na introductie?** Landelijke compliance aan kwaliteitsindicatoren is nauwelijks verbeterd in de zes jaar na introductie van de richtlijn. Vijf indicatoren verbeterden niet en alleen het percentage patiënten met niet-gemetastaseerde, niet-gereseceerde tumoren die chemotherapie kregen, nam toe van 23% naar 26% en 30% in de drie periodes van 2012 t/m 2017 (p-trend<0.001).
3	**Hoe beïnvloedt de implementatie van nieuwe, effectievere chemotherapieën (FOLFIRINOX en gemcitabine gecombineerd met nab-paclitaxel) voor patiënten met een gemetastaseerd pancreas ductaal adenocarcinoom de landelijke, klinische praktijk en overleving?** Na implementatie van FOLFIRINOX en gemcitabine gecombineerd met nab-paclitaxel is het gebruik van chemotherapie op landelijk niveau toegenomen en daalde de variatie in het gebruik van chemotherapie. Een aanzienlijk deel van de patiënten kreeg echter nog gemcitabine met een teleurstellende overlevingswinst. Overleving van alle geïncludeerde patiënten steeg slechts van 3,3 naar 3,4 maanden (p<0,001), maar van 5,6 naar 6,4 maanden (p<0,001) voor patiënten met chemotherapie.
4	**Wat is de huidige landelijke praktijkvoering betreffende het gebruik van metalen stents bij preoperatieve endoscopische biliaire drainage voor patiënten met een resectabele pancreaskop- en periampullaire carcinoom en wat zijn de uitkomsten?** Preoperatieve endoscopische biliaire drainage werd slechts in 43% verricht met een metalen stent. Metalen stents waren geassocieerd met minder cholangitis en postoperatieve pancreasfistels en een kortere ziekenhuisopname vergeleken met plastic stents. Daarnaast werd er geen relatie van metalen stents met een post-endoscopische retrograde cholangiopancreatografie pancreatitis gevonden.
5	**Verbetert een landelijke implementatie van best practices middels een multicenter, stapsgewijze, cluster gerandomiseerde trial (PACAP-1) de overleving en kwaliteit van leven van patiënten met een pancreascarcinoom?** De landelijke implementatie van best practices in de PACAP-1 trial is afgerond in juli 2020. Het effect van de implementatie op overleving en kwaliteit van leven kan na juli 2021 geanalyseerd worden, omdat dan de één-jaar follow-up compleet is.

6 **Is de resectiekans van patiënten met een niet-gemetastaseerd pancreaskop- of periampullair carcinoom veranderd in pancreaschirurgie centra ten opzichte van niet-pancreaschirurgie centra tussen 2009 t/m 2017 en heeft dit de overleving beïnvloed?**

In de periode van 2015 t/m 2017, na de centralisatie, zijn de resectiekansen tussen patiënten gediagnosticeerd in pancreaschirurgie en niet-pancreaschirurgie centra gelijk geworden. Overleving lag hoger in pancreaschirurgie centra.

7 **Wat is de kwaliteit van leven en status van exocriene en endocriene insufficiëntie op lange termijn bij patiënten na pancreaschirurgie voor benigne of premaligne ziekte?**

De lange-termijn kwaliteit van leven is vergelijkbaar met de algemene populatie. Bijna de helft van de patiënten had klachten gerelateerd aan de operatie en 8% zou de operatie niet opnieuw ondergaan. Diabetes gerelateerde stress was laag, maar de huidige behandeling van exocriene insufficiëntie behoeft meer aandacht.

8 **Welke micronutriënten zijn deficiënt bij patiënten gedurende follow-up na een pancreatoduodenectomie?**

De meeste micronutriënten bij patiënten gedurende follow-up waren binnen de referentiewaarden, maar deficiënties van ijzer, ferritine, vitamine A en vitamine D en een anemie kwamen veelvuldig voor. Prospectieve studies moeten uitwijzen of gestandaardiseerde laboratoriumafnames en het suppleren van deficiënties patiëntuitkomsten verbeteren.

9 **Wat zijn de korte termijn postoperatieve uitkomsten en lange termijn kwaliteit van leven bij patiënten na een totale pancreatectomie?**

De 90-dagen mortaliteit na een totale pancreatectomie was hoog met 8%. In vergelijking met de gezonde populatie hadden patiënten na een totale pancreatectomie een slechtere, zelf gerapporteerde globale gezondheidsstatus met meer symptomen en functionele klachten. Het is de vraag of dit verschil klinisch relevant is. Patiënten waren tevreden met hun diabetes mellitus behandeling en hadden vergelijkbare diabetes-gerelateerde stress met type 1 diabetes mellitus patiënten.

10 **Wat zijn de korte termijn postoperatieve uitkomsten na een electieve totale pancreatectomie in een multicenter pan-Europese snapshot studie?**

Bij patiënten na een totale pancreatectomie was het majeure complicatiepercentage 25% en de ziekenhuismortaliteit 5%. Ziekenhuismortaliteit lag lager bij patiënten die geopereerd waren in centra met een jaarlijks volume ≥60 pancreatoduodenectomieën in vergelijking met centra met een volume <60 (4% versus 10%, p=0,046). In een multivariabele analyse zijn risicofactoren geïdentificeerd. Ziekenhuismortaliteit was gerelateerd aan een jaarlijks volume van <60 pancreatoduodenectomieën, leeftijd en een geschat bloedverlies van ≥2L. Een American Society of Anesthesiologists (ASA) score ≥3 en een geschat bloedverlies van ≥2L waren geassocieerd met majeure complicaties.

11	**Wat zijn de korte termijn postoperatieve uitkomsten na een totale pancreatectomie bij patiënten geïncludeerd in vier registraties (de Verenigde Staten, Duitsland, Nederland en Zweden) en verschillen uitkomsten tussen de landen?** Het majeure complicatiepercentage na een totale pancreatectomie in vier registraties was 26,8% en de ziekenhuismortaliteit 5,4%. Uitkomsten zijn beter in de USA en Zweden, maar de vergelijking tussen landen is lastig door verschillen in het uitvoeren van een totale pancreatectomie en de opzet van de registraties. De verschillen tussen landen behoeven verder onderzoek, zodat uiteindelijk patiëntuitkomsten verbeterd worden.
12	**Wat zijn de gepersonaliseerde conditionele overlevingskansen van patiënten na een resectie voor een pancreascarcinoom?** Om zorgverleners en patiënten te informeren over gepersonaliseerde overlevingskansen na een resectie voor een pancreascarcinoom is een predictiemodel ontwikkeld en omgezet tot een online calculator. Dit predictiemodel toont dat de kans op vijf-jaar overleving stijgt van 15% direct postoperatief naar 61% nadat drie jaar na de resectie zijn overleefd.
13	**Is kwaliteit van leven gerelateerd aan overleving bij patiënten met pancreas- en periampullaire carcinomen?** Kwaliteit van leven is geassocieerd met overleving, onafhankelijk van patiënt-, tumor- en behandelkarakteristieken. Diverse kwaliteit van leven scores, gemeten bij diagnose, waren van prognostische waarde bij patiënten zonder resectie. In het gehele cohort was de delta obstipatiescore (tussen diagnose en drie maanden follow-up) prognostisch voor overleving.
14	**In hoeverre is cachexie aanwezig in de huidige praktijk bij patiënten met pancreascarcinoom en is dit geassocieerd met een consult bij de diëtist of met overleving?** Twee derde van de patiënten met een pancreascarcinoom had cachexie bij diagnose en bijna de helft daarvan had geen consult bij de diëtist. De overleving was vergelijkbaar bij patiënten met en zonder cachexie, maar was korter bij patiënten met ernstig gewichtsverlies (≥10%) in het laatste half jaar voor diagnose ten opzichte van patiënten met <10% gewichtsverlies.

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Fennie Wit
Hana Zavrtanik
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LIST OF PUBLICATIONS

1. Clinical Outcomes after Total Pancreatectomy: A Prospective Multicenter Pan-European Snapshot Study.
   A.E.J. Latenstein, L. Scholten, H.A. Al-Saffar, B. Björnsson, G. Butturini, G. Capretti, N.A. Chatzizacharias, C. Dervenis, I. Frigerio, T.K. Gallagher, S. Gasteiger, A. Halimi, K.J. Labori, G. Montagnini, L. Muñoz-Bellvis, G. Nappo, A. Nikov, E. Pando, M. de Pastena, J.M. de la Peña-Moral, D. Radenkovic, K.J. Roberts, R. Salvia, F. Sanchez-Bueno, C. Scandavini, M. Serradilla-Martin, S. Stättner, A. Tomazic, M. Varga, H. Zavrtanik, A. Zerbi, M. Erkan, J. Kleeff, M. Lesurtel, M.G. Besselink[#], J.M. Ramia-Angel[#] for the Scientific, Research Committee of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA).
   Ann Surg. 2020 Nov 9. Online ahead of print.

2. Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: A multicenter cohort study.
   A.E.J. Latenstein*, W.P.M. Dijksterhuis*, T.M. Mackay, S. Beijer, C.H.J. van Eijck, I.H.J.T. de Hingh, I.Q. Molenaar, M.G.H. van Oijen, H.C. van Santvoort, M.A.E. de van der Schueren, J. de Vos-Geelen, J.H.M. de Vries, J.W. Wilmink, M.G. Besselink[#], H.W.M. van Laarhoven[#] for the Dutch Pancreatic Cancer Group.
   Cancer Med. 2020 Dec;9(24):9385-9395.

3. Nationwide compliance with a multidisciplinary guideline on pancreatic cancer during 6-year follow-up.
   T.M. Mackay*, A.E.J. Latenstein*, B.A. Bonsing, M.J. Bruno, C.H.J. van Eijck, B. Groot Koerkamp, I.H.J.T. de Hingh, M.Y.V. Homs, J.E. van Hooft, H.W.M. van Laarhoven, I.Q. Molenaar, H.C. van Santvoort, M.W.J. Stommel, J. de Vos-Geelen, J.W. Wilmink, O.R. Busch, L.G. van der Geest[#], M.G. Besselink[#] for the Dutch Pancreatic Cancer Group.
   Pancreatology. 2020 Dec;20(8):1723-1731.

4. Relationship Between Quality of Life and Survival in Patients With Pancreatic and Periampullary Cancer: A Multicenter Cohort Analysis.
   T.M. Mackay, A.E.J. Latenstein, M.A.G. Sprangers, L.G. van der Geest, G.J. Creemers, S. van Dieren, J.W.B. de Groot, B. Groot Koerkamp, I.H. de Hingh, M.Y.V. Homs, E.J.M. de Jong, I.Q. Molenaar, G.A.

Patijn, L.V. van de Poll-Franse, H.C. van Santvoort, J. de Vos-Geelen, J.W. Wilmink, C.H. van Eijck, M.G. Besselink, H.W.M. van Laarhoven for the Dutch Pancreatic Cancer Group.
J Natl Compr Canc Netw. 2020 Oct 1;18(10):1354-1363.

5. Prophylactic total pancreatectomy in individuals at high risk of pancreatic ductal adenocarcinoma (PROPAN): systematic review and shared decision-making programme using decision tables.
L. Scholten, A.E.J. Latenstein, C.M. Aalfs, M.J. Bruno, O.R. Busch, B.A. Bonsing, B. Groot Koerkamp, I.Q. Molenaar, D.T. Ubbink, J.E. van Hooft, P. Fockens, J. Glas, J.H. DeVries#, M.G. Besselink# for the Dutch Pancreatic Cancer Group.
United European Gastroenterol J. 2020 Oct;8(8):865-877.

6. Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer.
A.E.J. Latenstein*, T.M. Mackay*, N.C.M. van Huijgevoort, B.A. Bonsing, K. Bosscha, L. Hol, M.J. Bruno, M.M.E. van Coolsen, S. Festen, E. van Geenen, B. Groot Koerkamp, G.J.M. Hemmink, I.H.J.T. de Hingh, G. Kazemier, H. Lubbinge, V.E. de Meijer, I.Q. Molenaar, R. Quispel, H.C. van Santvoort, T.C.J. Seerden, M.W.J. Stommel, N.G. Venneman, R.C. Verdonk, M.G. Besselink#, J.E. van Hooft# for the Dutch Pancreatic Cancer Group.
HPB (Oxford). 2020 Jul 16;S1365-182X(20)31056-X. Online ahead of print.

7. Conditional Survival After Resection for Pancreatic Cancer: A Population-Based Study and Prediction Model.
A.E.J. Latenstein, S. van Roessel, L.G.M. van der Geest, B.A. Bonsing, C.H.C. Dejong, B. Groot Koerkamp, I.H.J.T. de Hingh, M.Y.V. Homs, J.M. Klaase, V. Lemmens, I.Q. Molenaar, E.W. Steyerberg, M.W.J. Stommel, O.R. Busch, C.H.J. van Eijck, H.W.M. van Laarhoven, J.W. Wilmink, M.G. Besselink for the Dutch Pancreatic Cancer Group.
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8. Implementation of contemporary chemotherapy for patients with metastatic pancreatic ductal adenocarcinoma: a population-based analysis.
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Acta Oncol. 2020 Jun;59(6):705-712.

9. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial.
   T.M. Mackay, F.J. Smits, A.E.J. Latenstein, A. Bogte, B.A. Bonsing, H. Bos, K. Bosscha, L.A.A. Brosens, L. Hol, O.R.C. Busch, G.J. Creemers, W.L. Curvers, M. den Dulk, S. van Dieren, L.M.J.W. van Driel, S. Festen, E.J.M. van Geenen, L.G. van der Geest, D.J.A. de Groot, J.W.B. de Groot, N. Haj Mohammad, B.C.M. Haberkorn, J.T. Haver, E. van der Harst, G.J.M. Hemmink, I.H. de Hingh, C. Hoge, M.Y.V. Homs, N.C. van Huijgevoort, M.A.J.M. Jacobs, E.D. Kerver, M.S.L. Liem, M. Los, H. Lubbinge, S.A.C. Luelmo, V.E. de Meijer, L. Mekenkamp, I.Q. Molenaar, M.G.H. van Oijen, G.A. Patijn, R. Quispel, L.B. van Rijssen, T.E.H. Römkens, H.C. van Santvoort, J.M.J. Schreinemakers, H. Schut, T. Seerden, M.W.J. Stommel, A.J. ten Tije, N.G. Venneman, R.C. Verdonk, J. Verheij, F.G.I. van Vilsteren, J. de Vos-Geelen, A. Vulink, C. Wientjes, F. Wit, F.J. Wessels, B. Zonderhuis, C.H. van Werkhoven, J.E. van Hooft[#], C.H.J. van Eijck[#], J.W. Wilmink[#], H.W.M. van Laarhoven[#], M.G. Besselink[#] for the Dutch Pancreatic Cancer Group.
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10. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma.
    A.E.J. Latenstein, L.G.M. van der Geest, B.A. Bonsing, B. Groot Koerkamp, N. Haj Mohammad, I.H.J.T. de Hingh, V.E. de Meijer, I.Q. Molenaar, H.C. van Santvoort, G. van Tienhoven, J. Verheij, P.A.J. Vissers, J. de Vos-Geelen, O.R. Busch, C.H.J. van Eijck, H.W.M. van Laarhoven, M.G. Besselink, J.W. Wilmink for the Dutch Pancreatic Cancer Group.
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11. Outcome and long-term quality of life after total pancreatectomy (PANORAMA): a nationwide cohort study.
    L. Scholten, A.E.J. Latenstein, C. van Eijck, J. Erdmann, E. van der Harst, J.S.D. Mieog, I.Q. Molenaar, H.C. van Santvoort, J.H. DeVries, M.G. Besselink for the Dutch Pancreatic Cancer Group.
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12. Minimally invasive surgery for perihilar cholangiocarcinoma: a systematic review.
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    J Robot Surg. 2019 Dec;13(6):717-727.

13. Long-Term Colon Stent Patency for Obstructing Colorectal Cancer Combined with Bevacizumab.
    A.E.J. Latenstein, M.P. Hendriks, E.E. van Halsema, J.E. van Hooft, A.M. van Berkel.
    Case Rep Gastroenterol. 2017 Nov 29;11(3):711-717. eCollection Sep-Dec 2017.

* Shared first authorship

Shared senior authorship

PHD PORTFOLIO

Name PhD student: Anouk Latenstein

PhD period: November 2017 – October 2020

Promotores: Prof. dr. Marc G. Besselink and prof. dr. Hanneke W.M. van Laarhoven

Copromotores: Dr. Johanna W. Wilmink and Prof. dr. Casper J.H. van Eijck

PhD Training	Year	ECTS
Courses		
Practical biostatistics	2018	1.1
Basic course in legislation and organization for clinical researchers (BROK)	2018	0.9
Clinical Epidemiology: Randomized Controlled Trials	2018	0.9
Clinical Epidemiology: Observational epidemiology	2018	0.9
Scientific writing in English for publication	2018	1.5
RCT course, Centre for Statistics in Medicine, Oxford University	2018	2.5
Clinical Epidemiology: Systematic Reviews	2019	0.9
Project management	2019	0.6
Seminars, workshops, and masterclasses		
Academic Medical Center department of surgery seminars	2017 - 2020	2.0
Dutch Pancreatic Cancer group seminars	2017 - 2020	1.0
Journal Club	2017 - 2020	2.0
British Journal of Surgery: “How to Write a Clinical Paper workshop”	2018	1.0
Clinical Investigation of Medical Devices for Human Subjects (ISO 14155)	2018	0.5
Attended conferences		
Amsterdam Gastroenterology & Metabolism PhD-students retreat, Garderen	2018	1.0
Chirurgendagen, Veldhoven	2018	1.0
Pancreasdag, Gouda (organizing committee)	2018 – 2020	2.0
International Hepato-Pancreato-Biliary Association (IHPBA), Geneva and virtual meeting	2019 – 2020	1.5
Alpine Liver and Pancreatic Surgery Meeting (ALPS), Madonna di Campiglio	2019	1.0
Americas Hepato-Pancreato-Biliary Association (AHPBA), Miami	2019	1.0
European-African Hepato-Pancreato-Biliary Association (E-AHPBA), Amsterdam	2019 – 2020	0.5

Dutch Digestive Disease Days (DDD), Veldhoven and virtual meeting	2019 - 2020	2.0
United European Gastroenterology Week (UEGW), Barcelona and virtual meeting	2019	0.25
Symposium Experimenteel Onderzoek Heelkundige Specialismen, Amsterdam	2020	0.25
52th Meeting of the European Pancreatic Club, virtual meeting		
Pancreas Club, virtual meeting	2020	0.5
Oral presentations		
Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial at AGEM PhD-students retreat	2018	0.5
Outcome and long-term quality of life after total pancreatectomy (PANORAMA): a nationwide cohort study at the ALPS, AHPBA, and Chirurgendagen	2019	1.5
Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma at the E-AHPBA	2019	0.5
Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer at UEGW and DDD	2019	1.0
Conditional survival after resection for pancreatic cancer: a population-based study and prediction model at UEGW, SEOHS, IHPBA (virtual)	2019	1.5
Clinical outcomes after total pancreatectomy: a prospective multicenter pan-European snapshot study at ALPS, EPC (virtual), DDD (virtual), UEGW (virtual), Pancreas Club (virtual), IHPBA (virtual)	2020	3.0
Poster presentation		
Outcome and long-term quality of life after total pancreatectomy (PANORAMA): a nationwide cohort study at E-AHPBA	2019	0.5
Conditional survival after resection for pancreatic cancer: a population-based study and prediction model at Pancreasclub, E-AHPBA, and ALPS	2019 – 2020	1.5
Implementation of contemporary chemotherapy for patients with metastatic pancreatic ductal adenocarcinoma: a population-based analysis at Pancreasclub, E-AHPBA and AHPBA	2019 – 2020	1.5
Clinical outcomes after total pancreatectomy: a prospective multicenter pan-European snapshot study at AHPBA	2020	0.5

Nationwide practice and outcomes of endoscopic biliary drainage in resectable pancreatic head and periampullary cancer at Pancreas Club (virtual)	2020	0.5
Teaching		
Supervisor master thesis Physician Assistant Nicole van Zenden	2018 - 2019	4.0
Supervisor master thesis Nic Tjahjadi	2019	2.0
Teaching bachelor students	2018 - 2020	3.0
Invited lectures		
Voedingsgerelateerde consequenties op korte termijn na chirurgie at Post HBO cursus organized by Chirurgisch Overleg Diëtisten Academische Ziekenhuizen (CHIODAZ) and PIT Actief, Utrecht	2018	0.5
Pancreascarcinoom at Trainingsdag Pancreas organized by Landelijke Vereniging Psychosociaal Werkenden (LVPW), Maarn	2018	0.5
Grants and awards		
ALPS, bursary for young investigators	2019	
ALPS, best free paper	2019	
Citrien Regionaal oncologienetwerken, Gegevenssets Oncologie, subsidie	2019	
E-AHPBA, best poster (twice)	2019	
DPCG-IPSEN Science Award	2019	
UEGW, travel grant	2019	
ALPS, bursary for young investigators	2020	
ALPS, best poster presentation	2020	
AGEM clinical research matching grant for “Algorithm to control Postprandial, Post exercise and night glucose Excursions in a portable closed Loop format in patients after total pancreatectomy, APPEL 5+”	2020	

DANKWOORD

Dit proefschrift was niet tot stand gekomen zonder de bijdrage van vele mensen om mij heen. Enkelen wil ik hiervoor in het bijzonder bedanken.

Professor Besselink, beste Marc, wat ben ik blij dat jij mij de kans hebt gegeven om bij jou promotieonderzoek te mogen doen. Ik heb de afgelopen jaren ontzettend veel geleerd en onwijs veel mogelijkheden gekregen om alle kanten van het onderzoek te leren kennen: presentaties op (verre) congressen, belangrijke overleggen en natuurlijk het opzetten van het Deltaplan Alvleesklierkanker. Jouw enthousiasme voor onderzoek en de tijd die je altijd in jouw agenda vrijmaakte om samen te sparren, hebben tot dit prachtige boek geleid. Heel veel dank!

Professor van Laarhoven, beste Hanneke, pas later sloot jij aan als mijn promotor, maar daarvoor was jij al erg betrokken bij mijn onderzoeken. Jouw inzichten waren verhelderend en brachten mij altijd weer een paar stappen verder. Jij hebt mij geleerd om kritisch naar onderzoeken te kijken en het niet alleen maar uit te voeren omdat het kan. Bedankt voor jouw begeleiding!

Doctor Wilmink, beste Hanneke, wat heerlijk dat jij lange tijd om de hoek zat en ik voor korte vragen gewoon even langs kon lopen. De vertaalslag naar de klinische praktijk is één van de dingen waarvoor ik altijd bij jou terecht kon. Ik waardeer dat jij altijd even aandacht had voor alle aspecten buiten mijn promotie. Bedankt voor jouw support!

Professor van Eijck, beste Casper, ook jij sloot later aan bij mijn commissie, maar wij hadden al menig stuk met elkaar geschreven. Over de jaren hebben wij elkaar beter leren kennen en kregen wij steeds meer contact. Manuscripten werden met een kritische blik bekeken, maar ik weet zeker dat dit boek daardoor beter is geworden. Bedankt voor jouw hulp!

Leden van mijn promotiecommissie, beste prof. Klaase, prof. Dejong, dr. Mekenkamp, prof. Nieveen van Dijkum, prof. Fockens en prof. Tanis, zeer veel dank voor het lezen van mijn proefschrift en de tijd die u genomen heeft om hierover met mij te kunnen discussiëren.

Professor Busch en doctor van Hooft, beste Olivier en Jeanin, uiteraard mogen jullie niet ontbreken in mijn dankwoord. Ondanks dat jullie niet in mijn commissie zitten, hebben jullie toch de tijd en moeite

genomen om mij te begeleiden tijdens mijn promotie. Bedankt voor jullie hulp en interesse! Professor Molenaar, Q, bedankt voor de prachtige grappen op de ski's, ik heb genoten!

Lieve vriendinnen, Dees, Door, Dwergje, Eem, Juul, Max, Mier, Renée en Yvon, jullie snapten lang niet altijd wat ik precies aan het doen was, maar jullie waren er altijd. Dank voor het zijn van een luisterend oor voor de goede en slechte verhalen, maar ook voor de ontelbare herinneringen die wij de afgelopen jaren hebben gemaakt. Wals, mijn beste kennis, met jou geniet ik altijd en lach ik het állerhardst. Door, met jou ben ik eigenlijk het vaakst naar huis gefietst, bedankt voor de heerlijke belletjes. Jullie maken mij gelukkig. Ik kijk uit naar alle momenten die nog gaan volgen!

Secretaresses van G4, Els, Ilse, Indra, Jacq en Joke, bedankt voor al jullie hulp tijdens mijn promotie. Zonder jullie zou de afdeling niet draaien. Jacq, mag ik jou in het bijzonder bedanken voor al jouw hulp, maar vooral voor alle gezellige praatjes en de onaardige momenten. Wat lagen wij elkaar goed!

Onderzoekers van G4, dankzij jullie was promoveren leerzaam, maar bovenal ook heel erg leuk. Jullie boden steun, ontspanning en vooral veel mooie assistentenweekenden, skitrips, borrels en festivals. Eline, wat ben jij een goede aanwinst voor de afdeling en wat ben ik blij dat jij er tijdens mijn laatste maanden was. Ik kijk uit naar onze verdere vriendschap! Lot, Li en Marianne, vooral buiten werk zagen wij elkaar. Wijn of goede feestjes, met jullie haalden we altijd de volle 100% eruit. Fay en An, het deed mij altijd goed als jullie ook op de afdeling waren, alsof wij daar een beetje samen streden. Jullie maakten Frankrijk nog net een groter feestje. Volgend jaar weer een ritje op de vouwfiets?

Collega's van het OLVG, oude bekenden en nieuwe gezichten, maar zeker een warm welkom in de groep. Ik heb zin om heel veel bij jullie te leren en in de gezelligheid die daarbij komt kijken!

Bessies, Alicia, Alma, Annelie, Boris, Burak, Char, Charlotte, Daan, Deesje, Erna, Fred, Jony, Leia, Lianne, Lil, Maarten, Marcel, Marcel, Marin, Maurice, Nicky, Nine, Sanne, Simone, Sjors, Stijn, Sven, Thijs, Thomas, Timothy, Ward en eigenlijk ook Lydia, bedankt voor alle overleggen en klaagmomenten. Ik kijk met veel plezier terug op alle congressen en vergaderingen. Met jullie was dit altijd leuker. Nicky en Alma, gouden herinneringen aan de momenten dat Southampton en Amsterdam samen kwamen. Grote spelers, die naam hebben we zeker eer aan gedaan. Lydia, bedankt voor de hulp met de IKNL data, ik heb veel van jou geleerd! Bibi, met jou hebben we eindelijk iemand in het team die vele onderzoekers gaat begroeten en uit gaat zwaaien. Samen met jou zal PACAP en de DPCG verder groeien, dankjewel! Siem, jij bent oprecht de beste opvolger voor PACAP en PACAP-1. Wat pak jij alles snel op. Heel veel succes!

Utrechters, AC, Jas, Lil, Lois, Nota en Walma, wat genoot ik van de vergaderingen en congressen waar jullie ook waren. AC, dank voor al jouw hulp bij het onderzoek. Ik houd van jouw gele persoonlijkheid, als jij er bent, wordt iedereen vrolijk. Het onderzoek stopt, maar wij stoppen zeker niet. Lil, wie had dat ooit gedacht toen ik jouw oudste co was? Maar het had ook niet anders mogen zijn, want wat heb jij bijgedragen aan een mooie tijd. Barcelona met stip op één! Stiekem kijk ik weleens op tegen jouw wijsheid en volwassenheid, jij liet mij anders naar de dingen kijken. Dank voor alles! Nota, vuurtoren, hopelijk komen wij elkaar nog vaak tegen, zodat jij mijn grappen niet hoeft te missen.

Lieve Lotte, mijn connectie aan de overkant van de Amstel. Dank voor het samenwerken en jouw positiviteit, maar ook jouw relativisme dat mij soms iets wist af te remmen. De saaiste dataverzameldagen werden met jou een kleine competitie en eindigden altijd tevreden. Hopelijk dragen wij bij aan verbetering van de exocriene pancreasinsufficiëntie, maar jij draagt in ieder geval bij aan mijn promotie. Dank voor al het sparren!

Lieve Jo en Vi, jullie waren de beste kamergenootjes die ik kon wensen. Jullie gezelligheid maakten mijn dagen altijd beter. De klinische verhalen maakten dat ik uitzag naar toekomst. Ik vind het bijzonder hoe dit zich ontwikkelde en dank voor al jullie positieve woorden!

Bom, Jochem, Maarten, Nick, Niels en Stijn, wat was jullie mannelijke nuchterheid een heerlijke verademing op G4. Bedankt voor alle slechte grappen, het kletsen, mij duizend keer laten schrikken, de borrels en de prachtige fietsritten.

Lieve Charlotte, naast alle pancreatitis projecten kreeg jij ook nog even de APPEL5+ erbij. Heerlijk dat jij net zo enthousiast was over de kunstalvleesklier als ik en wat heb je deze studie geweldig uitgevoerd! Ik heb genoten van ons tripje naar Goor, nachtje in Lunteren en weekje Utrecht. Ik weet zeker dat jij een prachtige promotie tegemoet gaat. Maak er een mooie periode van, samen met Hanneke. Dank dat jullie mij in de laatste maanden gezelligheid boden!

Lieve Fred, honderden kilometers hebben wij gereden (soms gestreden) en luisterde jij naar mijn geklaag over de wind of lachte jij om mijn euforie. Met jou mocht ik genieten van Oxford en Londen, Miami en de Bahama's, Frankrijk, Lowlands en wandelingen door een uitgestorven Amsterdam. Lief en leed gedeeld, samen in de rollercoaster. Dankjewel voor al jouw steun en gezelligheid, met jou heb ik er een waardevolle vriendschap bij! Zullen wij onze droomtourtjes één voor één uitvoeren, zodat we nog jaren samen genieten?

Lieve Stino, een ware vriendschap ontstond in G4-130: jij was DJ en ik verstoorde graag de rust. Lil' Kleine uurtje op vrijdag blijft een van mijn lievelingsmomenten. Goede gesprekken vonden ook plaats en zelfs een ware van Roessel-Latenstein paper werd geschreven. Jouw passie voor onderzoek motiveerde mij, maar wat krijg ik een grote glimlach als ik denk aan al onze herinneringen daarbuiten. Jij maakte mijn promotie tot een intellectueel feestje.

Lieve Taar, wat was onze promotie mooi! Ik knijp echt in m'n handjes dat ik bij jouw project mocht aanhaken. Wat mogen wij trots terugkijken op wat wij gepresteerd hebben. Samen konden wij alle obstakels aan. Bedankt voor jouw hulp bij het schrijven en analyseren, maar nog veel meer bedankt voor jouw gezelligheid en humor. Ik hoefde maar naar rechts te kijken om nieuwe energie te krijgen. Alleen als het met jou is, zou ik het opnieuw kunnen doen. Hopelijk mogen wij nog heel lang samenwerken en doen we ooit misschien samen een Whipple.

Lieve Char, mijn paranimf, dat kon niet anders. Wat ben jij belangrijk geweest tijdens mijn promotie. Alles konden we delen en jouw adviezen waren vaak verhelderend. Hoe je het voor elkaar hebt gekregen, weet niemand, maar door jou ben zelfs ik dieren leuk gaan vinden. Door jou kwam ik iedere dag met plezier naar werk. Jij maakt het promotieavontuur compleet met Vélo en de AMC fietstochtjes (lepelaar!) daarna, maar vooral door alle spontane diners bij de Spagh, feestjes, logeerpartijen en vakantie. Wij hebben alles eruit gehaald wat erin zat en dat wil ik voor altijd samen blijven doen.

Lieve Car, kido, wij zijn al ons hele leven samen, maar wat ben ik blij dat jij ook tijdens mijn promotie als paranimf aan mijn zijde staat. Onze band is onbeschrijfelijk en ijzersterk. Ik ben benieuwd hoe onze wegen gaan verlopen, maar wat zou het fijn zijn als die voor altijd zo verbonden blijven. Wij kunnen schitterend ruzie maken, maar veel vaker heb ik keihard met jou gelachen. Het was heerlijk om zolang samen te wonen, bedankt voor alle gekke momenten. Ik ben trots dat ik zo'n geweldig zusje heb.

Lieve oma, u vertelt altijd aan iedereen hoe trots u bent, maar mogelijk ben ik nog trotser op u. Ik vind het heerlijk om even bij u langs te gaan en samen te kletsen. Onze telefoontjes maakten vele fietsritten dragelijk, want wij raakten nooit uitgepraat. Hopelijk kunnen we dit nog jaren doorzetten!

Lieve papa en mama, jullie bedanken is niet in een paar zinnen samen te vatten. Het is onbeschrijfelijk hoe jullie altijd voor mij en Carmen klaar staan en wat jullie voor ons doen. Mam, wat kan ik intens genieten als jij de slappe lach krijgt, maar ook van al jouw goede zorgen. Pap, ik houd zo van onze momentjes samen en vooral van onze slechte humor. Zonder jullie steun was ik nooit zover gekomen en met jullie blijf ik altijd in mijzelf geloven. Ik kijk uit naar alle mooie dingen die wij nog zullen doen.

CURRICULUM VITAE

Anouk Elisabeth Josina Latenstein was born in Alkmaar on May 28th, 1993. During her childhood, she lived together with her younger sister and parents in Bergen, surrounded by the forest and beach. In 2011, she graduated cum laude from the 'Willem Blaeu' in Alkmaar. After enjoying a long summer, she started medical school at the University of Amsterdam.

After finishing her bachelor's degree, Anouk went to Kampala, Uganda, to combine a clinical internship with travelling. During her master's degree, she wrote a thesis on the implementation of robot-assisted pancreatoduodenectomy in the Netherlands, supervised by prof. dr. Marc Besselink. Her interest for research grew, specifically in the area of hepato-pancreato-biliary surgery. Therefore, after graduating from medical school in 2017, Anouk started as a PhD-student under the supervision of prof. dr. Marc Besselink and prof. dr. van Laarhoven. Her research mainly focused on nationwide practice and survival in pancreatic and periampullary cancer, and on outcomes of pancreatic surgery. She coordinated the Dutch Pancreatic Cancer Project (PACAP) and the PACAP-1 trial together with Tara Mackay and was involved in the development of the Deltaplan Alvleesklierkanker by the Dutch Pancreatic Cancer Group, Maag Lever Darm Stichting, and Living with Hope. Anouk had the opportunity to present her work at multiple (inter)national conferences. She also joined Jong Amsterdam UMC to organize events and stimulate the connection between young professionals. Anouk likes to play field hockey, discover her surroundings by cycling, and to spend time with friends and family.

Anouk is currently working as a surgical resident not in training at the Onze Lieve Vrouwe Gasthuis under the supervision of dr. Michael Gerhards.


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