The Dutch Pancreatic Cancer Project

Tools for a tailored approach to pancreatic and periampullary cancer treatment

Strijker, M.

Link to publication

Creative Commons License (see https://creativecommons.org/use-remix/cc-licenses): Other

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
CHAPTER 1.

General introduction and outline of this thesis
THE PANCREATIC AND PERIAMPULLARY REGION

The pancreas is a secretory organ located in the upper abdomen behind the stomach. It is anatomically divided into the head, body and tail (Figure 1). Functions of the pancreas include the production of digestive enzymes by the acinar cells (exocrine function) and production of insulin by the islets of Langerhans (endocrine function). Pancreatic enzymes are secreted via the pancreatic duct. Bile is produced by the liver and secreted via the left and right hepatic ducts. These two ducts merge into the common hepatic duct and later the common bile duct which passes through the pancreatic head. In the pancreatic head, the common bile duct and pancreatic duct merge to form the ampulla, just before opening into the duodenum via de papilla of Vater (or major duodenal papilla).

![Pancreas Diagram](image)

Figure 1. Pancreatic and periampullary region.

PANCREATIC AND PERIAMPULLARY CANCER

Cancers can arise from several parts of the pancreatic and periampullary region, including pancreatic cancer, cholangiocarcinoma (cancer of the bile ducts), ampullary cancer (cancer of the ampulla/papilla of Vater), and duodenal cancer. Pancreatic cancer is the most common of these cancers with an incidence of around 15 per 100,000 in the Netherlands.\(^1,2\) The most common type of exocrine pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), harboring a very poor 5-year survival rate of \(9\%\).\(^3,4\) Around 50% of patients with PDAC present with metastatic disease, 30-35% with locally advanced disease, and only 15-20%
with resectable disease.\textsuperscript{1,5} Five-year survival for patients after resection is currently around 17%.\textsuperscript{1} For patients with metastatic disease receiving palliative chemotherapy median survival is around 6 months, and for patients with locally advanced PDAC receiving chemotherapy this is around 15 months. For patients receiving only best supportive care, median survival is around 2.3 months.\textsuperscript{1,5}

Most PDACs arise from microscopic non-invasive epithelial proliferations formed in pancreatic ducts, known as Pancreatic Intraepithelial Neoplasm (PanIN).\textsuperscript{6,7} A minority of PDACs develop from pre-neoplastic cystic lesions, being Intraductal Papillary Mucinous Neoplasms (IPMN) and Mucinous Cystic Neoplasms (MCN).\textsuperscript{7} Around 5-10% of PDACs are caused by one of the various familial cancer syndromes.\textsuperscript{8,9} Over several decades it has been well-established that four genes drive PDAC; the $\text{KRAS}$ oncogene (90% of tumors) and the inactivation of the tumor suppressor genes $\text{TP53}$, $\text{SMAD4}$ and $\text{CDKN2A}$. A typical morphological feature of PDAC is an abundance of stroma surrounding the cancer cells (Figure 2). This stroma comprises of extracellular matrix proteins, fibroblasts, endothelium, and immune cells, and is thought to hold tumor-promoting as well as tumor-restraining properties.\textsuperscript{10}

![Figure 2. Pancreatic ductal adenocarcinoma cells surrounded by stroma (adapted from image by Anne Steins, with permission).](image-url)
Treatment of patients with resectable PDAC has traditionally been upfront resection followed by adjuvant gemcitabine.\textsuperscript{11} The most commonly performed resections are a pancreatoduodenectomy and distal pancreatectomy. Due to the complex anatomy of the pancreatic and periampullary region, pancreatic surgery is amongst the most challenging and complex areas of abdominal surgery. Morbidity rates are as high as 30-40% and mortality rates are 1-3.5%.\textsuperscript{12,13} Recently, it has been shown that adjuvant treatment with gemcitabine-capecitabine or modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) improves survival when compared to gemcitabine alone.\textsuperscript{14,15} Additionally, neoadjuvant strategies are gaining increasing attention. In a meta-analysis, survival has shown to be 18.8 months for neoadjuvant treatment versus 14.8 months for upfront surgery in patients with (borderline) resectable disease.\textsuperscript{16} In the recent Dutch PREOPANC multicenter randomized controlled trial, it was shown that overall survival was not significantly better after neoadjuvant treatment when compared to immediate surgery, but the secondary endpoints (e.g. R0 resection and disease-free survival) showed improved outcomes after neoadjuvant treatment.\textsuperscript{17} For locally advanced PDAC, increased survival after FOLFIRINOX has been described in non-comparative studies.\textsuperscript{18,19} Several local ablative treatments for locally advanced disease are being studied in randomized controlled trials.\textsuperscript{20} In the setting of metastatic disease, gemcitabine/nab-paclitaxel and FOLFIRINOX have shown to be the most effective therapeutic regimens.\textsuperscript{21,22}

The group of periampullary cancers (tumors around the ampulla of Vater) are anatomically and biologically closely related to PDAC, and include distal cholangiocarcinoma, ampullary cancer, and duodenal cancer. Of these tumors, distal cholangiocarcinomas have the poorest prognosis with a median survival of 11.5 months compared to 26.3 months for ampullary cancer and 13.3 months for duodenal cancer (all stages).\textsuperscript{23} Treatment of patients with potentially resectable disease currently consists of upfront surgery. The multicenter randomized BILCAP trial studied whether resection of biliary tract cancer should be followed by adjuvant capecitabine, and reported a median overall survival of 53 months in the capecitabine group and 36 months in the observation group (adjusted HR 0.75, 95\% C.I. 0.58-0.97; \(P=0.028\); per-protocol analysis).\textsuperscript{24} In the unresectable setting, palliative chemotherapy using gemcitabine-cisplatin is the standard of treatment with a median survival of 11.7 months.\textsuperscript{25}

**THE DUTCH PANCREATIC CANCER PROJECT**


To improve outcomes of patients with pancreatic and periampullary tumors in the Netherlands, the nationwide, multidisciplinary Dutch Pancreatic Cancer Group (DPCG) was founded. In this group medical specialists from all disciplines involved in pancreatic or periampullary cancer
care, researchers, and patients’ representatives work together. One of the flagship projects of the DPCG is the Dutch Pancreatic Cancer Project (PACAP).

PACAP is one of the three comprehensive nationwide cohorts of pancreatic, esophageal/gastric, and colorectal cancer patients in the Netherlands; PACAP, the Prospective Observational Cohort study of Oesophageal-gastric cancer Patients (POCOP), and the Prospective Dutch ColoRectal Cancer cohort (PLCRC). Collaborating as the 3P initiative, these three cohorts collect clinical data, tumor tissue, blood samples, and patient reported outcomes of gastrointestinal cancer patients with a nationwide coverage. The goal is to facilitate research by (inter)national research groups to improve the survival rates and quality of life of patients with one of these three types of cancer.

In the 3P initiative, clinical data are obtained from the Netherlands Cancer Registry, hosted by the Netherlands Comprehensive Cancer Organization. The Netherlands Cancer Registry contains clinical data from all relevant medical charts registered by trained data managers for every patient diagnosed with cancer in the Netherlands. In 2015, the item set of the Netherlands Cancer Registry was renewed and expanded to meet the requirements of the gastrointestinal cancer cohorts and to facilitate research. Items focus on patient, tumor and treatment characteristics, adverse events, and survival. For every new cancer patient, 200–400 clinical data items are stored in a secured online database. Besides the Netherlands Cancer Registry, data are also collected through surgical audits (e.g. the Dutch Pancreatic Cancer Audit (DPCA) for pancreatic resections) in which oncologic surgeons collect data for auditing purposes, supervised by the Dutch Institute for Clinical Auditing (DICA). Participation in these audits is mandatory for each hospital. For POCOP and PACAP, tissue and blood sampling is organized in close collaboration with the Parelsnoer Institute, a national initiative facilitating biobanking for 17 different diseases, including esophageal/gastric and pancreatic cancer. Fresh frozen tumor and normal tissue samples are taken from the surgical resection specimen of the primary tumor. Blood samples are withdrawn before and after surgery. As of February 2020, 2000 patients have been included in the PACAP cohort, over 1350 patients have signed informed consent for the patient reported outcomes and around 1700 patients have been included in the biobank.

TOOLS FOR A TAILORED APPROACH
Despite all efforts, median survival for PDAC (all stages) has only marginally improved from 3.1 to 3.8 months over the last two decades in the Netherlands. In other types of cancer, much more improvements have been made due to the introduction of personalized medicine, meaning that care is customized based on the individual patient and tumor characteristics. Well-known examples include the use of trastuzumab in breast cancers with HER-2 overexpression, and the use of EGFR tyrosine kinase inhibitors in non-small-cell lung cancer patients with EGFR mutations.
In PDAC, substantial progress in the molecular characterization has been made over the last 10 years. This is largely due to the wider availability and decreased costs of next generation sequencing techniques, leading to several whole exome and whole genome sequencing studies with large numbers of patients.\textsuperscript{29-31} Although many of the revealed pathways were not targetable, it provided the groundwork for further classification studies. Collisson et al., Moffitt et al., and Bailey et al.\textsuperscript{32-34} classified biological subgroups based on gene expression. Strong overlap between their classifications was found.\textsuperscript{35} All seemed to identify a quasimesenchymal/squamous/basal-like subtype, which has the poorest prognosis, but may also show better response to chemotherapy.\textsuperscript{32-34,36} Very recently, the DPCG also presented an unsupervised classification based on RNA-sequencing. The classification revealed four subtypes, with, again, a subgroup with the poorest prognosis characterized by mesenchymal gene signatures.\textsuperscript{37} Translation of these and other biological classifications into clinical practice seems the way forward, but has shown to be challenging. The most well-known efforts to introduce multiple tailored treatment options into clinical practice are the IMPaCT and COMPASS trial.\textsuperscript{38,39} In the IMPaCT trial, targeted sequencing (\textit{BRCA1}, \textit{BRCA2}, \textit{PALB2}, \textit{ATM}, and \textit{KRAS} genes) and \textit{HER2} amplification assessment were performed, and patients were randomized to gemcitabine monotherapy or a tailored strategy. Of the 93 eligible patients, there were problems in the availability of tumor tissue for adequate molecular testing in 17 patients (unable to access the tissue or material was unsuitable for testing). After testing, in 22 patients an IMPaCT study-eligible genetic target was found. However, no patient was successfully treated in this trial, mainly due to the rapid disease progression during the time needed to return results (median 21.5 days).\textsuperscript{39} In the COMPASS trial, whole-genome sequencing and RNA sequencing was performed on tumor tissue of 63 patients. Twenty potentially actionable mutations were identified in 18 patients (\textit{ARID1A}, \textit{BRAF}, \textit{CDK4/6}, \textit{PIK3CA}, \textit{PTEN}, \textit{RNF43}). Eventually, in 5 patients, the second-line therapy was based on the COMPASS results.\textsuperscript{38}

\section*{OUTLINE OF THIS THESIS}

Following the results of the IMPaCT and COMPASS trial,\textsuperscript{38,39} it can be concluded that incorporating personalized medicine strategies in clinical practice is difficult, not only due to limited biological targets, but also because of practical issues such as obtaining sufficient tumor tissue for analysis and suboptimal logistic pipelines. Because of the retroperitoneal location of the pancreas, obtaining tumor tissue requires the invasive, and sometimes technically challenging, procedure of an endoscopic ultrasound-guided fine needle aspiration which has a complication risk of 1-2\%.\textsuperscript{40} Also the low cellularity of PDAC makes it more difficult to obtain representative tumor material and perform molecular analyses.\textsuperscript{30,41} As PDAC has such poor prognosis, timely return of results is even more essential than in other types of cancer. Other issues may include insufficient biomaterial collections for research purposes preventing discovery of new treatment targets, and the inability to integrate all available information on patient and tumors characteristics in analyses; basing treatment on only one or two characteristics is less likely to lead to success than a more integrated approach.
This thesis aims to discover and evaluate potential tools to overcome the before-mentioned challenges, aiming to provide a more personalized approach for patients with pancreatic and periampullary cancer. As most of the research in this thesis is performed in the multicenter, multidisciplinary setting of the DPCG, this working group is further discussed in the remainder of Part I (Chapter 2). In Part II currently available prognostic factors are evaluated, including clinicopathological factors and prediction models. In Part III novel tools are described, including a biobank and biomarker analyses.

**Part II: Current prognostic factors**

Median overall survival of patients with resected PDAC is around 17 months but varies widely. Several prognostic factors for survival have been identified thus far, including tumor size, lymph node status, differentiation grade, and resection margins. Also, a variety of prediction models for survival after resection have been developed, but their use in clinical practice is very limited. Chapter 3 is a systematic review summarizing the currently available prediction models for survival after resection of PDAC. We aimed to identify the most promising models for use in future clinical practice. Subsequently, one of the most promising models (the Amsterdam model) has been validated in a large international cohort (Chapter 4).

However, in distal cholangiocarcinoma less data are available about survival and prognostic factors for both resectable and unresectable carcinomas when compared to PDAC. Because of its low incidence and the difficult diagnosis in the non-resectable setting, available data are mainly derived from patients with resectable disease, who underwent surgery in high-volume expert centers. The first steps towards more tailored treatment for this type of cancer is a better understanding of outcomes and prognostic factors. Therefore, in Chapter 5, we present a nationwide study on the current outcomes of resected and unresected distal cholangiocarcinoma and the prognostic factors for survival. Data were derived from the Netherlands Cancer Registry (part of the PACAP project). In Chapter 6 we studied whether the characteristics and outcomes of distal cholangiocarcinoma differ from other anatomical subtypes of biliary tract cancer (i.e. perihilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancer). This is a preparation for future studies on prognosis, prediction models, and tailored therapy in distal cholangiocarcinoma.

**Part III: Beyond current practice**

The first step towards high-quality biomarker research are large well-organized collections of biomaterials. This includes well-annotated samples, broad informed consent, and uniformly collected materials. Chapter 7 describes a national biobank initiative on pancreatic- and periampullary tumors, and chronic pancreatitis; the Dutch Pancreas Biobank (PancreasParel). In this biobank several biomaterials including serum, plasma, DNA, and fresh frozen tissue are collected for future research.
Subsequently, samples derived from the Dutch Pancreas Biobank were used to evaluate the novel stromal biomarker A Disintegrin And Metalloprotease 12 (ADAM12). Previous exploratory research has shown that ADAM12 is upregulated specifically in the tumor stroma and that ADAM12 associates with prognosis and treatment outcomes in gastrointestinal cancers.44,45 We assessed the prognostic value of serum ADAM12 as a preoperative marker for survival in PDAC and periampullary cancers, and explored its predictive value for benefit of adjuvant chemotherapy (Chapter 8).

In Chapter 9 we assessed whether non-invasive, inexpensive and easily available biomarkers (e.g. albumin, CRP, LDH) can help to predict prognosis. Data for this study were derived from the Netherlands Cancer Registry, providing a population-based view.

Lastly, we studied circulating tumor DNA (ctDNA) as a novel tool for personalized medicine. Tumor cells may release fragments of cell-free DNA into the blood stream, referred to as ctDNA.46,47 ctDNA can be detected and sequenced, providing a non-invasive method to obtain information about the tumor characteristics. To study the potential role of ctDNA in PDAC, a systematic review of the literature was performed (Chapter 10). Based on the knowledge gaps identified in this review, the study presented in Chapter 11 was designed. In this study we assessed the detectability of ctDNA using two different techniques (next generation sequencing and digital droplet PCR). Additionally, ctDNA levels were correlated to the total tumor volume as measured in 3D reconstructions from routine imaging.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Research questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>How to establish and coordinate a nationwide multidisciplinary working group such as the DPCG?</td>
</tr>
<tr>
<td>3</td>
<td>Which prediction models for survival in patients with resectable pancreatic cancer are currently available in literature, and which models are the most promising for eventual use in clinical practice or clinical trials?</td>
</tr>
<tr>
<td>4</td>
<td>How is the performance of the Amsterdam model for prediction of survival after pancreateoduodenectomy when externally validated and updated in a large international cohort?</td>
</tr>
<tr>
<td>5</td>
<td>What are (trends in) incidence, treatment and outcomes, and independent prognostic factors for survival in patients with distal cholangiocarcinoma in a nationwide registry?</td>
</tr>
<tr>
<td>6</td>
<td>What are the differences in clinicopathological characteristics, short-term and long-term outcomes between the four anatomical subtypes of biliary tract cancer in a Western high-volume center?</td>
</tr>
<tr>
<td>7</td>
<td>What is the Dutch Pancreas Biobank and why was it established?</td>
</tr>
<tr>
<td>8</td>
<td>What are the prognostic and predictive value of serum ADAM12 in resected pancreatic and periampullary cancer in a cohort from the Dutch Pancreas Biobank?</td>
</tr>
<tr>
<td>9</td>
<td>Do readily available biomarkers predict 90-day mortality in a nationwide cohort of patients with metastatic pancreatic cancer, and do they have predictive value for benefit of palliative chemotherapy?</td>
</tr>
<tr>
<td>10</td>
<td>What is the current knowledge on ctDNA as a biomarker for clinical application in esophageal, gastric, and pancreatic cancer?</td>
</tr>
<tr>
<td>11</td>
<td>What is a) the capability of targeted sequencing using a custom-made pancreatobiliary specific next generation sequencing panel to detect ctDNA and are results comparable to droplet digital PCR validation; b) the relationship between tumor volume and ctDNA quantity; c) the independent prognostic value of ctDNA detection and tumors volumes for overall survival in metastatic PDAC?</td>
</tr>
</tbody>
</table>
REFERENCES


