The Dutch Pancreatic Cancer Project
Tools for a tailored approach to pancreatic and periampullary cancer treatment
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CHAPTER 12.

Summary
PART I: INTRODUCTION
In Chapter 1, we introduced the design of the Dutch Pancreatic Cancer Project (PACAP), a nationwide project in which clinical data, biomaterials, and patient reported outcomes measurements are prospectively collected for all patients with pancreatic and periampullary tumors. Clinical data are collected in the Netherlands Cancer Registry (NCR) and Dutch Pancreatic Cancer Audit (DPCA). Biomaterials are collected in the Dutch Pancreas Biobank (see Chapter 7). Requests for use of PACAP data are discussed in the multidisciplinary scientific committee of the Dutch Pancreatic Cancer Group which also includes patient involvement (DPCG; see Chapter 2).

The establishment and coordination of a nationwide, multidisciplinary study group was described in Chapter 2, using the lessons learned from the DPCG as an example. The DPCG is a nationwide collaboration of clinicians from all medical specialties, researchers, nurses, and patient associations involved in care for/research on patients with pancreatic and periampullary tumors. The DPCG initiated several multicenter randomized trials and prospective cohorts (including PACAP), organizes education, and serves as a point of contact for those interested in organizing pancreatic cancer-related activities in (collaboration with) the Netherlands. When establishing such a multidisciplinary study group, the first step is a group of experts who are willing to collaborate within a culture of commitment and mutual trust. Other important issues are transparency in workflows and regulations (e.g. authorships, use of data), and the involvement of all specialties, researchers of all interested centers, and patient advocates in an early stage of protocol development.

PART II: CURRENT PROGNOSTIC FACTORS
Pancreatic cancer
Prediction models enable clinicians and patients to calculate the risks of a specific endpoint individualized to a patient, using combinations of predictors. The systematic review on prediction models for survival after pancreatic resection for pancreatic ductal adenocarcinoma (PDAC) identified 21 models (Chapter 3). Most models were of low methodological quality and few have been externally validated. Two models were identified as the most promising, based on methodological quality, easy availability and validation; the model from the Memorial Sloan-Kettering Cancer Center (MSKCC) and the Amsterdam model. The MSKCC model (overall C-statistic 0.63; 95%CI 0.60-0.65) has been successfully externally validated several times, but includes 14 variables impeding its clinical applicability. The Amsterdam model (C-statistic 0.66; 95%CI 0.62-0.70) had the advantage of requiring only four easily available parameters (tumor grade, lymph node ratio, margin status, and adjuvant chemotherapy), but was not validated at that time.

Therefore, in Chapter 4, the Amsterdam model for prediction of overall survival (OS) after pancreatoduodenectomy for PDAC was validated and updated. A large international cohort
of 3081 patients with resected PDAC from 11 centers in eight countries across four continents was used. The study showed that the predicted and observed three-years OS were similar (calibration). After updating the model, the C-statistic (discrimination) was 0.65 (95% CI 0.64-0.65), which was 0.62 to 0.67 across the different countries. Median OS was 36, 25, and 15 months for the low, intermediate, and high-risk groups, respectively ($P<0.001$). The nomogram and web-based calculator (www.pancreascalculator.com) were updated; these tools facilitate easy use in clinical practice and future studies.

**Distal cholangiocarcinoma**

The first step towards a more tailored approach for DCC is improved knowledge about outcomes and prognostic factors. In Chapter 5 we studied a nationwide cohort of 1338 patients with resected and unresected DCC derived from the NCR. We found that median OS was 10.4 months across all stages; 21.9 months for resected, 6.7 months for unresected non-metastatic, and 3.6 months for metastatic DCC ($P<0.001$). Patients with metastatic DCC who received palliative chemotherapy had a median OS of 8.2 months versus 2.8 months for those not treated ($P<0.001$). Over time (2013-2016 versus 2009-2012), resection rates and use of palliative chemotherapy in metastatic DCC increased, without improvement in OS. Independent prognostic factors for poor OS in resected disease were increasing age, pT3/T4 stage, higher lymph node ratio, poor differentiation, and R1 resection.

In studies on biliary tract carcinomas, characteristics and outcomes for the four anatomical subtypes (intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, DCC and gallbladder carcinoma) are often combined. In order to design and interpret future studies, more knowledge about the differences in clinicopathological characteristics and outcomes between biliary tract carcinoma subtypes is needed. In Chapter 6 we evaluated 361 patients with resected biliary tract carcinoma. Complications (Clavien-Dindo grade III or higher) and 90-day mortality were higher in intrahepatic and perihilar cholangiocarcinoma than in DCC and gallbladder carcinoma. Differences in tumor stage, perineural growth, angioinvasion, differentiation grade and residual disease status between the subtypes were identified. Median OS did not differ between the subgroups, and anatomical subtype was not an independent predictor for OS.

**PART III: BEYOND CURRENT PRACTICE**

For the development of novel tools for personalized therapy, such as biomarkers and genomic signatures, the availability of large collections of uniformly collected, high-quality biomaterials with associated clinical data is essential. Chapter 7 describes the design of the Dutch Pancreas Biobank (In Dutch: PancreasParel). This biobank is part of the Parelsnoer Institute and involves all eight Dutch university medical centers and five non-academic hospitals. All adult patients undergoing pancreatic surgery (all indications) are eligible for inclusion. Preoperative blood samples, DNA, tumor and normal tissue from resected specimens, pancreatic cyst
fluid, follow-up blood samples, and clinical data (in conjunction with the DPCA) are collected. Subsequent translational research will aim to improve treatment decisions based on disease characteristics.

In Chapter 8, the first use of the samples from the Dutch Pancreas Biobank is described. This research studied the value of the novel serum activated stroma marker A Disintegrin And Metalloprotease 12 (ADAM12) in pancreatic and periampullary tumors. It was shown that median ADAM12 levels were higher in adenocarcinomas than in a control group of intraductal papillary mucinous neoplasms. In univariable analysis, ADAM12 levels predicted poor OS in the total group of adenocarcinomas but not after adjustment for other preoperative factors. In the subgroup of DCC, high ADAM12 predicted poor prognosis, while it did not in the subgroup of PDAC. However, PDAC patients with high levels of ADAM12 seemed to have more benefit from adjuvant treatment than those with low levels. However, these findings need further validation. The results suggest that the interaction of stroma with tumor cells and cytotoxic agents is complex and needs further study.

Identification of metastatic PDAC patients with worst prognosis could help tailor therapy. In Chapter 9 we evaluated whether readily available biomarkers (CA 19-9, LDH, CRP, albumin, and three existing CRP-albumin combination scores) predict 90-day mortality in metastatic PDAC. Using data from 4248 patients derived from the NCR, we found that all before-mentioned biomarkers predicted 90-day mortality in univariable analysis, after adjustment for age, WHO performance status, cardiovascular disease, primary tumor location, lymph node status, and location/number of metastatic sites, and after additional adjustment for all biomarkers (all $P<0.001$). In patients receiving palliative chemotherapy, all biomarkers except for albumin, were predictors for OS after adjustment for clinical factors and other biomarkers. The prognostic value of the four biomarkers combined was at least similar to that of WHO performance status. The biomarkers did not predict benefit from palliative chemotherapy. We concluded that these readily available and non-expensive biomarkers should be incorporated in future prognostic studies, can be used to better inform patients and to stratify in clinical trials.

Circulating tumor DNA (ctDNA) is currently gaining much attention as a potential novel tool to personalize therapy. In the systematic review described in Chapter 10, the current literature on the clinical value of ctDNA in esophageal, gastric, and pancreatic cancer was summarized. For pancreatic cancer, it was found that the pooled sensitivity and specificity of ctDNA as a diagnostic tool were 28% and 95%, respectively. Patients with pancreatic cancer and detectable ctDNA demonstrated worse OS compared to patients with undetectable ctDNA. It was concluded that the use of ctDNA in clinical practice is promising, although standardization of sequencing techniques and further development of high-sensitive detection methods is needed.
Following the results of Chapter 10, we designed the study on ctDNA described in **Chapter 11**. We used samples of 58 treatment-naive metastatic PDAC patients. Pathogenic mutations were detected in 26/58 (45%) samples using a custom-made pancreatobiliary next generation sequencing panel. Cross-check with droplet digital PCR showed good agreement. In patients with liver metastases, ctDNA was detected more frequently. Moreover, tumor volume and ctDNA levels were correlated. As expected, median OS was worse in patients with detectable versus undetectable ctDNA (3.2 versus 8.4 months, \( P = 0.005 \)). Both ctDNA levels and tumor volume independently predicted OS after adjustment for CA19-9 levels and treatment regimen. Analyzing a limited amount of follow-up samples, we found that tumor burden, CA19-9, and ctDNA levels often, but not always, show similar trends over time. We concluded that ctDNA and tumor burden are related, but measurements may also diverge and, thus, can provide complementary information.
Chapter 12

SUMMARY OF RESEARCH QUESTIONS AND MAIN FINDINGS

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<th>Chapter</th>
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| 2       | How to establish and coordinate a nationwide multidisciplinary working group such as the DPCG?  
The first step is to identify a group of experts who are willing to collaborate within a culture of commitment and mutual trust. Other important issues are transparency in workflows and regulations (e.g. authorships, use of data), and involvement of all parties in an early stage of research protocol development. |
| 3       | 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?  
Twenty-two models are available, but most were of low methodological quality and have not been externally validated. The MSKCC model and Amsterdam model were the most promising based on methodical quality, validation, and the availability of clinically usable tools. |
| 4       | How is the performance of the Amsterdam model for prediction of survival after pancreatoduodenectomy when externally validated and updated in a large international cohort?  
The predicted and observed three-year overall survival (OS) were similar (calibration). After updating the model, the C-statistic (discrimination) was 0.65, which varied from 0.62 to 0.67 across the different countries. |
| 5       | What are (trends in) incidence, treatment and outcomes, and independent prognostic factors for survival in patients with DCC in a nationwide registry?  
Median OS for DCC was 10.4 months across all stages. Over time, resection rates and use of palliative chemotherapy in metastatic DCC increased, without improvement in OS. Independent poor prognostic factors for OS in resected disease were increasing age, pT3/T4 stage, higher lymph node ratio, poor differentiation, and R1 resection. |
| 6       | What are the differences in clinicopathological characteristics, short-term and long-term outcomes after resection between the four anatomical subtypes of biliary tract cancer in a Western high-volume center?  
Clavien-Dindo grade III or higher complications and 90-day mortality were higher in intrahepatic and perihilar cholangiocarcinoma than in DCC and gallbladder cancer. Differences in several pathological outcomes between the subtypes existed, but median OS did not statistically differ between the subgroups. |
| 7       | What is the Dutch Pancreas Biobank and why was it established?  
This nationwide biobank is part of the Parelsnoer Institute. All adult patients undergoing pancreatic surgery (all indications) are eligible for inclusion. The most important collected materials are pre- and postoperative blood samples, tumor tissue, and clinical data. Samples will be used for translational research on tailored therapy. |
What are the prognostic and predictive value of serum ADAM12 in resected pancreatic and periampullary cancer in a cohort from the Dutch Pancreas Biobank?

ADAM12 was an independent predictor for OS in the total group of pancreatic and periampullary adenocarcinomas. ADAM12 was not a predictor in PDAC only, but it was in DCC. Patients with high ADAM12 seemed to have more benefit from adjuvant chemotherapy than patients with low ADAM12, but these findings require validation.

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?

Readily available biomarkers (CA19-9, CRP, albumin, LDH) and albumin-CRP combination scores were strong predictors of 90-day mortality, also after adjustment for clinical factors and the other biomarkers. These biomarkers did not predict benefit from palliative chemotherapy.

What is the current knowledge on ctDNA as a biomarker for clinical application in esophageal, gastric, and pancreatic cancer?

For pancreatic cancer, pooled sensitivity and specificity of ctDNA were 28% and 95%, respectively. Detectable ctDNA was associated with worse OS. Use of ctDNA in clinical practice is promising, but standardization and further development of sequencing techniques is needed.

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 3D-measured tumor volume and ctDNA quantity; c) the independent prognostic value of ctDNA detection and tumors volumes on overall survival in metastatic PDAC?

a) Pathogenic mutations were detected in 45% of samples of metastatic PDAC patients using next generation sequencing. Cross-check with droplet digital PCR showed good agreement. b) Tumor volume and ctDNA levels were correlated. c) Both ctDNA levels and tumor volume independently predicted OS after adjustment for CA19-9 levels and treatment regimen.