Improvement of diagnosis and treatment of pancreatic diseases
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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS
Over the past decades, our knowledge of the pancreas and pancreatic diseases increased enormously and we made remarkable progress in (minimally-invasive) endoscopic and surgical treatment options. However, several challenges remain and our current diagnostic and treatment strategies have room for improvement. In this thesis we investigated some of these unresolved issues in diagnosis and treatment of pancreatic diseases. In each part of the thesis studies are presented that aimed to improve diagnosis and treatment of pancreatitis, pancreatic cysts and pancreatic cancer.

PART I – PANCREATITIS

Chronic pancreatitis (CP) is an inflammatory disease characterized by progressive fibrosis of the pancreatic parenchyma, which can eventually lead to exocrine and endocrine insufficiency. There are several causes and risk factors associated with the development of CP, summarized as the TIGAR-O classification system; Toxic/metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, Obstructive. The most prominent symptom of CP is usually intermittent or constant abdominal pain. Other symptoms are, for example, steatorrhea or gastric outlet obstruction caused by a pancreatic fluid collection (PFC). CP is usually diagnosed based on a combination of clinical (e.g. typical abdominal pain), biochemical (e.g. exocrine pancreatic insufficiency (EPI)) and imaging features (e.g. calcifications and concrements in the pancreatic duct).

EPI develops in 40-50% of CP patients and can cause steatorrhea, malabsorption, malnutrition and weight loss. The secretin-cholecystokinin (secretin-CCK) test, a direct pancreatic function test, is considered the gold standard to diagnose EPI. However, this test is invasive, time-consuming and expensive, and is therefore not considered suitable for daily clinical practice. Because of these disadvantages, the fecal Pancreatic Elastase (PE)-1 ELISA test is often used, in which only a portion of stool has to be collected without a prior diet. However, it takes about 4 weeks to receive results of the PE-1 ELISA test. Recently the Quick test became available; a rapid fecal PE-1 test. In chapter 2 we compared the diagnostic accuracy of the Quick test with the fecal PE-1 ELISA test for diagnosing EPI.

Since EPI can result in reduced absorption of fat-soluble vitamins, CP patients might be at risk for vitamin D deficiency. Known consequences of long-term vitamin D deficiency are, amongst others, osteoporosis and increased risk of bone fractures. Although there are no clear data available, it has been recommended to regularly determine vitamin D levels in CP patients. In chapter 3 we performed a systematic review and meta-analysis to determine the prevalence of vitamin D deficiency in patients with CP, to evaluate the clinical necessity of this recommendation.

A rare form of chronic pancreatitis is groove pancreatitis (GP), which is characterized by focal inflammation in the paraduodenal groove area, located in the C-loop of the duodenum.
between the duodenal wall and the pancreatic tissue. Data on GP is scarce, therefore we provided an overview of all relevant studies reporting on GP in chapter 4, with a pooled analysis of clinical and imaging features. If the diagnosis GP is clear, patients can be treated conservatively (e.g. analgesia and abstinence from alcohol), endoscopically (e.g. biliary or PFC drainage) or surgically (most often with pancreatoduodenectomy). We performed a pooled analysis of clinical outcome after treatment of GP. Unfortunately, most studies also included GP patients with more extensive CP without reporting on patient outcome separately.

Therefore in chapter 5 we evaluated clinical outcomes after conservative, endoscopic or surgical treatment of 28 patients who presented with GP without more extensive CP. Because GP is a focal disease, differentiation between GP and pancreatic cancer can be challenging. Therefore we also determined the prevalence of cancer in patients presenting with possible GP and evaluated the factors that could help to differentiate between GP and cancer.

PART II – PANCREATIC CYSTS

Because of increasing use of cross-sectional imaging pancreatic cysts are being identified more frequently, with higher prevalence with increasing age. Many pancreatic cysts have (virtually) no risk of malignant progression, for example serous cystic neoplasms (SCN) or PFC. However, a subset of neoplastic pancreatic cysts are considered to be premalignant, such as mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). It is therefore essential to differentiate between the different types of pancreatic cysts and to assess the risk of malignant progression for each individual with a pancreatic cyst.

Depending on the risk of malignancy, presence of symptoms and patient’s condition, treatment options are discharge, surveillance or surgery. The primary goal is preventing malignancy and/or treatment of symptoms. The current guidelines on pancreatic cysts are those of the International Association of Pancreatology (IAP), the European Study Group on Cystic tumours of the Pancreas and the American Gastroenterological Association (AGA). The majority of patients present with an asymptomatic pancreatic cyst and will never show signs of malignant progression. If a premalignant cyst is diagnosed, surveillance is generally suggested in a surgically fit patient. In chapter 6 we report the findings of a study on changes during follow-up of pancreatic cysts. We evaluate resection rate and the risk of pancreatic malignancy during surveillance of patients with initially non-suspicious cysts.

As stated, surgery is indicated when there is suspicion of malignant progression. Although all the three available guidelines are based on the same literature, recommendations on when cysts should be resected vary. Surgery is considered warranted for cysts
with malignancy or high-grade dysplasia, and for neuroendocrine tumors and solid pseudopapillary neoplasms. However, we retrospectively consider surgery overtreatment in patients with cysts without malignant potential (e.g. SCN or PFC) or premalignant cysts with maximally borderline dysplasia. It is unknown how accurate the current guidelines are in identifying cyst that require surgery. Therefore, we evaluated outcomes of surgery when the IAP, European or AGA guideline would have been followed strictly. Results are shown in chapter 7.

PART III – PANCREATIC CANCER

Pancreatic cancer accounts for 2.1-2.2% of all cancers in the Netherlands. Although it is not the most common type of cancer, it is one of the most deadliest. Despite of the progress that has been made in our understanding of the biology of pancreatic cancer, over the past 25 years the 5-year survival increased only slightly; from 4 to 8%. Most pancreatic cancers are discovered once distant metastasis are already present and at that point 5-year survival is only 2%. The only curative treatment option is surgery, but no more than 10-20% of patients are eligible at diagnosis. Furthermore, many patients are found to have microscopically incomplete (R1) resections, leading to decreased survival compared to a microscopically complete (R0) resection.

Although there are no randomized controlled trials available yet, neo-adjuvant radiochemotherapy (RChT) seems promising in increasing the number of R0 resections and thereby improving survival. However, radiotherapy for pancreatic cancer is challenging because of variation of the location of the pancreas, within and between radiation fractions, and because delineation of a pancreatic tumor on cone beam CT is inaccurate. To overcome these challenges, image-guided radiation therapy (IGRT) is used for which radiographically visible tumor markers (fiducials) are placed in the tumor for localization. These fiducials can be placed during EUS. In chapter 8 we describe our findings on the safety and feasibility of EUS-guided fiducial placement using a 22-gauge needle.
REFERENCES


20. Netherlands Cancer Registry.


