Chronic pancreatitis
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SUMMARY

In this chapter, the content and conclusions from chapter 1 to 9 are summarized. The first part of the thesis explored the diagnostics in chronic pancreatitis (CP), with the focus on imaging modalities and diagnostic tools. The second part of this thesis focused on the natural course of CP and the third part evaluated the treatment of patients with CP.

PART I – DIAGNOSTICS IN CHRONIC PANCREATITIS

Imaging of pancreatic morphology is a crucial part of the diagnostic and therapeutic evaluation of patients with CP. In Chapter 2, the result of a systematic review and meta-analysis on imaging modalities in patient in CP are described. Included were 43 studies evaluating 3460 patients. Endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US) all showed comparable high diagnostic accuracy in the initial diagnosis of CP. EUS and ERCP were outperformers and US had the lowest accuracy. As diagnostic sensitivity of CT and MRCP was not significantly lower than that of ERCP and EUS, and specificity was comparable, non-invasive modalities except for US are a likely first choice in patients suspected of pancreatic disease including CP. The choice of imaging modality can therefore be made based on invasiveness, local availability, experience and costs.

In Chapter 3, CT and MRI features of CP were compared head-to-head. We identified all consecutive patients with CP from two Dutch academic medical centers (Academic Medical Center Amsterdam and University Medical Center Maastricht) using the CARE (CP Registry) database from 2010 to 2014, and patient administration systems, from 2004 to 2014. Seventy-five patients were included. CT was best for assessment of acute episodes of CP, evaluation of parenchymal calcifications and intraductal stones. Conversely, MRI was best for diagnosis of CP for equivocal cases and evaluation of ductal pathology. CT and MRI are complementary imaging modalities for CP. In patients who are candidates for planning invasive treatment, using both imaging modalities side by side may be useful in clinical decision making.

In Chapter 4, we compared three of the most commonly used diagnostic tools for CP in a cross-sectional analysis of the development of CP in a prospectively collected multi-centre patient cohort including 669 patients after a first episode of acute pancreatitis. First, we were able to find the differences between tools that resulted in the largest discrepancies in the diagnosis of CP. These were mainly the inclusion criteria of clinical symptoms (i.e. abdominal pain or recurrent pancreatitis), diabetes mellitus and certain morphological complications (e.g. enlarged glands, pseudocysts, heterogeneous reflectivity). Secondly, despite differences, the agreement between the various tools was substantial. On the other hand, the agreement between diagnosis by physician and different tools was much lower. This emphasizes the importance of a methodological approach to the diagnosis of a complex disease such as CP. Finally, the Büchler tool had the highest sensitivity (94%), followed by the Mannheim (87%) and finally the Lüneburg tool (81%). The specificity ranged from 97% to 99%. This provides insights in how the different tools compare, but should be interpreted with caution due to lack of a reference test.
PART II – NATURAL COURSE OF CHRONIC PANCREATITIS

Prospective follow-up of patients with CP over time has considerable advantages. First, it allows to study various aspects of the natural course including levels and patterns of pain over time, impact of pancreatic function on pain (‘burn-out’ hypothesis) and patients’ lives. It also permits to evaluate the efficacy and timing of current treatment strategies. It also can shed more light on development and treatment of CP associated complications such as pancreatic cysts, bile duct and gastric outlet obstruction, and cancer development. The Dutch CP Registry (CARE) is a nationwide registry aimed at prospective evaluation and follow-up of patients with CP. In Chapter 5 we describe the CARE study, in which all patients with (suspected) chronic or recurrent pancreatitis are eligible for inclusion. Patients are followed-up by yearly questionnaires and review of medical records. Study outcomes are pain, disease complications, quality of life, and pancreatic function. The CARE registry has successfully recruited over 1200 patients with chronic and recurrent pancreatitis in about 3 years. A total of 1218 patients were included by 76 participating surgeons and gastroenterologist from 33 hospitals. Participation rate was 90% of eligible patients. Patient centred outcomes were assessed by yearly questionnaires, which had a response rate of 85 and 82% for year 1 and 2, respectively.

In Chapter 6, a cross-sectional analysis of patients with a first episode of acute pancreatitis shows that in 17% of the cases this leads to a recurrent pancreatitis, and almost 8% of patients progress to CP within 5 years. Progression was associated independently with alcoholic aetiology, smoking, and a history of pancreatic necrosis. Smoking is the predominant risk factor for recurrent disease, whereas the combination of alcohol abuse and smoking produces the highest cumulative risk for CP.

PART III – TREATMENT OF CHRONIC PANCREATITIS

In Chapter 7, we reviewed the outcome of thoracoscopic splanchnicectomy in patients with CP. The results support the hypothesis that preoperative opioid use reduces the success rate of thoracoscopic splanchnicectomy, as evidenced by the strong association between high rates of preoperative opioids with low rates of long-term pain relief. Results indicate that thoracoscopic splanchnicectomy should be considered before patients with CP receive opioids for their pain.

In Chapter 8, we performed a survey, which showed that worldwide there is little consensus regarding the diagnosis and treatment of CP. Clinical decision-making in CP is largely based on local expertise, beliefs and disbeliefs. Further development of evidence-based guidelines based on well-designed (randomized) studies is strongly encouraged. This lack of consensus was visible in different clinical cases, such as in patients with a dilated main pancreatic duct and intraductal stones, about half of the responders choose endoscopic treatment in combination with extracorporeal shock wave lithotripsy (ESWL), 30% preferred initial surgical treatment, and 20% would prefer stronger opioid therapy. Or in patients with an enlarged pancreatic head, were about half of the pancreatologists would perform upfront surgery (pancreatoduodenectomy) and the other half would prefer upfront endoscopic treatment. This survey also showed, that about half of the specialists use a classification tool for the diagnosis of CP. Overall, CT is the preferred imaging modality for evaluation of an enlarged pancreatic head, pseudocyst, calcifications, and peripancreatic fat infiltration. MRI was preferred for assessment of main pancreatic duct abnormalities. About half of the gastroenterologists use ESWL in the treatment of CP. Total pancreatectomy with islet auto-transplantation was the preferred treatment in patients with parenchymal calcifications without MPD abnormalities and in patients with refractory pain despite maximal endoscopic and surgical treatment.
In Chapter 9, the ESCAPE trial is described. A randomized controlled, parallel, superiority multicenter trial. Patients with CP, a dilated pancreatic duct (≥ 5mm) and moderate pain and/or frequent flare-ups are registered and followed monthly as potential candidates for the trial. When a registered patient meets the randomization criteria (i.e. need for opioid analgesics) the patient is randomized to either early surgical intervention (group A) or optimal current step-up practice (group B). An expert panel of CP specialists oversees the assessment of eligibility and ensure that allocation to either treatment arm is possible. Patients in group A undergo pancreaticojejunostomy or a Frey-procedure in case of an enlarged pancreatic head (≥ 4cm). Patients in group B undergo a step-up practice of optimal medical treatment, if needed followed by endoscopic interventions, and if needed followed by surgery, according to predefined criteria. Primary outcome is pain assessed with the Izbicki pain score during a follow-up of 18 months. The ESCAPE trial investigates whether early surgery in CP is beneficial in terms of pain relief, pancreatic function and quality of life, compared with current step-up practice.