Improvement of diagnosis and treatment of pancreatic diseases

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Citation for published version (APA):

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CHAPTER 9
SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES
This thesis contains studies that provide new insights in diagnosing and treating pancreatitis, pancreatic cysts and pancreatic cancer.

PART I – PANCREATITIS

In chapter 2 we used the STARD statement\(^1,2\) to prospectively evaluated a new, rapid fecal pancreatic elastase-1 (PE-1) test, the Quick™ test (ScheBo Biotech AG, Giessen, Germany) to diagnose exocrine pancreatic insufficiency (EPI) in patients with (suspected) pancreatic disease or pancreatic surgery. We assessed the diagnostic accuracy of the Quick test by comparing the Quick test outcome with the fecal PE-1 enzyme-linked immunosorbent assay (ELISA) test, which is most often used in clinical practice. Furthermore, we evaluated the interobserver variability of scoring the Quick test outcome by three observers. Quick test and PE-1 ELISA were compared in 101 patients of whom 70\% had EPI according to the reference standard. The agreement between the Quick test and PE-1 ELISA was only fair (kappa 0.27, p<0.01). If we would consider the PE-1 ELISA test as the golden standard for diagnosing EPI, the Quick test would have an accuracy of 0.60, sensitivity of 0.50, specificity of 0.84, positive predictive value of 0.88 and negative predictive value of 0.43. In 21/101 (21\%) patients Quick test outcome was not scored unanimously and interobserver agreement was substantial (kappa 0.70, p<0.01).

Discussion and future perspective

Based on our findings we concluded that the Quick test is inferior to the PE-1 ELISA test for diagnosing EPI. Although the agreement between observers was substantial, all raters indicated that it was often very challenging to score the Quick test outcome because of the widely varying visibility of the test line.

Since the Quick test did not show the desired results, the need for an inexpensive and easy-to-use test to diagnose EPI still exist. Our findings clearly indicate how crucial it is to adequately evaluate new diagnostic tests, therefore we want to accentuate the importance to perform a clinical study if a new test is developed before it becomes commercially available.

In chapter 3 we aimed to determine the impact of one of the possible consequences of EPI, namely vitamin D deficiency. Therefore we provided an overview of the currently available literature on vitamin D insufficiency and deficiency in patients with CP. Our meta-analysis of 9 studies including 465 CP patients (mean age 41 years (range 18-60), 81\% male) and in 378 controls (mean age 40 years (range 18-67), 76\% male) showed a high prevalence of vitamin D insufficiency (<75 nmol/l) and deficiency (<50 nmol/l) in CP patients (83\% and 65\%, respectively). However, there was no significant difference with the healthy population.
Discussion and future perspective

Since we found a high prevalence of vitamin D insufficiency and deficiency in CP patients as well as in the healthy control group, valuing the clinical impact of these findings is difficult. Although the current recommendation is supported by our meta-analysis, we are still facing the fact that there seems to be a high number of normal people who also have a vitamin D insufficiency. That fact could be used as an argument against the measurement of vitamin D levels in CP patients.\textsuperscript{3,4}

One of the main complications of vitamin D deficiency is decreased bone mineral density (BMD), which can lead to osteoporosis and bone fractures. A recent systematic review showed a high prevalence of BMD in CP patients; 65\% of patients had osteoporosis or osteopenia.\textsuperscript{5} However, the prevalence of osteopenia and/or osteoporosis was not compared with a control group. Furthermore, a direct association between low vitamin D and reduced BMD in CP patients could not be found.\textsuperscript{8} A higher low-trauma fracture risk has been reported for CP patients (n=3,192, 4.8\% fractures) compared with the control group (n=1,436,699, 1.1\% fractures, p<0.01).\textsuperscript{7} However, the authors stratified for age and gender, but they did not adjust for other confounders such as alcohol use, smoking and medication. So, based on the current knowledge it is unclear if decreased values of vitamin D are the decisive cause for the high prevalence of osteoporosis and low trauma fractures in CP patients.

It would be particularly interesting to perform a subgroup analysis on prevalence of vitamin D deficiency in patients with more severe CP, but unfortunately only one study subdivided patients with or without EPI and/or treatment with PERT.\textsuperscript{8} Ideally a large case-control study with CP patients and matched healthy controls should be performed to determine prevalence of vitamin D deficiency, mean vitamin D levels, PTH and BMD and to evaluate the influence of EPI and PERT on these variables. Preferably with follow-up vitamin D serum levels and BMD to determine if there is an association between low vitamin D and decreased BMD in CP patients. The need to determine fat soluble vitamin serum levels and/or vitamin D supplementation in (a subset of) patients with CP should be evaluated, as well the effect of supplementation on vitamin D levels and BMD.

In chapter 4 and 5 we focused on groove pancreatitis (GP), a form of focal CP for which consensus on diagnosis and management is lacking. Therefore we systematically evaluated the published literature on patient and imaging characteristics of GP and clinical outcomes after treatment in chapter 4. Eight studies were included reporting on 335 GP patients (90\% male, 87\% smokers, 87\% alcohol consumption). Abdominal pain (91\%) and/or weight loss (78\%) were the most common symptoms reported. Imaging frequently showed cystic lesions (91\%) and duodenal stenosis (60\%), 64\% of patients had more extensive CP. Final treatment was conservative in 29\% of patients and 19\% of patients were treated endoscopically, of which 34\% were subsequently referred for surgery. Overall, 59\% of patients were operated on. Complete symptom relief was reported in
50% of patients who were treated conservatively, 57% who underwent endoscopic treatment and 79% who underwent surgery.

Since most studies from our systematic review in chapter 4 also included GP patients with more extensive CP, we performed a retrospective study on patients who presented with the suspicion of GP excluding patients with infiltration outside the groove area. This study is shown in chapter 5. Alongside our aim to evaluate outcomes after treatment of GP, we also determined the prevalence and predictors of cancer in patients in whom the diagnosis GP was considered. From the 38 possible GP patients, 10 had cancer (26%) and 28 had GP (74%). Compared with cancer patients, patients with true GP more frequently had cysts in the groove area and less often jaundice, an abrupt caliber change of the CBD or suspicious cytology. Of the 28 GP patients, 14 patients were treated conservatively of whom 12 reported symptom improvement. All 6 patients who were treated endoscopically and 7/8 patients treated surgically reported symptom improvement. Surgery was performed because of treatment failure (3/8) or inability to exclude malignancy (5/8).

Discussion and future perspective

Suspicion of pancreatic cancer should be high in patients presenting with signs and symptoms of GP. Our results suggest that there are several descriptors that can help to differentiate between GP and pancreatic cancer. GP patients are more often smokers who present without jaundice and without an abrupt change of caliber of the CBD, but with cystic lesions in the groove area. These findings are in line with most previous studies. However, one study also reported a high prevalence of cysts in cancer patients (57%). Since presence of cysts is one of the major discriminating factors in our cohort, future studies should focus on prevalence of cyst in patients with GP and cancer to evaluate the diagnostic value. Although only based on a limited number of patients (8/28 GP patients and 6/10 cancer patients), we found that carbohydrate antigen 19.9 (CA19.9) levels were significantly higher in cancer patients. The value of CA19.9 for differentiating between GP and cancer should be further assessed and, if valuable, the optimal cut-off level should be determined. Ideally a multi-center prospective study should be performed with patients presenting with possible GP to determine the optimal management to exclude cancer. According to our findings follow-up imaging in patients with suspected GP is important to increase certainty of a benign diagnosis.

Most previous research focused on the effects of surgical treatment of GP, without evaluating patients who did not undergo surgery. Our results indicate that almost half of patients with GP can be successfully treated conservatively and 21% of patients with endoscopic treatment. Only two previous studies also point out the role for conservative and endoscopic treatment in a subset of patients (28-33% of their patients underwent resection). Although surgery seems the most definitive solution, mortality and morbidity rates of pancreatoduodenectomy are considerable (2-3% and 37-40%, respectively). Therefore we feel that, if cancer is excluded, an attempt at conservative
or endoscopic treatment should be the first treatment option in GP patients. Since conservative, endoscopic and surgical treatment can all lead to symptom improvement a ‘step-up approach’ seems advisable. Future research should be carried out to evaluate clinical outcomes of this approach, although this will be difficult considering the rarity of this disease.

**PART II – PANCREATIC CYSTS**

In chapter 6 and 7 we determined the outcomes of patients with pancreatic cysts who are registered in our prospective pancreatic cyst database. First we evaluated the resection rate and rate of malignancy in 146 patients with initially non-suspicious pancreatic cysts who underwent surveillance for a median of 29 months (IQR 13.5-50 months) (chapter 6). In the majority of patients (84.9%) no changes in clinical or imaging characteristics occurred. Thirteen patients (8.9%) developed an indication for surgery after a median follow-up of 25 months (IQR 12-42 months). Two patients did not undergo surgery because of comorbidity, 11 patients (7.5%) underwent resection. Postoperative histology showed one pancreatic malignancy not originating from the cyst, six premalignant cysts, one neuroendocrine tumor (NET) and three benign cysts. The highest grade of cyst dysplasia was borderline dysplasia. So most neoplastic pancreatic cysts that are non-suspicious at initial presentation show no substantial change during 1-4 years follow-up. Only 7.5% of patients underwent surgery and less than 1% of patients developed pancreatic malignancy.

In chapter 7 we focused on the outcomes of all surgically resected pancreatic cysts. We compared the final pathological outcome of 115 surgically resected pancreatic cysts with an indication for resection according to the three different guidelines; the International Association of Pancreatologists (IAP), the European Study Group on Cystic tumours of the Pancreas and the American Gastroenterological Association (AGA). The final histopathological diagnosis was compared with the initial indication for surgery as determined by each of the three guidelines. We considered surgery in retrospect justified for malignancy, high-grade dysplasia, solid pseudopapillary neoplasms, NET or symptom improvement. Furthermore, we evaluated the patients with suspected intraductal papillary mucinous neoplasm (IPMN) separately. In retrospect, surgery was justified according to the above-mentioned criteria in 45% of patients. For patients with suspected IPMN (n=75) resection was justified in 54%, 53% and 59% of patients based on the IAP, European or AGA guideline, respectively. The AGA guideline would have avoided resection in 29% of patients, versus 11% and 9% when the IAP or European guideline would have been applied strictly. Nevertheless, 12% of patients with high-grade dysplasia or malignancy would have been missed with the AGA guideline, compared to none with the IAP or European guidelines.
Discussion and future perspective

The primary goal of the management of patients with pancreatic cysts is treatment of symptoms and preventing malignancy, while avoiding unnecessary surgery and its complications. Because of the relatively high surgical mortality and morbidity rate as previously stated, it seems inappropriate to simply resect all potentially premalignant cysts. Apart from invasive malignancy, resection of pancreatic cysts with high-grade dysplasia is generally accepted for prevention of malignant progression. Premalignant cysts without high-grade dysplasia are suitable for surveillance and resection of these cysts could be considered overtreatment. In chapter 6 we demonstrated that most initially non-suspicious neoplastic pancreatic cysts have a rather indolent behavior during follow-up. Only 7.5% of patients underwent surgery during surveillance; pancreatic malignancy developed in one patient (0.7%), distant from the presumed side branch (SB)-IPMN, and none of the resected cysts developed high-grade dysplasia or invasive malignancy. As we showed in chapter 7, surgery of pancreatic cysts is often not (yet) warranted in retrospect, whereas 55% of resected cysts had no, low-grade or borderline dysplasia. So currently the main area of concern is that we are not able to sufficiently identify when cysts warrant surgical resection.

We need to improve non-surgical differentiation between cysts with high-grade dysplasia or invasive malignancy and premalignant cysts with lower grades of dysplasia. Since such a definitive marker is not yet available, combinations of established and new clinical and molecular factors to help predict progression are being evaluated. Al Haddad et al. classified patients according to the presence or absence of clinical features (size >3 cm, growth rate >3 mm/year, duct dilation >10 mm, CEA >1000 ng/ml, atypical cells on cytology) and molecular criteria (availability of high-quality DNA, presence of KRAS and/or GNAS mutations or loss of heterozygosity (LOH) of tumor suppressor genes). They compared their new classification with the surgical criteria as stated by the IAP guideline and found a higher specificity (90.6% vs. 46.2%, p < 0.0001) and positive predictive value (57.9% vs. 20.8%, p < 0.0001) without a difference in sensitivity (83.3% vs. 90.9%) and negative predictive value (97.2% vs. 97.0%). These results are promising and should be validated in a large, prospective study.

As previously stated, we showed that surgery is not warranted at time of resection in the majority of patients. Although 12-13% fewer patients will undergo unnecessary surgery with the AGA guideline, 12% of all pancreatic cysts with high-grade dysplasia or malignancy would have been missed when the AGA guideline would have been used, compared to none with the IAP or European guidelines. These findings are in line with Singhi et al. who also evaluated the AGA guideline. They also included patients without a definitive diagnosis but with molecular analysis on cyst fluid and showed that with the AGA guideline 5/14 patients (36%) with malignancy, high-grade dysplasia or a NET would have been missed. So, although fewer patients undergo unnecessary surgery based on the AGA guideline, the risk of missing malignancy or high-grade dysplasia with this guideline seems to be significant. Further studies are needed to decrease the rate of
Summary, discussion and future perspectives

Overtreatment that appears to be inevitable when applying the current guidelines, without missing malignancies.

PART III – PANCREATIC CANCER

In chapter 8 we performed a prospective study to evaluate the safety and feasibility of EUS-guided placement of fiducials using a 22-gauge (G) needle in patients with pancreatic cancer who are eligible for radiotherapy (RT). We included 23 consecutive patients with proven pancreatic cancer who were planned to undergo RT. We aimed to insert at least two fiducials under EUS guidance, which was achieved in all patients. A total of 63 fiducials were placed and technical difficulties were encountered in 8 out of the 71 attempts to place a fiducial (11.3%). One adverse event (4.3%) occurred; a minor bleeding. Six of the 63 fiducials completely migrated (9.5%), hampering the treatment in only one patient. Fiducials were suitable for image guided RT (IGRT) in 95.2% of the patients.

Discussion and future perspective

Based on our results we can conclude that EUS-guided fiducial placement with a 22-G needle is a safe and feasible procedure in patients with pancreatic cancer, allowing IGRT in the majority of patients in whom fiducials are inserted. These findings are in line with previous studies that evaluated fiducial placement in pancreatic tumors with the more stiff 19-G needle.24

Although the technical success rate is high, several aspects may improve EUS-guided fiducial placement. For example by using the Beacon™ FNA Exchange system (Medtronic, Minneapolis, USA), in which the needle can be removed from the outer sheath. After a fiducial is inserted the needle can be exchanged for another preloaded needle, while keeping the sheath in place. In this way the position towards the tumor can be maintained. Draganov et al.25 evaluated a multi-fiducial delivery system for EUS-guided fiducial placement. In this preliminary study a porcine model was used and fiducials were inserted in the gastrointestinal tract, unfortunately not in the pancreas. The device consisted of four preloaded gold fiducials in a 22-G needle. Of course clinical studies are necessary to evaluate this multi-fiducial delivery device in humans.

More importantly, however, is to further determine the clinical impact of RT in the treatment of patients with pancreatic cancer and thereby the usefulness of placement of intratumoral fiducials. Hopefully this question can be answered by the PREOPANC study (Nederlands Trial Register 3709, EudraCT nummer: 2012 003181-40), a phase III trial that aims to test the hypothesis that median overall survival of patients with (borderline) resectable pancreatic cancer can be improved with preoperative radiochemotherapy.26
REFERENCES


