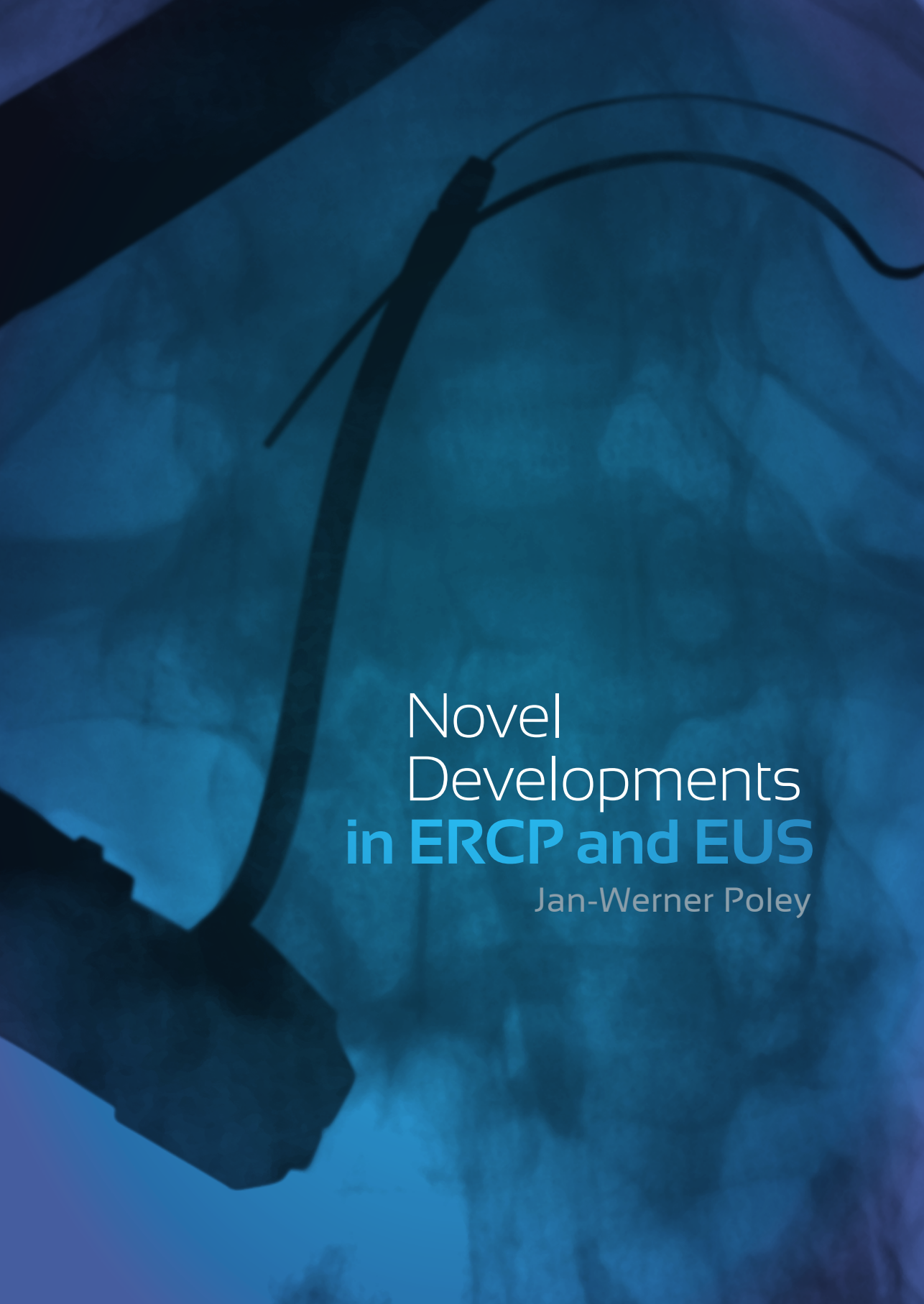

Novel Developments in ERCP and EUS

Jan-Werner Poley

Novel developments in ERCP and EUS

Jan-Werner Poley

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Novel Developments in ERCP and EUS

Nieuwe ontwikkelingen in ERCP en EUS

PROEFSCHRIFT

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Prof.dr. H.J. Metselaar

Eindelijk….

Voor Emma, Wick, Raf en Joost

TABLE OF CONTENTS

1

Introduction and outline of the thesis

This thesis focuses on the diagnostic and therapeutic role of endoscopic retrograde cholangiopancreaticography (ERCP) and endoscopic ultrasonography (EUS) in benign and malignant pancreaticobiliary disease. Since the first practical applications of ERCP and EUS were developed in the first half of the nineteen-seventies and nineteen-eighties, respectively, both techniques have evolved in concurrence with the general trend in endoscopy from being merely diagnostic tools to full-fledged therapeutic procedures during which complex diseases can be treated and invasive surgical procedures can be avoided.

In a way the pancreas and, to a lesser extent, the biliary system are orphan organs. Due to their relative inaccessibility both for physicians and surgeons and the poor prognosis of malignant pancreaticobiliary disease, the quantity and quality of research in this field traditionally has not been up to par compared with standards in some other areas of research in the medical field. Fortunately times have changed and the pancreas, bile ducts and its associated diseases are now one of the most actively researched topics in basic, translational and clinical research.

The aim of this thesis is to investigate the role of EUS in the diagnosis of benign, premalignant and malignant pancreatic disease, to evaluate a novel method of tissue acquisition through EUS and summarize the latest developments of therapeutic endosonography. Furthermore the role of the endoscopic treatment of chronic pancreatitis and benign biliary strictures are evaluated.

This thesis is divided in three sections. In section one, **EUS in screening and diagnosis of pancreatic disease**, the value of EUS as a screening tool for individuals with a markedly increased risk for the development of pancreatic cancer is investigated in **chapter 2.** In these high-risk individuals, cystic lesions are identified at a much higher frequency as compared to the general population. It is often thought that fine needle aspiration (FNA) of these cysts is helpful in establishing a definite diagnosis. In **chapter 3** we demonstrate that the usefulness of EUS FNA is limited both with regard to biochemical and pathological analysis.

Despite the huge developments in accuracy of modern helical multi-slice CT scanning machines, the cause of obstructive jaundice sometimes cannot readily be identified on CT scan. The value of EUS in this particular clinical setting in which patients are suspected to have pancreatic cancer is investigated in **chapter 4**.

In section 2, **EUS: from diagnosis to intervention**, both improvements in the diagnostic and therapeutic capabilities of EUS are covered. In **chapter 5** the results of an international multi-center study are described in which a novel EUS needle is tested in a variety of patients. This needle was developed to routinely acquire histological specimens through EUS (EUS-guided fine needle biopsy or FNB), thereby possibly improving diagnostic accuracy of EUS. Although the acquisition of the specimen is very important,

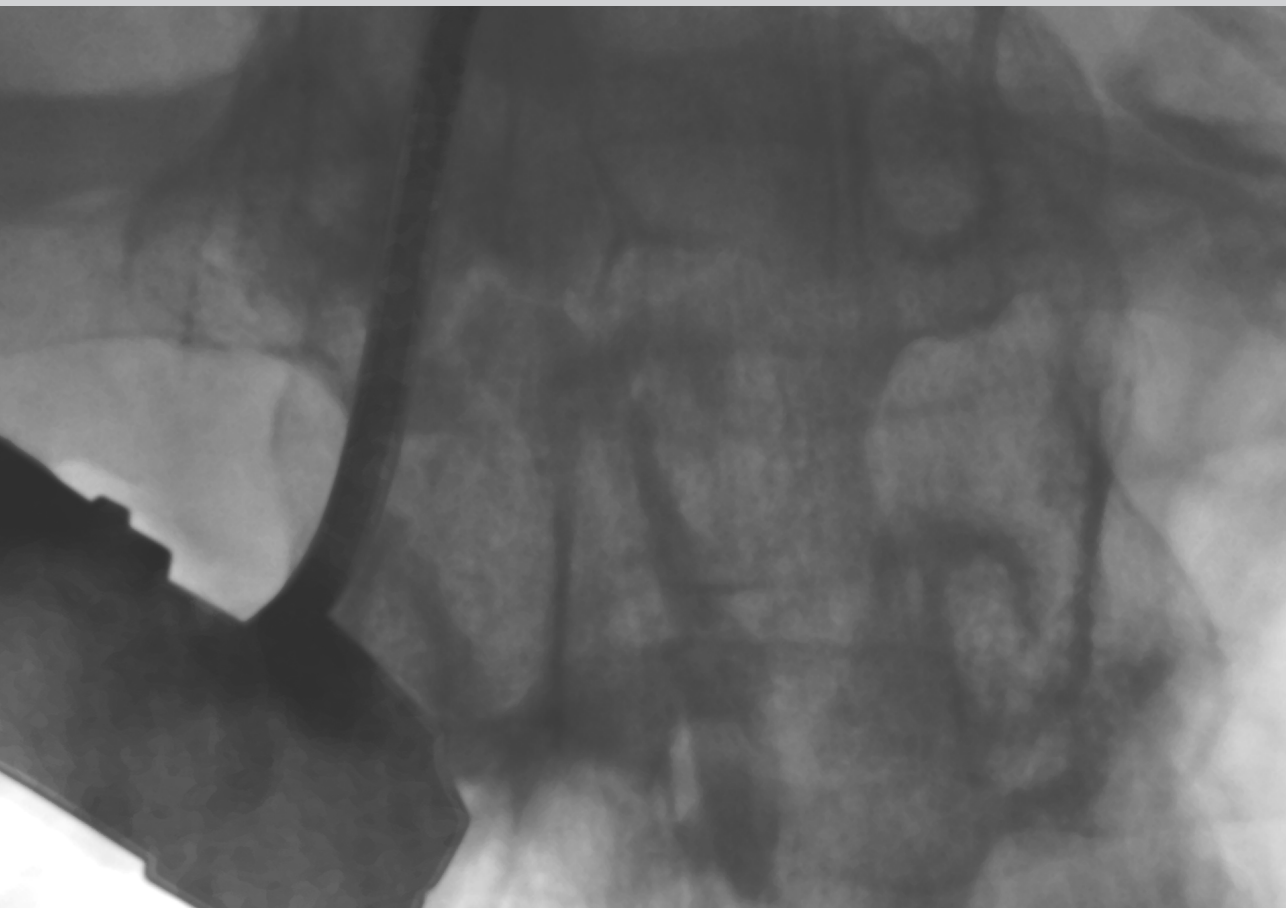
the ability of pathologists to accurately assess the material and to be able to perform for example additional immunostainings is as important. To investigate the concurrence of opinions, a study was performed in which experienced and dedicated gastrointestinal pathologists independently graded specimens acquired through EUS-guided FNB in **chapter 6**. The latest developments and techniques of interventional endosonography are discussed in **chapter 7**.

Although chronic pancreatitis is a benign disease, its clinical course is highly variable and may be complicated by a variety of conditions. Not infrequently, the quality of life of patients with chronic pancreatitis is severely impaired by pain, pseudocyst formation or benign biliary strictures. In section 3, **Novel developments in the endoscopic treatment of benign biliary and pancreatic disease**, the endoscopic treatment of chronic pancreatitis but also other causes of benign biliary strictures (BBS) are discussed. In **chapter 8** an extensive review is given of the endoscopic treatment of chronic pancreatitis.

Although chronic pancreatitis is one of the most common causes of benign biliary strictures, other conditions may also give rise to BBS. One very important cause is orthotopic liver transplantation with the creation of a duct-to-duct biliary anastomosis. In the past these patients were usually treated with a progressive stenting protocol requiring multiple ERCP's with cumulative side by side insertion of plastic stents. Another possible strategy is the temporary placement of fully covered self expandable metal stents (fcSEMS). Since no randomized comparative trials comparing both methods are available, we sought to evaluate the outcome of liver transplant patients with anastomotic strictures whom were treated according a progressive stenting protocol. These results are described in **chapter 9**. In **chapter 10** both strategies are compared with regards to cost-effectiveness.

When fcSEMS are used for the treatment of benign conditions safety and removability are of paramount importance. In **chapter 11** the results of a group sequential study on the safety and efficacy of a novel type of fcSEMS are described in a cohort of patients with BBS due to chronic pancreatitis, orthotopic liver transplantation and laparoscopic cholecystectomy. A special category of BBS are those extending into the liver hilum. Initially it was thought that these strictures were not amenable for treatment with fcSEMS due to blockage of secondary and tertiary ducts when fcSEMS are placed above the hilum. In **chapter 12** however we show that use of a fcSEMS in such conditions is technically feasible, safe and effective when its placement is combined with a protective plastic contralateral stent.

Section 1



Endoscopic ultrasonography in screening and diagnosis of pancreatic disease

2

The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer

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ABSTRACT

Objectives

Approximately 10–15% of all pancreatic cancers (PCs) may be hereditary in origin. We investigated the use of endoscopic ultrasonography (EUS) for the screening of individuals at high risk for developing PC. In this paper the results of first-time screening with EUS are presented.

Methods

Those eligible for screening in this study were first-degree family members of affected individuals from familial pancreatic cancer (FPC) families, mutation carriers of PC-prone hereditary syndromes, individuals with Peutz–Jeghers syndrome, and mutation carriers of other PC-prone hereditary syndromes with clustering (≥2 cases per family) of PC. All individuals were asymptomatic and had not undergone EUS before.

Results

Forty-four individuals (M/F 18/26), aged 32–75 years underwent screening with EUS. Thirteen were from families with familial atypical multiple-mole melanoma (FAMMM), 21 with FPC, 3 individuals were diagnosed with hereditary pancreatitis, 2 were Peutz–Jeghers patients, 3 were BRCA1 and 2 were BRCA2 mutation carriers with familial clustering of PC, and 1 individual had a p53 mutation. Three (6.8%) patients had an asymptomatic mass lesion (12, 27, and 50 mm) in the body (n = 2) or tail of the pancreas. All lesions were completely resected. Pathology showed moderately differentiated adenocarcinomas with N1 disease in the two patients with the largest lesions. EUS showed branch-type intraductal papillary mucinous neoplasia (IPMN) in seven individuals.

Conclusions

Screening of individuals at a high risk for PC with EUS is feasible and safe. The incidence of clinically relevant findings at first screening is high with asymptomatic cancer in 7% and premalignant IPMN-like lesions in 16% in our series. Whether screening improves survival remains to be determined, as does the optimal screening interval with EUS.

INTRODUCTION

Pancreatic cancer is one of the most lethal cancers with mortality rates that almost equal incidence and a 5 year survival rate of maximally 5%[1,2]. One of the reasons for the dismal prognosis of this disease is that only approximately 20% of patients have a resectable tumour at the time of diagnosis. However, even after radical resection, the 5 year survival rate is at best no more than 24% and in most series between 7 and 17%.[3-5]. Survival of pancreatic cancer is strongly dependent on stage[6]. Five-year survival in patients with stage IA after curative surgery is 31%. Survival rates drop dramatically in more advanced stages of the disease. Especially lymph node status is a strong predictor of survival[7]. At present one of the hopes for improving survival lies in identifying those individuals with asymptomatic disease or precursor lesions through a screening programme. Due to the overall low incidence of the disease, screening of the general population is not feasible at present. However, screening may be appropriate in selected populations with an increased risk.

For many years anecdotal case reports have suggested that pancreatic cancer may aggregate in families[8-10]. Several case-control studies have shown that patients with pancreatic cancer are more likely to have a family history of pancreatic cancer than controls[11-13]. Although the majority of pancreatic cancer cases are believed to be sporadic, about 10 to 15% of cases are thought to be caused by inherited genetic factors[14]. Other authors suggest a much lower incidence of no more than 2.7% when stricter criteria are used[15,16]. Based on clinical criteria these individuals can be divided into two groups. At present, the largest group consists of individuals from families in which pancreatic cancer accumulates with at least two affected first-degree relatives without a known underlying gene defect. This condition is most commonly referred to as familial pancreatic cancer (FPC).

The second group of patients with hereditary pancreatic cancer consists of kindreds with various hereditary syndromes or diseases that predisposes them to the development of pancreatic cancer. Although these syndromes inherit in an autosomal dominant fashion the penetrance for PC is highly variable. In most of these syndromes the risk of developing other types of cancer is higher than the risk of PC. Therefore familial clustering of pancreatic cancer can be less obvious or indeed completely absent. An overview of the syndromes known at present that are accompanied by an increased risk of pancreatic cancer are listed in table 1. The estimated life-time risk of individuals can be as high as 50% in smoking men with hereditary pancreatitis and up to 36% in one series of patients with Peutz-Jeghers syndrome[17,18].

An ideal technique or method to screen high-risk individuals should not only detect (small) asymptomatic pancreatic cancer lesions, but also, and more preferable, known and recognizable, benign precursor lesions. In recent years it has become clear that

Table 1: Genetic syndromes with a known elevated lifetime risk for pancreatic cancer

Syndrome	*Gene*	Lifetime risk	RR
FAMMM	**CDKN2A**	**10-15%**	**20-34**
HBOC	**BRCA2**	**5%**	**10**
HBOC	**BRCA1**	**??**	**2**
Hereditary pancreatitis	**PRSS1/TRY1**	**30-50%**	**50**
Lynch syndrome	**MLH1/MSH2**	**??**	**??**
Peutz-Jeghers syndrome	**STK11/LKB1**	**36%**	**136**
FAP	**APC**	**??**	**4**
Li-Fraumeni syndrome	**p53**	**??**	**??**
FPC	**??**	**Up to 50%**	**18-57**

three types of lesions can be detected when screening asymptomatic individuals with familial or hereditary pancreatic cancer. First, small, usually asymptomatic malignant mass lesions can be detected by various imaging methods and are associated with better survival rates than symptomatic pancreatic cancer[19]. Second, it has become clear that intraductal papillary mucinous neoplasms (IPMN) of both main pancreatic duct (main branch IPMN) and its branches (branch type IPMN) can be precursor lesions of pancreatic cancer in high-risk individuals and are also associated with other malignancies[20-23]. Third, pancreatic intraepithelial neoplasia (Pan-IN) is an accepted precursor lesion of pancreatic cancer in which the accumulation of genetic abnormalities is accompanied by the progression of dysplastic features of the ductal epithelium[24].

We aimed to investigate the diagnostic yield of a first time EUS screening investigation in all individuals with an increased risk for the development of pancreatic cancer, including individuals from families with FPC, known inherited genetic syndromes with a high risk of developing pancreatic cancer, and hereditary pancreatitis.

METHODS

Inclusion

After extensive evaluation by a clinical geneticist those individuals estimated to have a lifetime risk for the development of pancreatic cancer of 10% or more based on available evidence from the literature were eligible for pancreatic screening. Diagnoses in these individuals and their families are depicted in Table 2.

Families with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, Lynch syndrome and Li-Fraumeni syndrome were only eligible when familial clustering of pancreatic cancer occurred with at least 2 affected family members. Further inclusion criteria were: mutation carriers of known pathogenic mutations. Individuals had to be

Table 2. Characteristics of asymptomatic high-risk individuals who underwent screening EUS.

		Age (mean/range)	Sex male/female
Familial pancreatic cancer (≥ 2 FDR)	21	53 (32-68)	11 / 10
FAMMM syndrome (CDKN2A)	13	52 (41-75)	3 / 10
HBOC (BRCA1)	3	43 (41-44)	1 / 2
HBOC (BRCA2)	2	42(42)	1 / 1
Peutz-Jeghers syndrome	2	40 (34-45)	2 / 0
Hereditary pancreatitis	2	40 (37-43)	0 / 2
Li-Fraumeni syndrome (p53)	1	40	0 / 1

asymptomatic for signs or symptoms that could be attributed to PC and age 40 or older (or at least 5 years before the youngest affected case in the family). Enrolment for the study started in March 2005 and is ongoing. All individuals signed informed consent before participating in this study. Individuals were not included if they underwent abdominal imaging by either CT, MRI or EUS in three years previously.

Endoscopic ultrasonography

All EUS procedures were performed by 3 experienced endosonographers (J.W.P., P.F., and M.J.B; each with an experience of > 2500 EUS procedures). Both electronic radial (Olympus UC-160 AE, Olympus Europe, Hamburg, Germany with Aloka α5 ultrasound-processor, Zug, Switzerland) and curvilinear (Olympus UCT / UCP 160, Olympus Europe, Hamburg Germany with Philips HDI 5000 ultrasoundprocessor, Philips Healthcare Medical Systems, Best, Netherlands) instruments were used according to the personal preference of the endosonographer. Procedures were performed under conscious sedation with midazolam and/or fentanyl intravenously. Imaging of the pancreas was done from the duodenum and stomach in a standardized fashion. Video and still images were obtained from the uncinate process, pancreatic head and periampullary region, neck, body and tail of the pancreas. Abnormalities specifically looked for were mass lesions, cystic lesions, duct aberrations, and signs of chronic pancreatitis. The diagnostic criteria used for chronic pancreatitis have been published previously[25]. Fine needle aspiration (FNA) was not performed during the initial procedure. In case of abnormal findings at EUS, EUS was followed by CT scan and/or MRI and multidisciplinary discussion of all findings.

RESULTS

Between April 2005 and October 2007 46 individuals were prospectively included in the protocol for a first time EUS screening investigation. Characteristics are given in Table 2.

All individuals were Caucasian. No complications related to the EUS investigations occurred. Twenty-one individuals s in this cohort stemmed from families with FPC. Of note, the majority of individuals screened, twenty-three in total, were therefore from families with a well-defined genetic syndrome associated with an increased risk of pancreatic cancer. Thirteen were from families with FAMMM, five from families with HBOC and clustering (at least 2 cases) of pancreatic cancer and carrying a BRCA1(n=3) or BRCA2 (n=2) mutation. Two individuals were known to have Peutz-Jeghers syndrome, two patients hereditary pancreatitis with both clinical and EUS signs of chronic pancreatitis, one had a proven PRSS1 mutation, and finally one patient with Li-Fraumeni syndrome and a proven p53 mutation.

Mass lesions

In three individuals out of 44 (6.8%) asymptomatic mass lesions in body or tail of the pancreas were found (table 3). The first patient was a 69 year old male with a proven pathogenic BRCA2 mutation and familial clustering of pancreatic cancer (2 affected family members). He underwent EUS screening during which an approximately 29 mm mass lesions in the pancreatic tail was identified (figure 1). The rest of the pancreatic parenchyma showed some signs of chronic pancreatitis with hyperechoic strands, hyperechoic foci and lobularity of the parenchyma. The lesion was closely related to splenic artery and vein but without vascular involvement. CT scan did not reveal distant metastases and surgical resection was performed. During surgery pancreatic tail and

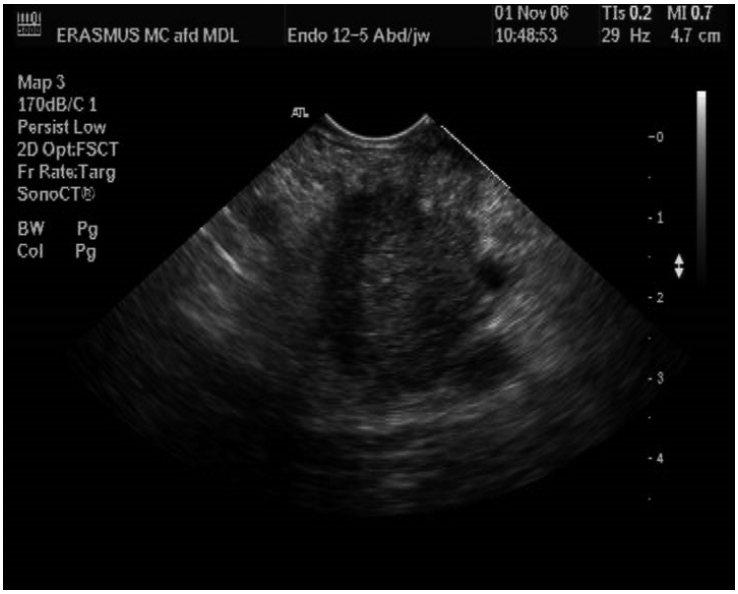

Figure 1: hypoechoic mass in tail of pancreas, adjacent to splenic artery and vein

Table 3: Patients with pathological findings at EUS

ID	Sex	Age	Genetic background	EUS	MRI	CT	nr. EUS features of chronic pancreatitis
5	F	52	Suspicious for FAMMM with UV CDKNA2	Multifocal branch type IPMN 8 – 15 mm	Multifocal branch type IPMN	Two areas with less enhancement corresponding to cystic lesions observed with EUS and MRI	0
9	F	48	FPC	Branch type IPMN 5 mm in pancreatic head; hepatic adenoma	Hepatic adenoma; small abnormal area in pancreatic head; too small for characterization	Not performed	0
18	M	69	HBOC (BRCA2)	Mass 27 mm pancreatic tail	Not performed	Suspicious mass pancreatic tail	1
21	M	57	FPC	Branch type IPMN 4 mm in pancreatic head	Not performed	Not performed	1
31	M	54	FPC	2 branch type IPMN 5 mm in pancreatic body			0
33	F	42	HBOC (BRCA1)	Branch type IPMN 5 mm pancreatic body			0
34	F	75	FAMMM	Mass 50 mm pancreatic tail	Suspicious mass	Not performed	1
35	F	51	FAMMM	Mass 10 mm pancreatic tail	No abnormalities		0
36	M	57	FAMMM	Branch type IPMN 7 mm pancreatic body			0
37	M	59	FAMMM	Branch type IPMN 6.5 mm pancreatic tail			0

spleen resection were performed. Histopathological examination revealed an approximately 30 mm moderately differentiated adenocarcinoma in the pancreatic tail with perineural and vascular invasion. Nine lymph nodes were identified in the resection specimen of which one contained metastasis (T3N1M0, stage IIb). No adjuvant therapy was administered. After an uneventful recovery from surgery 10 months later a local recurrence of the tumor was demonstrated and he died 16 months after surgery.

The second patient was a 76-year old female from a genetically proven FAMMM family. EUS showed atrophy of the pancreatic tail with a dilated main pancreatic duct that tapered into an ill-defined mass at the level of the pancreatic body. CT scan showed this mass without signs of vascular involvement or metastases. The patient underwent surgi-

cal resection of pancreatic body and tail with en bloc resection of the spleen. Histology revealed a poorly differentiated ductal adenocarcinoma with a diameter of 5 cm with perineural invasion and 4 out of 8 regional lymph nodes were tumour positive (T3N1M0, stage IIb). After adjuvant chemotherapy the patient is doing reasonably well, now 18 months after surgery.

The third case involved the daughter of patient 2, 51 years old, also a proven CDKN2A carrier. EUS showed a small (10 mm) hypoechoic mass lesion in the pancreatic body. MRI and CT did not show any abnormalities. En bloc resection of pancreatic body, tail and spleen was performed. The resection specimen contained a 12 mm moderately differentiated ductal adenocarcinoma without nodal involvement (T1N0M0, stage Ia). Sixteen months after surgery local recurrence and liver metastases were demonstrated and the patient is currently receiving chemotherapy and doing quite well.

Cystic lesions

In seven patients (15.9%) small cystic lesions were identified. Details of these patients can be found in Table 3. The size of the lesions was between 4 and 15 mm. All cystic lesions were unilocular without intramural nodules or solid components and with EUS communication with the main pancreatic duct was at least very likely. In one patient, a 52-year-old female from a family with familial pancreatic cancer, multifocal (three) cystic lesions were found in the head, body and tail of the pancreas (Figures 2 and 3).

Both EUS findings and MRI were highly suggestive of branch type IPMN since these cysts clearly communicated with the main pancreatic duct. On CT scan no further abnormalities were found. During 2 years of follow-up with both EUS and MRI/MRCP no apparent changes in these lesions have been observed. For the cystic lesions in the remaining individuals, due to their small size and the absence of signs suggestive of malignancy, a policy of intensive follow-up with bi-annual EUS and MRI was chosen as well. These individuals, as are all other participants, were included in a prospective study in which the yield of EUS and MRI are compared.

Extra-pancreatic findings

In a 40-year-old female with Li-Fraumeni syndrome and a proven p53 mutation a 25 mm mass lesion of the left adrenal was identified during EUS. Endosonographic examination of the pancreas was normal. The left adrenal was laparoscopically resected and contained a non-malignant, non-functioning adenoma. Recovery from surgery was uneventful.

In a 48 year old woman from a family with FPC a 16 mm hypoechoic lesion without an obvious central scar was seen in the left liver lobe. EUS-FNA demonstrated this lesion to be a hepatic adenoma and no change has occurred during 18 months follow-up.

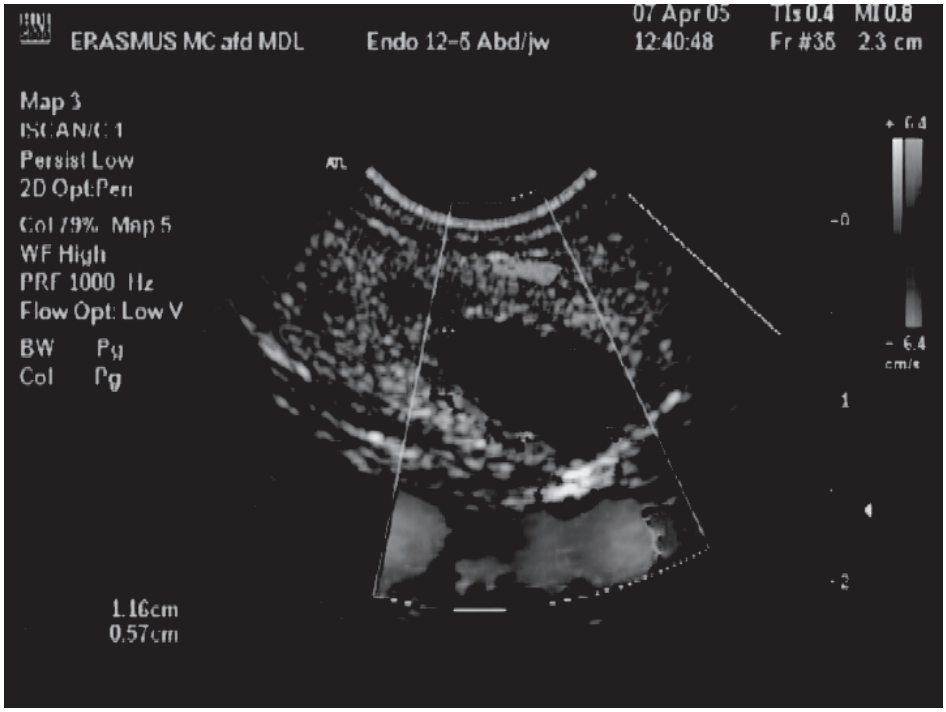

Figure 2: EUS image of unilocular cyst in tail of pancreas in patient with FPC

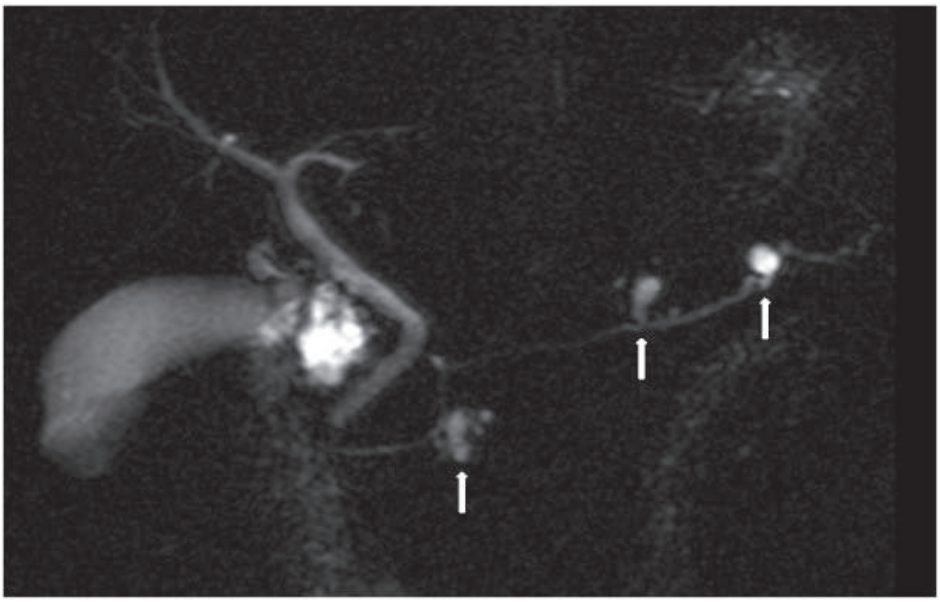

Figure 3: MRI image of multifocal branch type intraductal mucinous neoplasia in a patient with familial pancreatic cancer highlighted by the white arrows

Complications

During a total of 46 EUS investigations no complications have occurred. All individuals left the hospital maximally 2 hours after the procedures.

DISCUSSION

In this study we have shown that EUS-based screening of individuals at a high risk of developing pancreatic cancer is feasible and safe. Although the number and length of follow-up of individuals included in this study is too small to answer the question whether this improves outcome in individuals with a family history of PC it is clear that first time EUS yields a considerable number of both malignant and potentially premalignant lesions which is in line with previous studies from the US in cohorts which mainly consisted of families with familial pancreatic cancer. These studies also demonstrated the ability of EUS to identify both mass and potentially premalignant lesions in up to 10% of asymptomatic persons[22,23]. In symptomatic individuals from FPC kindreds however multifocal dysplasia was detected in 7 out 14 patients that underwent pancreatectomy after abnormal ERCP and EUS[26].

Modalities that have been used to screen high-risk individuals are CT-scan, endoscopic retrograde cholangio-pancreaticography (ERCP), magnetic retrograde cholangiopancreaticography (MRCP/MRI) and endoscopic ultrasound (EUS). Although there is no scientific evidence to support the use of CT scan for this purpose, it is used by several institutions[27,28]. The sensitivity of CT-scan in detecting small pancreatic lesions is lower compared to EUS, thereby limiting its potential usefulness for screening purposes[29]. Perhaps the most important consideration is the fact that the cumulative radiation dose of repeated CT scans should not be neglected, especially in individuals already at an increased risk of developing cancer.

Although MRI does not involve radiation exposure and therefore is perhaps more suitable for use in a surveillance setting, it has not been formally investigated in individuals at risk for pancreatic cancer. From comparative studies it is known that the sensitivity of MRI in detecting small (<3 cm) lesions is comparable to helical CT-scanning. An additional value of MR is the visualization of the pancreatic duct and cystic lesions through the use of MRCP sequences. The use of secretine improves visualization of the pancreatic duct and cystic lesions[30]. Furthermore, another benefit of MRI images compared with EUS is that they are relatively easy to compare over time. The inherent complication risks do not make ERCP a suitable test for screening purposes.

EUS seems to be an almost ideal test for imaging of pancreas and detecting early lesions. Indeed, several studies have shown in still relatively small cohorts, mainly consisting of individuals with familial pancreatic cancer, its ability to identify early neoplastic

lesions[22,23,26]. Although EUS is an invasive procedure that usually requires conscious sedation, the complication risk of diagnostic EUS is very low[31]. EUS is however an operator dependent technique that requires considerable skills and experience to reliably examine the pancreas[32].

Our study is the first study on this subject in Europe and differs in one important aspect from previously published studies in that the proportion of individuals with a clearly defined genetic syndrome was much higher. Whether this explains solely the higher incidence of both solid lesions and cystic precursor lesions remains to be investigated although all mass lesions in our series were found in mutation carriers. The aim of the present study was not to establish differences between these groups and lacks statistical power to reliably ascertain whether this is explained by genetic background. Furthermore, other risk factor, e.g. smoking, needs to be taken into account. The incidence of cystic lesions in FPC individuals in our series is 15% (3 out of 20), which is still higher than in the US series mentioned above.

Several important questions still need answering. Obviously, it is not the goal of an oncological screening program to find advanced cancers. This applies in particular to pancreatic cancer with its dismal prognosis. The detection of asymptomatic (advanced) malignancies will only introduce a lead time bias since individuals will become patients earlier without improving the actual prognosis. This is illustrated by the patient with a BRCA2 mutation who survived only 16 months after the detection of an asymptomatic carcinoma followed by a radical surgical resection and the patient who underwent resection of a very small cancer and still developed local recurrence and liver metastases despite a radical resection with negative lymph nodes. One could argue however, that screening started too late in the three patients with advanced lesions and that having commenced screening at an earlier stage in their lives might have detected these lesions at a curable stage. This however should be demonstrated in larger prospective series, preferably multicenter, before embarking on any formal screening and surveillance program in these families.

One argument for this is the ability of EUS to identify these precursor lesions in the form of cystic lesions as shown by our study and others[22,23,26]. Although in 2 out of 3 resection specimens at the edges some formations of pancreatic intraepithelial neoplasia (PanIN) grade I-II were found, at present there is no reliable way to identify these Pan-IN's with EUS. It might be that Pan-IN's are represented by the occasionally observed extensive changes in the pancreatic parenchyma in these individuals that are reminiscent of chronic pancreatitis (Table 3). It is possible to acquire pancreatic tissue for histopathological evaluation either through surgery or EUS guided with a thrucut needle. At present the potential complications of these procedures combined with the possible patchy distribution of Pan-INs withhold us from this strategy. We also do not know at the current time whether the finding of Pan-INs justify a total pancreatectomy given its inherent morbidity and mortality.

Another important and still unanswered question is how to manage the IPMN-like cystic lesions that we and others found to be present at an relatively high frequency in individuals at high risk of developing pancreatic, especially in light of the assumption that these may represent precursor lesions of pancreatic cancer. It is known know from several retrospective cohort studies that the likelyhood of malignancy in branch type IPMN's without involvement of the main pancreatic duct, intramural nodules or solid components is quite small. In sporadic cases a follow-up policy with regular interval screening for these lesions is safe and acceptable[33-36]. However, the biological behavior of such lesions in patients with a hereditary increased risk for the development of cancer is not known. Whether these high-risk patients should be offered surgery at an earlier stage than what is considered acceptable in sporadic cases or if the same wait-and-see policy can be adopted is unknown. It is also unclear whether the possible development of these precursor lesions into more advanced neoplastic or even malignant lesions is gradual over time with ample opportunity for early detection during surveillance, or sudden and abrupt. These very important questions need to be addressed in further follow-up studies.

When the principles formulated by the World Health Organization in 1968 with regard to screening for disease are applied to EUS based screening of high-risk individuals for the development of pancreatic cancer, most of these criteria are fulfilled.[37] Despite the fact that we have not yet identified the best management of patients with precursor lesions nor have evaluated the cost-effectiveness of EUS-based screening of individuals at risk, this strategy at present seems to be the most appropriate and sensible. However, because of the many unanswered questions that still remain we strongly believe this should only be done in research programs with well-established protocols and registries. We have therefore started in the Netherlands a prospective study in which the yield of annual EUS and secretin-administered MRI will be compared in mutation carriers of PC-prone syndromes, other syndromes with PC clustering and FPC.

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3

Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study

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ABSTRACT

Background

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is considered a valuable and safe technique for further investigation of pancreatic cystic lesions. In the framework of a prospective study on the accuracy of EUS-FNA we report our initial technical results regarding puncture access, sample adequacy, and complications

Methods

Consecutive patients with indeterminate pancreatic cystic lesions underwent EUS and EUS-FNA. Pancreatic cyst fluid was collected for cytopathological analysis and measurement of amylase, carcinoembryonic antigen (CEA), and carbohydrate antigen 19.9 (CA 19.9) levels. Main outcome parameter for this analysis was the percentage of samples adequate for cytologic and laboratory analysis.

Results

Of 143 patients (median age 63 years; median cyst size 2.8 cm) who underwent EUS, FNA was performed in 128 (90%). The various reasons for not doing FNA included large distance between transducer and cystic lesion (n = 9), cyst not seen or too small (n = 2), and evident diagnosis not requiring FNA (n = 3). FNA was not possible in four patients (technical failures). Cyst fluid sent for cytology provided adequate cellular material in 44 cases only, accounting for an intention-to-diagnose yield of 31% (44/143). Sufficient fluid for biochemical analysis was obtained in 68 cases (49%). Complications occurred in three patients (2.4%).

Conclusions

Although EUS-guided FNA was technically feasible in the majority of patients with pancreatic cystic lesions (87%), it was possible to obtain a classifying cytopathologic diagnosis and a chemical analysis in only a third and a half of cases, respectively.

INTRODUCTION

An increasing number of individuals are diagnosed with cystic lesions of the pancreas because of more frequent use of cross-sectional abdominal imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). In two recent studies the prevalence of cystic pancreatic lesions was 2.6% and 2.4%, respectively [1, 2]. Although little is known about the natural history of small asymptomatic cysts, it is well known that a subset of pancreatic cysts have malignant potential [3 – 5]. Whereas simple cysts seem to be harmless, mucinous subtypes including mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) have an undisputed malignant potential [4, 6 – 8]. For this reason, the majority of pancreatic cysts are extensively analysed in order to decide whether surgery or follow-up is indicated. In the diagnostic work-up, imaging tests such as dedicated CT and MRI are excellent diagnostic modalities to describe morphologic features of pancreatic cysts [9, 10]. In addition, endoscopic ultrasound (EUS) has emerged as valuable in the evaluation of pancreatic cystic lesions, providing fine detail of the morphological characteristics of the cyst[11 –13]. Nevertheless even after high resolution imaging using either technique it is still difficult to distinguish between the different types of pancreatic cysts based on morphologic criteria only [14, 15]. EUS-guided fine needle aspiration (FNA) may be helpful in achieving a diagnosis by providing pancreatic cyst fluid and is considered by many to be a safe and valuable technique[16 – 18]. However, cytopathological examination is often nondiagnostic due to the low cellularity of the cyst fluid obtained [14, 19]. The value of cyst fluid tumor markers is also controversial [14, 16, 20, 21]. Despite the large number of reports on the value of cytology and tumor markers, there is to our knowledge no prospective study reporting the actual percentage of consecutive cases where EUS- guided FNA is technically successful in obtaining a sufficient amount of cyst fluid for performance of cytological and laboratory investigations of the fluid.

We initiated a prospective cohort study involving patients with cystic lesions of the pancreas, with a standardized protocol which includes, among other techniques, EUS-FNA. In this study we investigated the technical success and safety of FNA in a prospective cohort of consecutive patients with cystic pancreatic lesions of unknown origin.

PATIENTS AND METHODS

Study design

This was a prospective, observational cohort study of consecutive patients referred to the Departments of Gastroenterology and Hepatology or Surgery at our institutions for the evaluation of cystic pancreatic lesions. The study was performed in The Netherlands,

at the Departments of Gastroenterology and Hepatology of the Academic Medical Center at the University of Amsterdam and of the Erasmus MC University Medical Center in Rotterdam. Approval for the study was given by the local ethics committees of both centers. Written informed consent was obtained from all patients before they entered the study. Enrolment started in December 2006 and is ongoing.

Patients

Consecutive patients above 18 years of age with a cystic pancreatic lesion of unknown aetiology seen on cross-sectional imaging (transabdominal ultrasound, CT, MRI) were included in our study after written informed consent had been obtained. Exclusion criteria included the following: known coagulation disorders (prothrombin time-international normalized ratio [Pt-INR] > 1.5, partial thromboplastin time (PTT) > 50 s, platelets < 50 000/nL), acute pancreatitis in the previous 6 months, and a synchronous malignancy elsewhere in the body.

EUS procedures

All patients received one dose of intravenous prophylactic quinolone prior to the procedure followed by oral quinolone for 3 days after the procedure in order to minimize the risk of infectious complications.

For the EUS procedure, patients were placed in the left lateral position. Procedures were performed with patients under conscious sedation with intravenous midazolam and/or fentanyl. Four experienced endosonographers (J. W. P., J. E. H., M. J. B., P. F.), who had each carried out more than 500 EUS examinations of the pancreas, performed all the procedures, using linear-array echo endoscopes (GF-UC(T)140(P); Olympus Medical Systems, Hamburg, Germany).

All procedures were done according to a standardized protocol. When the lesion was identified, the following morphologic characteristics were recorded at the time of examination: location of the cyst, cyst diameter, multiplicity of cysts, microcystic versus macrocystic character, maximal wall thickness, presence of septations, nodules or calcifications, communication with pancreatic duct, dilatation of pancreatic duct, and presence or absence of vascular involvement.

For EUS-guided FNA, lesions in the pancreatic head were approached via the duodenum, while lesions in the body and tail were targeted transgastrically. Color Doppler was used to identify intervening blood vessels and to diminish the risk of bleeding. Reasons for nonperformance of FNA could be: intervening normal pancreatic tissue over a distance of more than 1 centimeter, unavoidable intervening vessels, strong suspicion of a large complex (debris) pseudocyst in the presence of parenchymal features of chronic pancreatitis with a presumed increased risk of infection, or clear suspicion of malignancy with straightforward indication for surgery.

EUS-guided FNA was done using a 19- or 22-gauge needle (Wilson-Cook, Limerick, Ireland) at the discretion of the endosonographer. All lesions were preferably punctured with a single pass to minimize the risk of infection through repeated punctures. Once the needle was inside the lesion, a vacuum was applied and the contents of the cystic lesion were aspirated, with the needle being moved slowly back and forth through the lesion until no more fluid could be obtained. If solid components were visualized they were specifically targeted with the needle. At both centers, patients were observed in the recovery area for a minimum of 2 hours after the procedure.

Cyst fluid analysis

After aspiration, the cyst fluid was divided to provide material for cytopathologic examination, biochemical analysis, and research purposes. The cytopathologic examination was considered the most important and thus cyst fluid was primarily used for this. All cytological specimens were processed as direct smears of aspirated material (on eight glass slides).

Secondly, aspirate was sent for biochemical analysis of amylase levels and tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen 19.9 [CA 19.9]). The aspirates were delivered immediately after the procedure and a minimum of 500 µl was needed for determination. Tumor markers and amylase were measured with commercially available immunoassays.

When sufficient fluid (2ml) was available, spin cytology was also carried out. Depending on the amount of fluid, additional fluid was stored for research purposes in a freezer at −80°C.

Complications

Complications were defined as any unexpected event occurring during or after the procedure that caused morbidity or mortality [22]. Complications that might occur during or within 2 hours of the procedure were defined as immediate; complications occurring within 30 days after the procedure were defined as early; and complications occurring more than 30 days after the procedure were regarded as late [23]. Definition of severity of complications was based on the length of hospitalization: mild < 3 days, moderate 4 – 10 days, and severe > 10 days or admission to the intensive care unit or department of surgery [23].

Patients were asked to contact the hospital in case of abdominal discomfort, pain, or fever. In addition, patients were seen at the outpatient clinic between 1 and 2 weeks after the procedure for discussion of the results, enquiry about complications, and decisions about further management.

Data collection and statistical analysis

Data were collected and recorded in a prospective database. Statistical analysis was performed using SPSS 16.0 (Statistical Pack- age for the Social Sciences, Chicago, Illinois). Quantitative data are presented using median values with the range or mean values with standard deviations, wherever appropriate. For the comparison of continuous variables, appropriate t tests or nonparametric tests were used. P values (two-sided) of less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Between December 2006 and September 2009, 143 consecutive patients (median age 62.8 years, range 19 – 80; women 54%) were included in the protocol and underwent EUS. A total of 65 patients (45%) had abdominal complaints at the time of presentation. In the other 78 patients the cyst was considered to be an incidental finding on either ultrasound, CT or MRI.

Median cyst size was 28 mm (range 7 – 220): 14 cysts (10%) had a size of 1 – 10 mm, 38 (27%) were 11 – 20 mm, 33 (23%) were 21 –30 mm, 19 (13%) were 31 – 40 mm, and 39 cysts (27%) were > 40 mm in size. Anatomically, 71 of the lesions (50%) were in the pancreatic head, 37 (26%) in the body and 35 (24%) were in the tail. Table 1 shows the characteristics of the patients and the cyst features.

Table 1: Evaluation of pancreatic cysts by endoscopic ultrasound-guided fine needle aspiration (EUS – FNA): characteristics of patients (n=143) and cysts

Gender, female, n (%)	78 (54)
Age, median (range), years	63 (19-80)
Patients with abdominal complaints*, n (%)	64 (45)
Cyst size, median (range), mm	29 (7 – 220)
Pancreatic location, n (%)	
Head	71 (50)
Corpus	37 (26)
Tail	35 (24)
FNA performed, n (%)	124 (87)
Fluid volume obtained, median (range), ml	3.0 (0.5 – 600)

* In the remaining patients, the cyst was an incidental finding

Technical success

EUS-guided FNA was done in 128 out of 143 (90%) patients. It was not done in 15 patients for the following reasons: risk of post-procedural pancreatitis because the distance between the transducer and cystic lesion was considered to be too great (n = 8) (figure 1); unavoidable intervening blood vessel (n = 1) (figure 2); presumed pseudocyst with the EUS image compatible with chronic pancreatitis (n = 2); image compatible with cyst- adenocarcinoma with a clear indication for surgical resection, to avoid the risk of seeding (n = 1); cyst not identified at EUS examination (n = 1); cyst size considered too small for successful puncture (n = 1); and the lesion was hyperechogenic (n = 1). In this

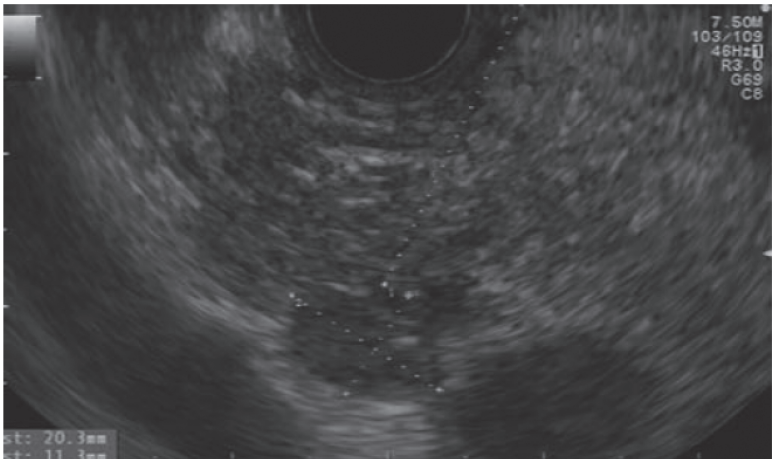

Figure 1: Pancreatic cyst: endoscopic ultrasound-guided fine needle aspiration (EUS – FNA) was not done because of the distance between the point of entry to the pancreas and the cyst was too great.

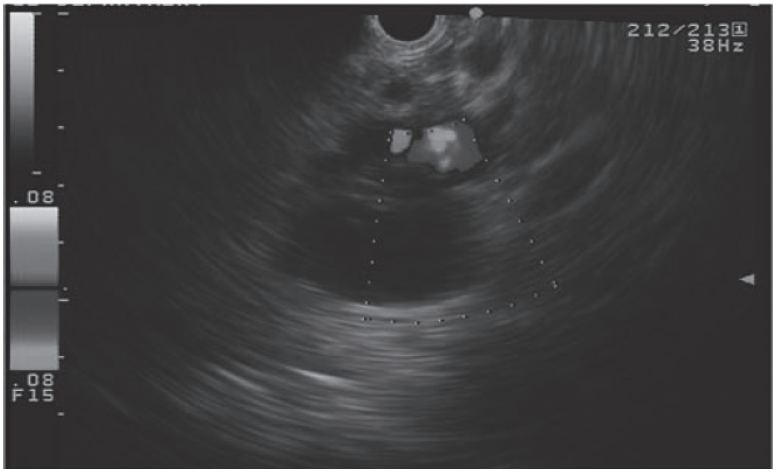

Figure 2: Pancreatic cyst: endoscopic ultrasound-guided fine needle aspiration (EUS – FNA) was not done because of intervening blood vessels.

last patient EUS showed a benign-appearing, poorly demarcated, hyperechoic area in the pancreatic head. Review of the MRI images and report suggested that this was not a cyst but a lesion compatible with fatty tissue.

Fluid could not be obtained in four of the 128 patients in whom FNA was done because of technical failure of the puncture.

The median size of the cysts in which FNA was performed was 29 mm (range 7 – 220) versus 15 mm (range 9 – 65) for the cysts in which FNA was not performed (P = 0.025). Median amount of cyst fluid obtained at EUS-FNA was 3 ml (range 0.5 – 600). Material was sent for cytology from 124 patients (87% of all patients). A classifying diagnosis was obtained in 44 (31% of all patients). The median size of the cysts with a classifying diagnosis was 29 mm (9 – 220) compared with 28 mm (7 – 140) for the cysts without a classifying diagnosis (P = 0.396).

Sufficient fluid was available for biochemical analysis in 80/143 cases (56%) and analysis succeeded in 70/143 (49%). Median size of cysts for which biochemical analysis was performed was 33 mm (7 – 220) versus 22 mm (7 – 145) for the cysts without biochemical analysis (P = 0.072). Findings are summarized in figure 3.

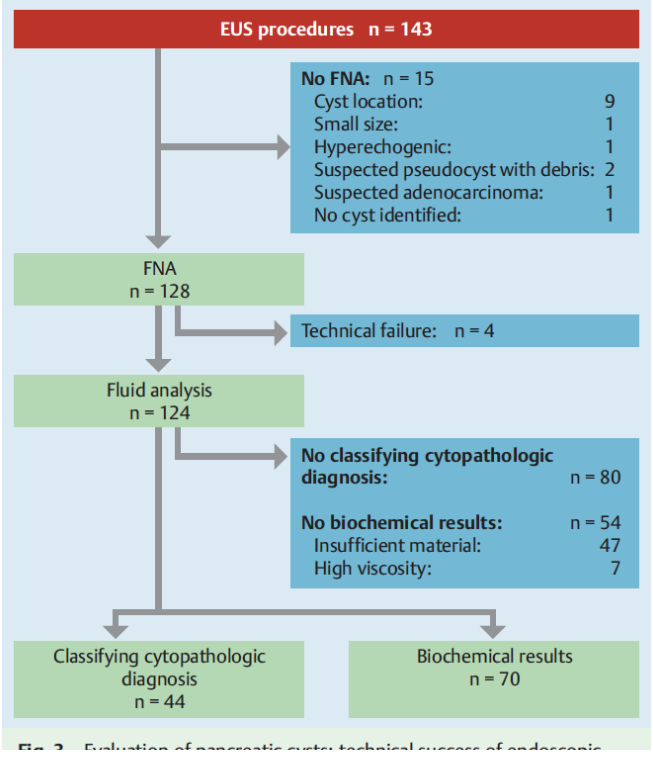

Figure 3 Evaluation of pancreatic cysts: technical success of endoscopic ultrasound-guided fine needle aspiration (EUS – FNA)

Safety

Three patients (2.4%) developed complications: two had symptoms consistent with an infection of the pancreatic cyst and one developed mild pancreatitis.

In one of the patients with infectious complications, a 140-mm cystic lesion in the tail of the pancreas had been punctured. The patient presented with abdominal pain, fever and elevated white blood cell count. Abdominal CT did not show signs of perforation or leakage and infected pancreatic cyst was considered to be the most likely cause of the fever and abdominal pain. The patient was admitted and received intravenous antibiotics, upon which the symptoms resolved and the patient was discharged after 7 days. At 2 months later she underwent surgery with complete resection of the lesion. During surgery no signs of the earlier infection were seen. Histopathology showed a mucinous cystadenoma without signs of malignancy.

The second patient had a 33-mm cyst in the corpus and presented a week after the procedure with fever, abdominal pain and nausea. Laboratory tests showed that the C-reactive protein (CRP) level was raised and the amylase level was normal. Transabdominal ultrasound was performed and showed no signs of perforation, leakage, or pancreatitis. The patient was treated as an outpatient with oral antibiotics for 5 days, after which the symptoms resolved.

The third complication occurred in a patient with a 28 mm cystic lesion in the corpus. The patient presented with abdominal pain within 24 hours after EUS-guided FNA. Laboratory tests showed an increased amylase level of 435 U/L and raised CRP of 64.2 mg/L. This patient was also observed as an outpatient with a diagnosis of EUS-associated pancreatitis and symptoms spontaneously resolved within a week, without medication.

DISCUSSION

Cystic lesions of the pancreas can be subclassified into mucinous and nonmucinous cysts. Whereas nonmucinous cysts are usually harmless and do not require follow-up, mucinous cysts may have a malignant potential and require surgical resection or surveillance depending on size and other characteristics. Even with currently available diagnostic modalities, accurate diagnosis is still challenging. The dilemma for clinicians is that on the one hand patients should not be exposed to unwarranted surgery or surveillance with associated morbidity or even mortality, but on the other hand a correctly indicated resection or surveillance of a malignant or premalignant cyst should not be withheld. In recent years EUS has evolved into a technique that is widely used to obtain detailed images of the pancreas including of pancreatic cysts [15]. Despite the high resolution of the EUS images, there is controversy about the accuracy of EUS in discrimination between mucinous and nonmucinous cysts [15, 24, 25]. FNA is considered to be an

important technique in the diagnostic work-up of pancreatic cysts. Many studies have been published reporting on the performance and yield of FNA for the evaluation of pancreatic cysts but little is known on the technical success and safety of this procedure. Therefore, the aim of this prospective two-center study was to investigate the technical success and safety of EUS-FNA in our prospective cohort of patients in all of whom EUS-FNA was planned.

In our study a total of 143 persons underwent EUS, and FNA could be performed in 128 (90%) of them. In some cases no puncture was done, for various reasons including unfavorable location: more than 1 cm of pancreatic tissue would have to be passed to puncture the cyst and the risk of causing pancreatitis was considered too high. Another reason for not carrying out the puncture was the presence of an unavoidable intervening blood vessel.

Cytological examination was performed in all cases in which fluid was obtained but a classifying diagnosis was only obtained in approximately one third of cases (31%). Other studies performed so far have focused on the sensitivity of cytology to predict a mucinous cyst. Two studies have reported similar results with sensitivities of 13% and 35%, respectively [26, 27]. These numbers are lower than those reported in another prospective study by Frossard et al. [28]; in that study cytological analysis was performed in 127 patients with pancreatic cysts and a classifying diagnosis was provided in 98 cases (77%). However, in that study an additional minibiopsy was obtained and a cell preparation processor was used which provided a monolayered cell population. Successful cytopathologic analysis is largely dependent on acquiring a sufficient number of cells in the specimen. We conclude that the interpretation of these cytologic specimens remains challenging, even in the hands of experienced pathologists.

Our second goal for analysis after cytopathology was biochemical analysis of CEA, CA 19.9 and amylase. This was possible in only approximately half of the patients (49%), mainly because we primarily chose to send material for cytological evaluation and in many cases no fluid was left for biochemical analysis. In an additional 10 cases, material was sent to the laboratory but analysis could not be done because of high viscosity or an insufficient amount of fluid. Cyst fluid biochemical analysis (amylase) and tumor markers have been evaluated for several years on the basis that markers secreted into the cyst fluid might identify the epithelial lining. Markers commonly used are CEA, CA 19.9, CA 15.3 and CA 72.4 [18, 29 – 31], amongst which CEA is considered one of the best discriminatory markers for the diagnosis of mucinous cystic neoplasms [20], providing the highest sensitivity and specificity in most studies.

We also looked at the correlation between the size of the cysts and the success of FNA. Cysts in which FNA was performed were significantly larger than cysts in which no FNA was performed. Since the latter cysts were smaller it is more likely that the distance between the transducer and the cystic lesion was larger in the cases in which no FNA

was performed. However, cysts for which a classifying diagnosis was obtained were not significantly larger than cysts without a classifying diagnosis. The cysts for which biochemical analysis was performed were not statistically significantly larger than the cysts for which it was not done, although a trend (P= 0.07) was found.

The overall complication rate was 2.4% (3 of 124 patients) with one patient being admitted to hospital and two treated as outpatients. There were no deaths and no patients required surgery. In two patients the cyst was infected after FNA and one patient suffered from a mild pancreatitis attack. This complication rate is comparable to that reported in the study by Lee et al. [32], where a retrospective analysis of 603 EUS-FNA procedures of pancreatic cysts showed 13 complications (2.2%). Two earlier studies showed higher complication rates of 3.5% and 14% after FNA for pancreatic cysts [33, 34]. In the study with a complication rate of 3.5% prophylactic antibiotics were also administered [33], whereas no antibiotics were given in the one with the 14% complication rate [34]. The majority of complications after FNA are mild, and the most common complication is pancreatitis though the latter was not the case in our study. Infection of cysts after FNA is rare, and data are lacking that support the use of prophylactic antibiotics although it is common practice in most centers. Furthermore, to minimize the risks of subsequent infection one should keep the number of punctures to a minimum and attempt to aspirate the cyst completely whenever possible. Intracystic hemorrhage is a rare complication that occurred in 6% of all cases reported by Varadarajulu et al. [35]. We did not identify any intracystic hemorrhage, but we may have missed instances since this often occurs without clinical symptoms.

To interpret the results of this study, the following strengths and limitations have to be considered. The study is strengthened by its collection of a large prospective cohort of consecutive patients, in contrast to the retrospective studies published earlier [32, 34]. In addition, all EUS procedures were carried out by four endosonographers with extensive experience in pancreatic EUS. Finally, standard follow-up was done 7–14 days after the procedure.

A limitation of the study is the potential selection bias since both the hospitals are tertiary referral centers. Additionally, in some patients FNA was not done, because of clinical considerations, although the protocol did specify performance of FNA in all patients. Another limitation could be that we may have missed some mild early complications since patients were only seen in the outpatient clinic 7–14 days after the procedure. In some studies patients were seen 1 or 2 days after the procedure [33, 34]. Finally, we do not yet have long-term follow-up of our patient cohort. Long-term surveillance of all patients will show the true value of EUS-FNA in cystic lesions of the pancreas, but the present study was only investigating the technical success and safety of EUS-guided FNA.

New methods to improve the yield of FNA are urgently required. The current yield is often small; this may be caused by the microcystic aspect of some cysts, the high

viscosity of the fluid, or by the minimum amount of fluid required for certain analyses. The standard use of a 19-G needle could be helpful to aspirate both larger cysts and cysts which contain fluid with a high viscosity. Also the development of new techniques to minimize the fluid needed for analysis may well be valuable. In addition, the development of new techniques to increase the cellularity of the fluid obtained could be helpful. Two recent reports study a new type of brush (EchoBrush, Cook Medical, Limerick, Ireland) aimed at improving the yield of cytologic examination [36, 37]. The EchoBrush is limited in that it can only brush cysts that are at least 2 cm in size. Another limitation of the EchoBrush has been the relatively high rate of complications. Since the procedures were performed by highly experienced endosonographers, it might be difficult to introduce this technique in a community setting. These studies suggest that this relatively new technique improves the yield, but larger randomized trials are necessary to confirm these results and to define the safety profile of this more aggressive approach. Existing tumor markers have only limited value and identification of more sensitive biomarkers is needed. New techniques including proteomics and molecular analysis may be helpful for the differential diagnosis of pancreatic cysts.

This study shows that EUS-FNA of cystic pancreatic lesions is safe but that the overall diagnostic value is limited. A definite cytopathological diagnosis was obtained in only 31% and a biochemical analysis in only 49%, even though EUS-FNA was technically possible in the majority of patients.

Competing interests: None

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4

Role of endoscopic ultrasonography in patients suspected of pancreatic cancer with negative helical MDCT scan

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Digestive Surgery; 28: 398 – 403

ABSTRACT

Background

In some patients suspected of pancreatic cancer no mass can be detected by MDCT-scan as the cause of biliary obstruction.

Methods

All patients suspected of pancreatic cancer between January 2007 and 2009 with a negative MDCT were identified from a database.

Results

MDCT was performed for suspected pancreatic cancer in 290 patients, in 258 a pancreatic mass was found. MDCT failed to establish a diagnosis in 32 (11%). In 23 (74%) with a complete EUS the cause of the obstruction was correctly diagnosed. A mass in the pancreatic head was found in 15 patients; 13 patients had a malignant tumour and 2 patients a benign cause of obstruction. Further, EUS diagnosed 3 patients with a superficial adenoma of the papilla and 8 patients with a benign cause of the obstruction. In 5 patients EUS couldn't detect the cause of obstruction but finally a pancreatic malignancy was diagnosed. The PPV of EUS was 86% and NPV 63%. Accuracy of MDCT and EUS decreased in the presence of pancreatitis or a biliary endoprosthesis.

Conclusion

In patients suspected of pancreatic cancer where MDCT fails to demonstrate the cause of obstructive jaundice, EUS identifies 74% of the underlying diseases correctly.

BACKGROUND

Pancreatic adenocarcinoma has a mortality rate almost equal to its incidence rate.[1] The only curative treatment is surgical resection, however most patients present at an advanced stage and only approximately 15% of patients are eligible for resection at time of diagnosis.[2, 3] It is important to detect pancreatic tumours at an early, locoregional stage because these patients are most likely to benefit from resection. Helical multi-detector computed tomography (MDCT) is the preferred initial imaging modality for patients suspected of pancreatic cancer in most centers because of a high sensitivity for detecting and determining resectability of pancreatic or peri-ampullary masses and the ability to demonstrate distant metastases.[4-7] If MDCT doesn't show the cause of obstruction either MRI or endoscopic ultraonography (EUS) is the propagated next step. EUS has a high sensitivity for detecting pancreatic and peri-ampullary masses,[4, 6, 8] differentiating these from other causes of cholestasis like choledocholithiasis.[9] Furthermore EUS has the possibility to obtain tissue for diagnosis by fine needle aspiration (FNA). However, this technique is invasive, operator-dependent and might be influenced by the presence of biliary endoprosthesis.[6] We retrospectively studied the value of EUS in patients suspected of pancreatic cancer with a negative MDCT.

METHODS

All patients referred to an academic tertiary referral centre (Erasmus MC, University Medical Center; Rotterdam, the Netherlands) or a large teaching hospital (Maasstadziekenhuis; Rotterdam, the Netherlands) for suspected pancreatic head malignancy between January 2007 and January 2009 were retrospective included in a database. Inclusion criteria were painless jaundice or a combination of cholestasis, weight loss and abdominal discomfort or back pain. These patients were analysed using a Siemens helical multidetector CT-scanner with a non-contrast enhanced scan and a contrast enhanced scan in the pancreatic phase after 40 seconds (2,5-3mm slices) and portal phase after 80 seconds (5mm slices), according to local pancreatic cancer protocol. The MDCT was reported by one of two experienced gastro-intestinal radiologist. We consciously choose not to review the original MDCT for this study or videos of the EUS but used the original reports to reflect everyday clinical practice. We identified patients with a negative MDCT and at least 6 months follow-up from this database. EUS was performed under conscious sedation by one of three experienced endosonographers, who performed over 500 procedures each. FNA was performed when doubt about the diagnosis existed or in case of an unresectable mass to get cytological diagnosis. FNA was not performed when morphological appearance suggested a resectable pancreatic

cancer on EUS. The EUS was performed with an electronic Olympus curved linear array echo-endoscope (Olympus GmbH, Hamburg, Germany) with a Philips ultrasoundprocessor (Philips Medical, Amsterdam, the Netherlands) or with an electronic Pentax linear echo-endoscope with an Hitachi ultrasoundprocessor (Hitachi Medical Systems, Zug, Switzerland). Patients were discussed in a multi-disciplinary meeting after MDCT and EUS. Surgical outcome was reported, as were histopathological examinations of resected tumours and intraoperative findings.

RESULTS

Between January 2007 and January 2009 a total of 290 patients were referred and analysed for suspected pancreatic cancer. Reasons for suspicion of pancreatic cancer were painless jaundice (60%) or weight loss with cholestasis and/or upper abdominal discomfort (40%). These patients included 149 women and 141 men, with a median age of 66 years (range 26-87 years). MDCT detected pancreatic masses in 258 patients, with a size varying between 6 and 110mm, with a median of 30mm. In 25% of these patients an endoprosthesis was present during analysis with MDCT. The MDCT was followed by EUS in 242 (94%) of the patients with a pancreatic lesion. In 92 (38%) of the 242 patients during EUS an endoprosthesis was present. EUS detected tumours varying between 8 and 95mm, with a median of 30mm. FNA was performed in 143 patients (59% of EUS); in 47% malignant cells were found, in 31% no malignant cells were found, in 15% there were not enough cells for cytological examination and in 7% neuro-endocrine cells were found. Of the 66 patients with not enough cells for cytological examination or no malignant cells, 47 (71%) were found to have a pancreatic malignancy after all by histological examination of the resected specimen, perioperative biopsy in case of unresectability or follow-up. In patients with a pancreatic lesion on MDCT, the overall positive predictive value (PPV) of FNA for malignancy was 100% and the negative predictive value (NPV) 29%.

We identified 32 patients (11%) where MDCT failed to determine the cause of bile obstruction. In 10 of these patients (30%) a biliary endoprosthesis was present during MDCT. All patients with negative MDCT underwent EUS. In one patient EUS was incomplete due to extrinsic compression of the descending part of the duodenum.

In figure 1 a flowchart of the patients with a negative MDCT can be found, showing the results of EUS and the definite diagnosis.

In 15 patients (48%) with a negative MDCT-scan, EUS detected a mass in the pancreatic head with morphological malignant appearance. The tumours varied between 13-45 mm with a median of 20 mm. In 3 of these patients FNA was obtained which showed malignant cells. In figure 2 EUS with FNA of one of these patients is shown.

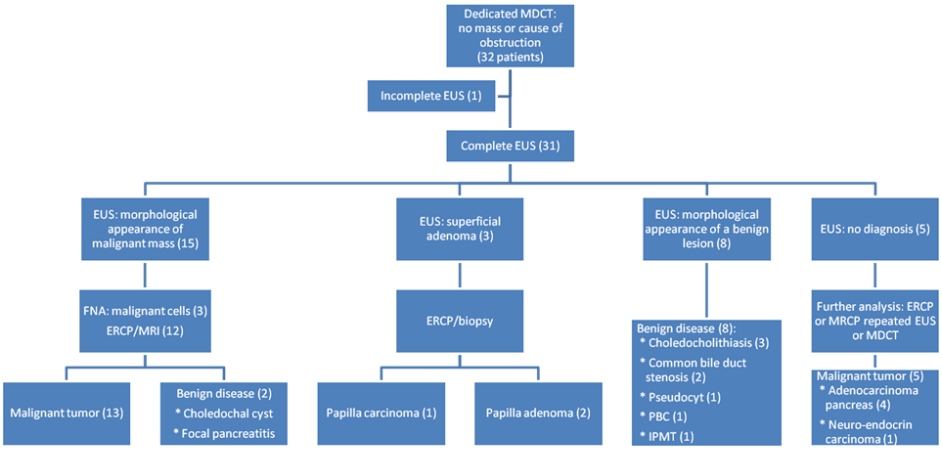

Figure 1 flowchart of patients with a negative MDCT with results of EUS and definite diagnosis

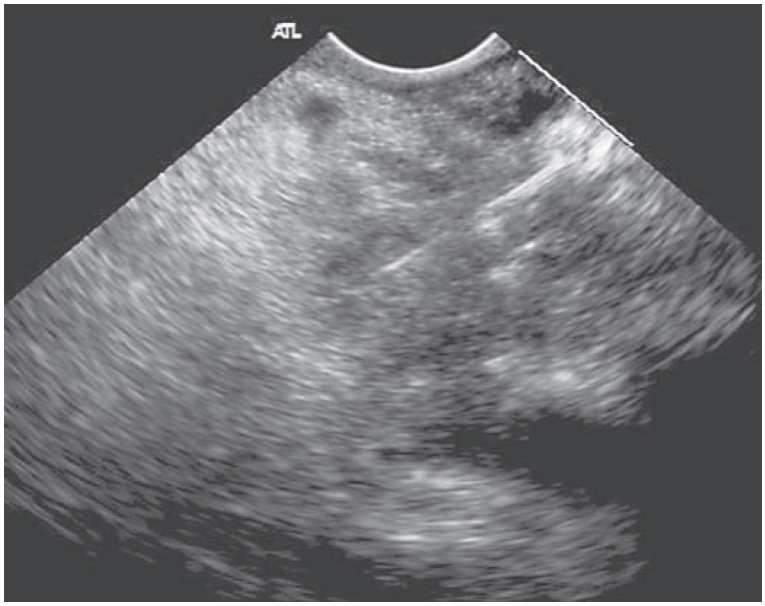

Figure 2: Endoscopic ultrasonography with fine-needle aspiration of a suspected lesion in the pancreatic head of a patient with a negative helical multidetector CT scan

Twelve patients underwent additional imaging with ERCP (with biopsy) and/or MRI to confirm the suspicion of malignancy. In addition 10 patients were found to have a pancreatic malignancy and 2 patients were diagnosed with benign disease (a choledochal cyst and focal pancreatitis). Ten of the 13 patients diagnosed with pancreatic cancer, underwent exploratory surgery: 7 pylorus-preserving pancreaticoduodenectomies (PPPD) were performed, 2 palliative surgery (due to vascular invasion) and in one

patient no resection was performed. Histological examination showed adenocarcinoma in all patients, resected tumours varied in size between 15mm and 40mm. Three patients were considered to be unfit for surgery due to co-morbidity and underwent endoscopic palliative treatment.

EUS: superficial adenoma of the papilla

In 3 patients a papillary tumour without infiltrative growth was found during EUS. FNA was obtained of 2 patients and showed no malignant cells. One patient underwent a PPPD- procedure due to the size of the tumour and one an endoscopic resection. In both patients histological examination showed adenoma. The third patient with a papillary tumour had an endoprosthesis in situ during MDCT and EUS and FNA could not be obtained. The patient underwent ERCP with biopsy that showed malignant cells. A PPPD-procedure was performed and histological examination showed adenoarcinoma (10mm).

EUS: benign cause of the obstruction

EUS found a benign cause of obstruction in 8 patients. In one patient main duct intraductal papillary mucinous tumour (IPMT), based on a dilated pancreatic duct with filling defects and a gaping papilla, was diagnosed. In 2 patients a post-infectious stenosis of the distal common bile duct was found and treated endoscopically. In 3 patients EUS revealed cholelithiasis as the cause of obstruction and with ERCP the stones were extracted. In one patient a pseudocyst was found, for which an expectant policy was followed and in one patient primary biliary cirrhosis (PBC) was diagnosed which was treated with medication. All patients had follow-up of at least six months. The patient with IPMT was not operated due to her age and clinical condition and had follow-up for over 2 years with EUS and MDCT and no signs of malignant behaviour were found.

EUS: no detectable cause of the obstruction

In 5 patients analyzed for painless jaundice with negative MDCT and subsequent negative EUS, clinical follow-up and/or additional imaging revealed a malignant lesion of the pancreatic head. In 3 of those patients an endoprosthesis was present during EUS. In the first patient analysis with EUS showed severe chronic pancreatitis and FNA couldn't be performed due to vascular structures. The patient was treated with an endoprosthesis. Due to significant co-morbidity that precluded surgery no further attempts to establish a definite diagnosis were made. After 3 months abdominal ultrasound showed a pancreatic mass and liver metastasis. Primary analysis of the second patient with MDCT, EUS and MRCP didn't show the cause of obstruction, but signs of pancreatitis were present. Because of the elevated bilirubin an endoprosthesis was placed by ERCP and after 3 weeks the EUS was repeated. During this repeated EUS examination a suspected

malignant lesion of 18 mm in the pancreatic head was seen and FNA was obtained, which showed malignant cells. A PPPD was performed and the pathologic examination showed a T3N1 adenocarcinoma of the pancreatic head of 23mm. The third patient was analyzed for painless jaundice and ERCP was suspicious of a pancreatic mass. Subsequent analysis with MDCT-scan and EUS (both with the biliary endoprosthesis in situ) revealed initially no cause of the stenosis and no mass could be visualized. However, after 6 weeks the MDCT-scan was repeated and an 18 mm suspected malignant, unresectable tumour of the pancreatic head was diagnosed due to encasement of the mesenteric artery. The fourth patient presented with an episode of acute pancreatitis. MDCT-scan after recovery showed a dilated common bile duct and pancreatic duct without a mass. EUS failed to show a mass either, but additional MRI/MRCP after 2 weeks showed a mass peri-ampullary. Subsequent ERCP with biopsy showed neuro-endocrine cells. A PPPD was performed and a 15 mm neuro-endocrine carcinoma with one lymphnode metastasis was found. The fifth patient had obstructive jaundice and was treated with an endoprosthesis. Subsequent MDCT and EUS didn't show a mass or cause of obstruction. ERCP after 1 and 3 weeks for endoprosthesis replacement showed a stenosis of the choledochal duct, but brush cytology and biopsy didn't show malignant cells. A PPPD was performed and the pathologic examination showed a T2N0 adenocarcinoma of the pancreatic head of 19mm.

Overall in our study the accuracy of EUS in determining the cause of obstruction in patients with a negative MDCT was 74%, with a positive predictive value (PPV) of 86% and a negative predictive value (NPV) of 63%.

DISCUSSION

MDCT and EUS are useful and nowadays most often used imaging techniques for diagnosing and staging pancreatic cancer.[4, 10] In the work-up of patients suspected of pancreatic cancer the first step in most centers is MDCT, because of the high sensitivity in detecting pancreatic or peri-ampullary masses and the ability to demonstrated distant metastasis (lung and liver). In our study MDCT failed to clarify the cause of cholestasis in 32 patients (11%) and in 31 patients a complete EUS examination could be performed. After additional imaging, histology and follow-up 19 (61%) of these patients were found to have a pancreatic or peri-ampullary malignancy, thus 12 negative MDCT's were considered to be true negative. In our analysis of the database MDCT has a sensitivity of 93% for detecting the cause of biliary obstruction. This is comparable with other studies that showed a sensitivity of 83-93% for detecting pancreatic masses with MDCT.[4, 6, 8] Of the 19 carcinomas that weren't found with MDCT- scan, 13 (68%) were discovered on initial EUS, which resulted in 8 potentially curative PPPD-procedures. The survival

rate of patients after PPPD for pancreatic malignancies after 3 and 5 year is respectively 10% and 5% for tumours larger than 4 cm and 56% and 40% for tumours smaller than 2 cm.[11] Patients with a histopathological stage I tumour (T1-2N0M0) have a 3 years and 5 years survival rate of respectively 45% and 15-26%,[2, 11] compared to stage II tumours (T3 or N1M0) with a 3 years survival rate of 8% en no survivors after 5 years.[11] Some authors propose that EUS is particularly useful for the detection of smaller tumours (<2cm), but insufficient data are present to support this.[4, 6] In our patients the size of the detected tumours between EUS and MDCT-scan didn't differ. There is also the benefit of EUS to obtain cytology when in doubt about the diagnosis and a mass is visualized. In 3 patients with negative MDCT and a mass on EUS, FNA showed malignant cells. In almost half of all patients with a suspected malignant mass on MDCT and EUS, no malignant cells or not enough cells for cytological examination were obtained. 71% of these patients were found to have a pancreatic malignancy after all by histological examinations and/or follow-up. This emphasizes that a FNA can be a useful in diagnosing malignancy, but that cytology without malignant cells doesn't exclude a malignancy.

In our 31 patients suspected of pancreatic cancer where MDCT fails to demonstrate the cause of obstructive jaundice, EUS identifies 74% of the underlying diseases correctly. EUS has a PPV of 86%, comparable with literature.[4, 6, 8, 10, 12] In 6 patients the malignant tumour was only diagnosed after additional examinations and follow-up, which makes the NPV of EUS in our study 63%, low compared to literature.[6, 8, 13] The low NPV we found is possibly due to factors known to influence the outcome of EUS. In 3 out of 5 patients with a false negative EUS, during EUS a biliary endoprosthesis was in situ. Endoprosthesis are known to influence the outcome of EUS.[7, 14, 15] In one study the NPV of EUS in detecting pancreatic masses decreased from 70% to 21% (P<0,001) when an endoprosthesis was in situ.[6] Other factors known to influence the outcome of EUS are signs of chronic pancreatitis or a recent episode of acute pancreatitis, which were present in 4 of our 5 patients with a false negative EUS.[14, 15] Using EUS as imaging method, chronic pancreatitis makes the detection of pancreatic cancer more difficult and additional analysis with PET-CT might be perfomed.[16] Also a prominent ventral/dorsal split may increase the likelihood of a false negative EUS.[14] Endoprosthesis are also found to lower the sensitivity and NPV of MDCT by alleviating biliary dilatation and producing artifacts that obscure anatomic detail and the assessment of vascular invasion.[16, 17, 18] In our population during analysis with MDCT 26% and during EUS 36% had an endoprosthesis in situ.

So in conclusion, in case of an equivocal MDCT in patients with an obstructive jaunidice the next step should be EUS, because of the high accuracy in detecting pancreatic or peri- ampullary masses and choledocholithiasis. When EUS shows an unresectable tumour or doubt about the diagnosis exists, FNA should be performed. We strongly advise to perform MDCT and EUS before drainage of the biliary tree with an en-

doprosthesis. The presence of a biliary endoprosthesis decreases the value of MDCT and EUS in the detection of pancreatic or peri- ampullary masses. In addition, preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head should only be done after good consideration, because it increases the rate of complications. [19] In case of an uncertain diagnosis after (repeated) MDCT-scan or EUS, additional imaging with ERCP with biopsy and brush should be performed to identify patients with pancreatic or peri-ampullary malignancies. The value of an additional MRI (or MRCP) in patients with an obstructive jaundice without a suspected mass or other cause of obstruction requires further investigation, since the overall detection rate for pancreatic carcinoma is comparable to MDCT.[20-22] MDCT is superior to MRI in assessment of locoregional extension of pancreatic carcinomas, since 3D reformations are excellent to delineate arterial or venous encasement. [23, 24] The superior tissue contrast of MR imaging makes it favourable for the definition of cysts and septations, but suspected benign causes of obstruction preferably need confirmation with cytology of histology. On the basis of detection rate, assessment of loco-regional extension and cost-effectiveness considerations the diagnostic approach to the characterization of solid pancreatic lesions should be performed with MDCT and we suggest the use of MRI when pancreatic findings are equivocal or inconclusive and in case of cystic lesions.

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COMPETING INTERESTS & FUNDING

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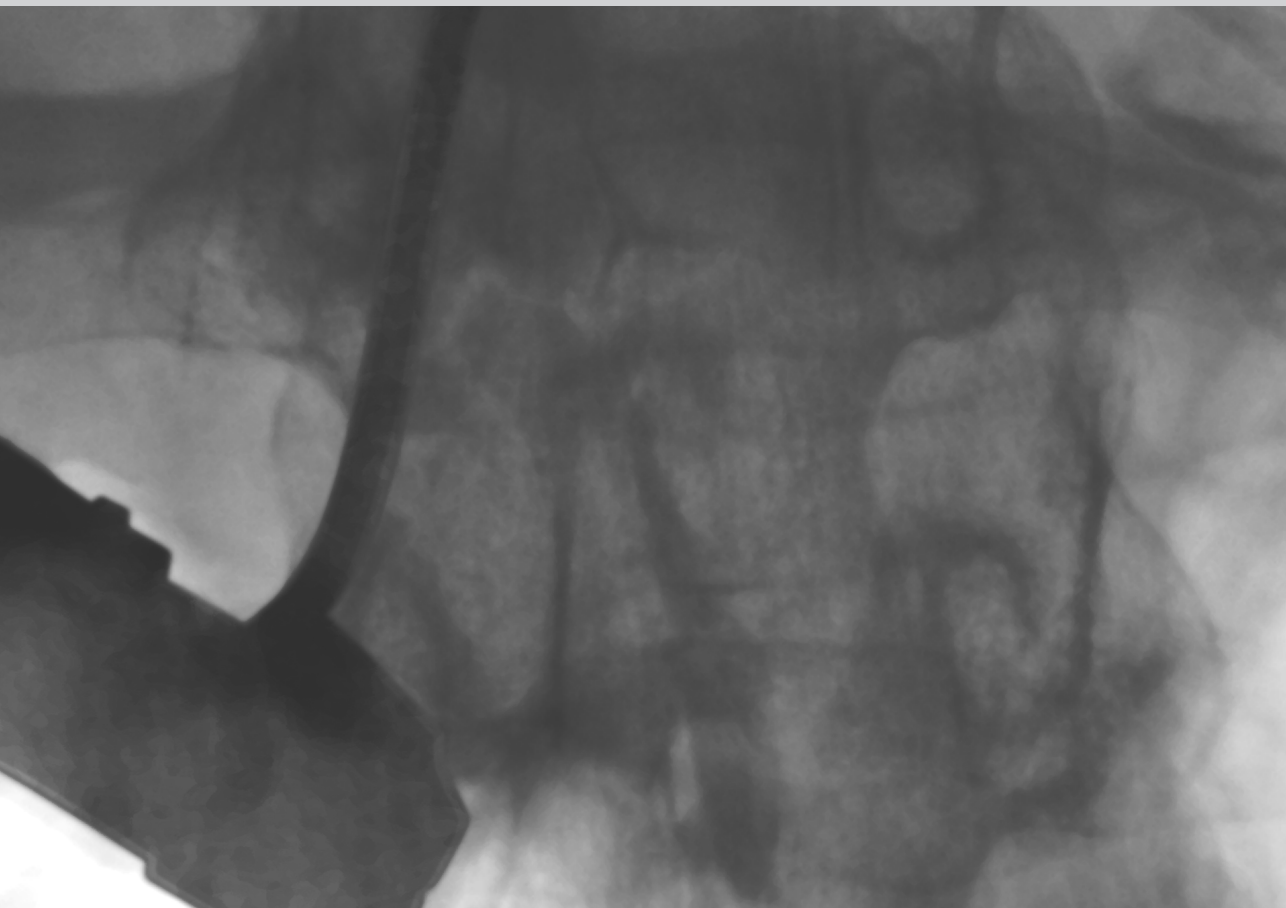
Section 2



EUS from diagnosis to intervention

5

Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study

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INTRODUCTION

EUS is a sensitive method for detecting intra-intestinal and extra-intestinal mass lesions and peri-intestinal lymphadenopathy (1-4). EUS-guided fine needle aspiration (EUS-FNA) has a diagnostic accuracy of 60% to 90% (5-7). Cytological study of the material obtained by FNA allows evaluating cellular findings suggestive of malignancy (anisonucleosis, nuclear membrane irregularity and nuclear enlargement). Unfortunately, inflammation causes a reactive and regenerative process leading to cellular changes, undistinguishable from well-differentiated neoplasia solely based on cytological evaluation. Moreover, certain neoplasm's such as lymphoma and stromal tumors are difficult to diagnose without histological samples, because in these cases tissue architecture and cell morphology are essential for accurate pathological assessment including immunohistochemical analysis (5, 8-10).

Whereas FNA only provides cells, largely disrupted from their original arrangement, larger-caliber cutting needles allow for true biopsy specimens (11-18). These specimens have been obtained by several routes (percutaneous, intraluminal and surgical) (16-22). Safety and accuracy of cutting biopsy have been demonstrated (16, 22-24).

Various EUS-guided techniques have been explored to retrieve tissue specimens, including FNA and Tru-Cut needles, with variable success and complication rates (25-29). Of particular interest is the Quick-Core® needle, designed to operate through an echoendoscope. EUS-guided use of Quick-Core® needle has demonstrated that histological samples representative of the target organs can be obtained safely (30-31). However, there are certain drawbacks with the Quick-Core® needle that restrict its use in clinical practice. Most importantly, its diagnostic yield is strongly limited for lesions located in pancreatic head due to mechanical friction of the needle firing mechanism ensuing from the bended scope position (32-35).

To overcome this limitations a new 19-gauge fine needle biopsy (FNB) device has been designed (Cook Endoscopy Inc (Limerick, Ireland). Aim of the present study was to evaluate the feasibility, yield and diagnostic accuracy of this newly developed needle. Targets included intestinal and extra-intestinal mass lesions and peri-intestinal lymphadenopathy.

MATERIAL AND METHODS

Patients, procedure and examination technique

For this multicenter study, the performance data of a newly designed 19-gauge FNB from five centers (Marseille, Milan, Rotterdam, Rome, and Santiago de Compostela) were pooled. FNB needle was used in consecutive patients referred for EUS-guided tissue ac-

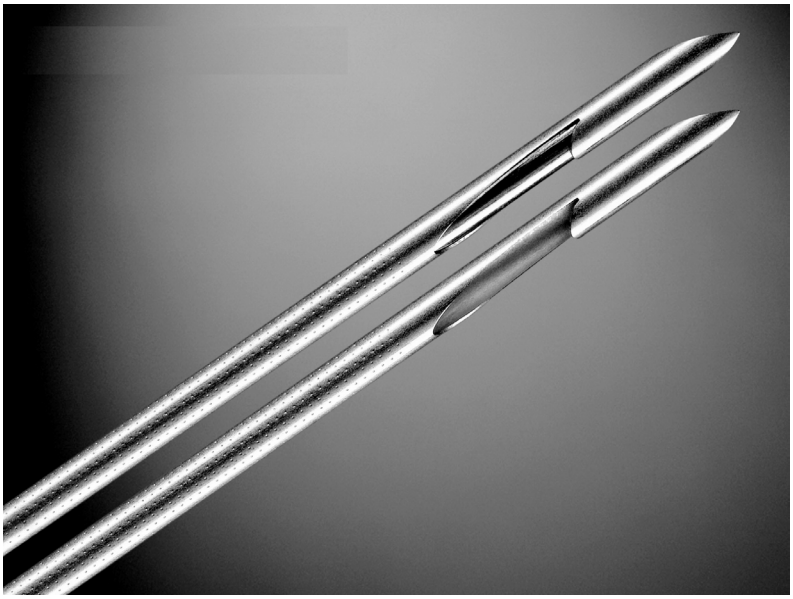

Figure 1: Detailed image of the tip of the new histology needle showing the notch in which the tissue sample is caught during puncture

quisition to evaluate intraintestinal or extraintestinal mass lesions and/or peri-intestinal lymph nodes, between March and July 2010.

EUS-FNB was performed using a convex array echoendoscope (Pentax EG-3870UTK® or Olympus UCT-140®). Tissue acquisition was done with the newly designed 19-gauge Echotip Ultra FNB needle, featuring ProCore reverse bevel technology (Figure 1). The needle is 1.705m long, made of stainless steel with a nitinol stylet. The stylet running through the cannula of the needle is matching the tip bevels. The sheat is 5.2Fr and the reverse bevel length is 4mm. Handle material is Lexan-121, Polystryene & Dynaflex.

Tissue acquisition was done according to a standard protocol but depending on local preference, certain differences were allowed: 1. Puncture with or without stylet, 2. Number of to and fro movements within the lesion (1 versus 3-4), 3. Number of passes (1 versus 2-3), 4. Use of the stylet versus flushing with water to harvest the core sample from the needle. Technical details of the standard tissue acquisition protocol were as follows. After the target lesion was endosonographically visualized and the region scanned for vessels using color and pulsed Doppler, FNB was performed either from duodenum, stomach, esophagus or rectum depending on lesion location. The FNB needle was advanced into the target tissue under endosonographic guidance. Once the lesion was penetrated, the stylet was removed and suction was applied for 10 to 20 seconds using a 10mL syringe while moving the needle to and fro within the lesion either 1 time or 3-4 times. Suction was released before removing the needle. One to three needle passes were performed. Tissue samples were recovered in cytolit and/or formalin by pushing

the stylet through the needle or by flushing the needle with 5cc of saline. All samples were processed at the pathology departments for histological analysis. There was no pathologist present in the endoscopy room and FNB samples were recovered and stored for further processing by the endoscopist. FNB samples in a particular center were evaluated by either one dedicated pathologist with a particular interest and expertise in evaluating tissue materials obtained via EUS or by multiple more general oriented pathologists. Samples were embedded in paraffin. Tissue sections of 3-4μ were stained by the haematoxylin-eosin technique for morphological evaluation and/or different immunohistochemical analysis. If pathologists were not able to obtain a core for histological evaluation, they processed the same material as cellblock for cytological evaluation.

Gold standard reference diagnosis of malignant versus benign disease

A final diagnosis of malignancy or benignancy was made according to either one of the following reference methods: 1) Definite benign or malignant histological diagnosis based on surgical resection specimens from operated patients; 2) Cytology or histology findings with definite proof of malignancy in patients with unresectable tumors according to EUS and CT scan findings and compatible clinical follow-up; 3) Cytology or histology findings without proof of malignancy and a minimum clinical follow-up time of six months.

Outcome parameters

Primary outcome parameter was the percentage of cases in which pathologist classified the quality of the sample as optimal for histological evaluation. Pathologists defined optimal histological sample that one suitable for histological evaluation by means of being able to obtain a real core sample, including recognizable structures of the targeted lesions. Pathologists grade less than optimal those cases in which the sample was suitable for histological evaluation, but without a real core or when the core was fragmented and difficult to be evaluated (36-37). Percentage of cases in which a final histological diagnosis was obtained was also evaluated. Visibility of the needle during the puncture, ease of FNB needle insertion through the scope, ease of FNB needle removal from the scope, ease of removal the stylet after advancement of the FNB needle in the target lesion, and optical impression of the tissue sample obtained after puncture by the endoscopist were also evaluated.

To assess the optimal tissue acquisition protocol, regression analysis was performed including variables such as puncture with or without stylet, number of passes, number of to and fro movements, use of stylet versus water flushing to harvest the core sample, puncture location (duodenal versus the rest), and whether one dedicated pathologist with a particular interest and expertise in evaluating tissue materials obtained via EUS or more generally oriented pathologists were involved in the analysis of the sample.

The study was approved by each local institutional review board and conducted in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines. All patients provided written informed consent to the study.

Data analysis

Results are shown as percentage and 95% confidence interval (CI). Normally distributed variables are presented as mean with standard deviation and range. A descriptive analysis is performed. Results are compared by chi-square test or Fisher's exact test as appropriate. A multivariate stepwise logistic regression analysis was also performed in order to determine variables independently associated to the obtainment of adequate histological specimens. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were also calculated. Because historical information on the performance of FNB needle were not available, formal sample size calculation was not performed. In order to minimize the impact of a potentially insufficient sample size, accuracy data are shown with 95% confidence interval.

RESULTS

109 patients (mean age 60.3±16.5 years, range 16-88, 57 female and 52 male), with 114 lesions (mean size 35.1±18.7 mm) were evaluated. Indications are listed in Table 1.

Table 1. Indications for EUS-FNB from all centers, percentage of adequate histology sampling and percentage of cases with correcti diagnosis

Lesion	No.	Adequate histology sample, no. (%)	Correct diagnosis, no. (%)
Pancreatic tumor	47	45/47 (95.7)	42/47 (89.4)
Mediastinal lymph nodes	17	14/17 (82.3)	14/17 (82.3)
Intraabdominal lymph nodes	14	10/14 (71.4)	11/14 (78.6)
Subepithelial tumor	11	10/11 (90.9)	9/11 (81.8)
Intraabdominal masses	5	4/5 (80.0)	4/5 (80.0)
Lung tumor	4	4/4 (100)	4/4 (100)
Perirectal lesion	4	4/4 (100)	4/4 (100)
Diffuse pancreatic enlargement	3	2/3 (66.7)	2/3 (66.7)
Left adrenal gland mass	3	3/3 (100)	3/3 (100)
Masses adjacent to gut	2	2/2 (100)	2/2 (100)
Gut wall thickening	2	2/2 (100)	2/2 (100)
Paravertebral mass	1	1/1 (100)	0/1 (0)
Mediastinal mass	1	1/1 (100)	1/1 (100)
Total	114	102/114 (89.5)	98/114 (85.9)

When analyzing all 114 cases included in the study, 84 lesions (73.7%) were finally considered as malignant and 30 lesions (26.3%) as benign. Final diagnosis was based on surgical specimens in 21 cases (15 malignant and 6 benign lesions). In 69 cases final diagnosis was based on the cytological or histological findings with definite proof of malignancy. Finally, in 24 cases without proof of malignancy final diagnosis was based on cytology or histology findings and a median follow-up time of 6.6 months (range 6-8).

EUS-FNB was technically feasible in 112 cases (98.24%). According to lesion location, all 79 punctures performed through esophagus, stomach and rectum were successful (100%), while two failures (33/35, 94.28%) occurred when puncture was performed through duodenum. Two failure cases included an intra-abdominal aorto-cava lymph node and a pancreatic head tumor in which removal of the stylet proved impossible.

There were no complications related to the technique.

The FNB device was easy to insert into the scope in all 114 cases (100%). The needle emerged from the scope easily in 93 cases (81.6%), with difficulty in 20 cases (17.5%), and with great difficulty in one case (0.9%). This appeared to be only a problem when punctures were performed through the duodenum with the scope in a bended position (57.1% vs 0%, $p<0.001$). Removing the stylet after puncturing the lesion was easy in 75 cases (65.8%), hard in 21 cases (18.4%), and impossible in 2 cases (1.7%). In 16 cases (14.1%) puncture was performed without stylet. Difficulties in removing the stylet was mainly related to punctures performed through the duodenum (79.1% vs 2.6%, $p<0.001$). The visibility of the needle was judged as optimal in 103 cases (90.3%), while in the remaining 11 cases suboptimal visibility was mainly related to a reduced visibility of the tip of the needle at the site where the notch is located (figure 2).

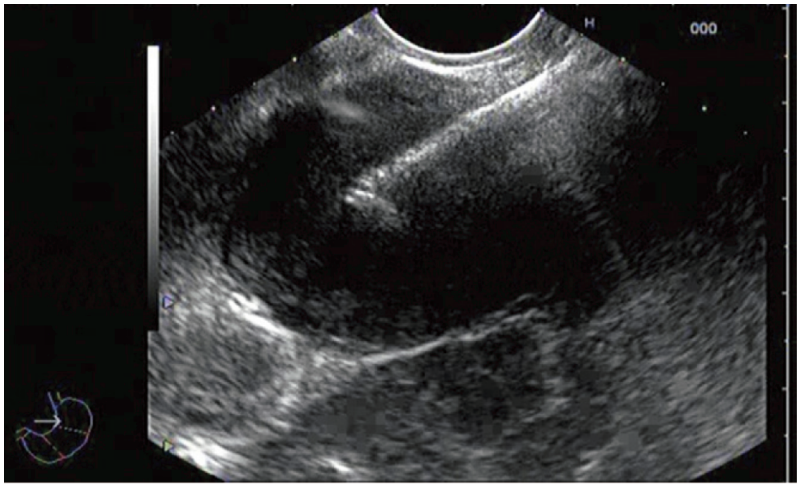

Figure 2: EUS-guided fine-needle biopsy of an intra-abdominal lymph node, corresponding to a lymphoma. The needle and needle tip are well visible.

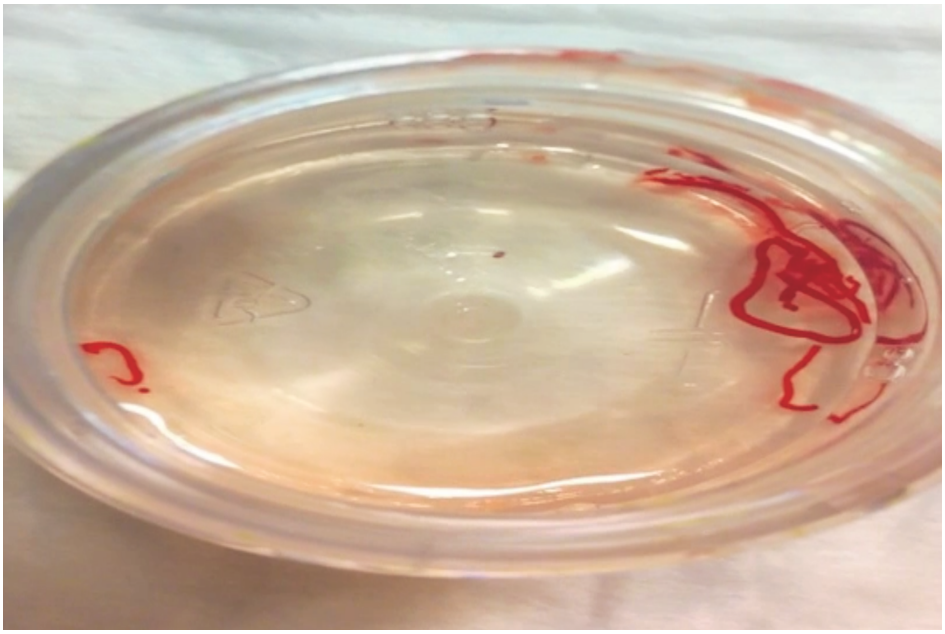

Figure 3: Core sample obtained with EUS-guided fine needle biopsy with the new histology needle after it has been flushed into a tube containing a liquid-based preparation.

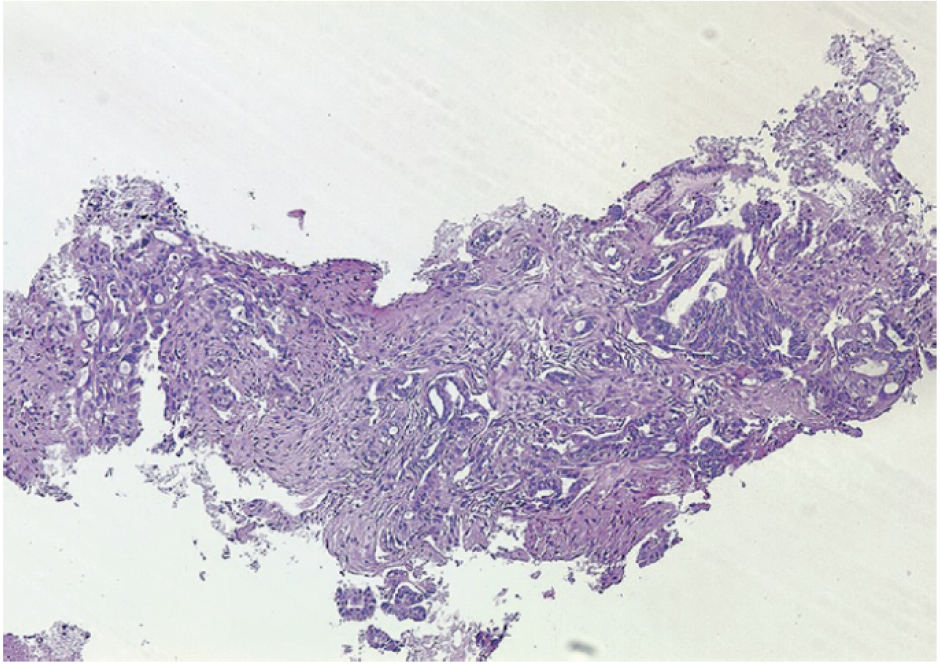

Figure 4: Histological tissue preparation of a pancreatic adenocarcinoma obtained by EUS-guided fine needle biopsy (H&E, orig. mag. X 10)

A sample suitable for pathological evaluation was obtained in 112 lesions (98.24%). When evaluating the sample optically after the needle content was flushed into cytolit and/or formalin, a tissue core could be observed in 78 cases (68.4%) (Figure 3); a tissue core mixed with blood in 15 cases (13.1%), multiple small core fragments in 12 cases (10.5%), only blood in 5 cases (4.4%) and scarce sample in 2 cases (1.75%).

Sample quality according to the pathologist was adequate for full histological assessment in 102 lesions (89.47%) (Table 1) (Figure 4). In the remaining 10 cases the sample was adequate for cytological evaluation (sample was processed as a cellblock).

Regarding the methodology of the procedure, 98 attempts (85.9%) were performed with stylet and 16 (14.1%) without stylet. In 96 punctures (84.2%) 3-4 to and fro needle movements through a lesion were performed and only 1 movement was done in 16 punctures (14.1%). In 89 cases (78.1%) only one needle pass was performed, 2 needle passes in 20 cases (17.5%) and 3 were done in 5 cases (5.3%). In 47 cases (41.2%) the sample was recovered by flushing saline through the needle, in 31 (27.2%) cases by injecting air, and in 34 cases (29.8%) by inserting the stylet through the needle. In 79 cases (69.3%) the sample was analyzed by a dedicated pathologist with extensive experience in evaluating EUS acquired samples, while in 35 cases (30.7%) this was done by pathologists for whom this was not routine.

At univariate analysis the only variable associated with obtaining an optimal sample for histological analysis and making correct final diagnosis was the intervention of an experienced pathologist to evaluate the sample (table 2). In the multivariate stepwise logistic regression analysis this did not change (odds ratio 6.04 (95%CI 1.43-25.53); p=0.014 and odds ratio 3.19 (95%CI 1.01-10.10); p=0.048, respectively).

A final diagnosis was provided in 112 (98.2%) cases, and in 98 (85.96%) this diagnosis proved to be correct according to the gold-standard (97 cases with the histological

Table 2. Univariate analysis of variables associated with obtaining an optimal sample for histological evaluation and obtaining a correct final diagnosis

Variables	Obtaining an optimal sample for histological evaluation OR (95% CI); *P* value	Obtaining a correct final diagnosis OR (95% CI); *P* value
Puncture through duodenum vs other sites	0.38 (0.11 – 1.30); $p = .11$	0.50 (0.17 – 1.48); $p = .21$
Puncture with stylet vs without stylet	0.52 (0.06 – 4.39); $p = .54$	0.36 (0.04 – 3.00); $p = .33$
No. of to-and-fro movements (3-4 vs 1)	0.52 (0.06 – 4.39); $p = .54$	0.36 (0.04 – 3.00); $p = .33$
No. of needle passes (2-3 vs 1)	0.67 (0.17-2.56); $p = .56$	0.51 (0.16-1.66); $p = .26$
Retrieving the sample (air/stylet vs saline solution)	0.43 (0.11-1.71); $p = .22$	0.60 (0.19-1.87); $p = .38$
Dedicated pathologist vs multiple pathologists	5.55 (1.54 – 19.94); $p = .004$	3.56 (1.20-10.53); $p = .02$

OR, Odds ratio; CI, confidence interval

evaluation and one by the cell-block analysis). Table 1 shows the percentage of correct diagnosis. When evaluating the performance of the needle for the detection of malignancy, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 90.2% (95%CI: 83.2-97.3), 100% (95%CI: 98.3-100), 100% (95%CI: 99.3-100), 78.9% (95%CI: 64.7-93.2), and 92.9% (95%CI: 87.6-98.1), respectively.

DISCUSSION

The present study shows that in the majority of cases it is possible to obtain adequate tissue samples for histological evaluation with the use of a newly designed EUS histology needle. The percentage of correct diagnoses reaches 86%, with an overall diagnostic accuracy for the detection of malignancy of 92.9%. The success of this novel technique seems to be dependent on the involvement of a pathologist with experience in handling and dealing with materials obtained by FNA/FNB. Differences in the technique of tissue acquisition did not show statistical significance in the present data set.

In many patients it is essential to obtain a tissue diagnosis to guide treatment. EUS-guided tissue sampling has emerged as a valuable technique for many indications (4). Conventional EUS-FNA has certain limitations. Its sensitivity drops by 10-15% in the absence of an on-site pathologist to evaluate the cellular adequacy of the samples (36). Without on-site evaluation, the recommended number of passes is 5-7 for solid pancreatic lesions and 2-3 for lymph nodes. In pancreatic cases, this necessitates the use of additional needles in 15% of cases, increasing the overall procedural time (9). The lack of cellular arrangement and preserved tissue architecture in cytology samples limits the possibility of making an adequate diagnosis (34). Furthermore, the yield of cytology in certain tumors such as lymphoma, poorly differentiated adenocarcinoma, and stromal tumors is limited; as for adequate diagnosis and subtyping in these cases immunohistochemistry is of pivotal importance. Sensitivity of EUS-FNA is also uniformly poor when used in certain anatomic locations such as thickened gastrointestinal wall or focal intramural lesions (5, 38).

In order to circumvent these problems related to cytological evaluation, several attempts have been undertaken to obtain EUS-guided core tissue specimens for histopathological analysis. Initial efforts were directed towards using large caliber (18-21-gauge) needles (25, 26) or even the standard 22-gauge needle (27). For instance, Binmoeller et al (25) were able to obtain adequate tissue core specimens in 40 out of 45 patients with pancreatic masses by using an 18-gauge needle. However, sensitivity for detection of malignancy was only 53%. On the other hand, Iglesias-Garcia et al (27) were able to obtain an adequate tissue sample for histological diagnosis of pancreatic masses in 95% of patients with a high diagnostic accuracy by recovering the pancre-

atic EUS-FNA specimen into a 10% formol solution by injection of saline through the needle. However, no further studies confirmed these data. Nowadays, the most widely use needle for obtaining histological samples by EUS is the Quick-Core® needle (29), which allows obtaining histological samples safely and being representative of the targeted organs (30, 31, 35). Several nonrandomized retrospective studies have compared sensitivity and diagnostic accuracy of EUS-FNA and EUS-guided biopsy with the Quick-Core® needle. Although biopsy with Quick-Core® needle has no clear advantage over EUS-FNA in terms of overall sensitivity and diagnostic accuracy, it does provide a more specific diagnosis in selected cases (34, 39) requiring less needle passes (29). More recently, combination of EUS-biopsy with Quick-Core® needle and EUS-FNA has shown a higher overall diagnostic yield compare to when each technique is performed alone (40-42). The overall accuracy of EUS-biopsy in these latter studies ranges between 61% and 84%. In our study, using the EUS-FNB needle a sample adequate for full histological evaluation was obtained in about 90% of the evaluated lesions. In the remaining cases, moreover, the collected sample allowed for cytological or cell block analysis.

In cases in which only one needle pass was performed, the overall accuracy of EUS-FNB was 89.6%. It is also noteworthy that such high accuracy rates were obtained from all sorts of lesions. In fact, focusing on some specific cases, we were able to correctly diagnosis and subclassifing different types of lymphomas, subepithelial tumors (GIST vs. leiomyomas), and pancreatic metastasis from different primaries such as colon cancer and lung cancer, and autoimmune pancreatitis. This illustrates the potential benefit and impact on patient management of this novel EUS-FNB device. An important advantage of this device is that overcomes certain shortcomings of Quick-Core® needle. Diagnostic yield of Quick-Core® needle biopsy is strongly limited for lesions that need to be punctured from duodenum, caused by the rigidity of the needle, limiting the degree of the echoendoscope tip deflection required to bring the target lesion into an adequate position for puncture (29, 32, 34, 35). Also, the bended scope position induces considerable friction within the needle firing mechanism that may impair its proper function. With the novel EUS-FNB histology needle, puncturing from a duodenal position was successful in 33 out of 35 cases and was not negatively associated with the sample quality. However, puncturing from a duodenal position was more difficult and in many cases the EUS-FNB needle needed to be pushed out of the scope in stomach before advancing the scope into the duodenum. EUS-FNB through the esophagus, stomach and rectum was easy and uneventful in the remaining 79 cases.

A critical point in the present study is the use and definition of the gold-standard reference method. Ideally, when the pathological results of the EUS-FNB are negative, histological confirmation from surgical specimens would be the gold-standard, which cannot be obtained for ethical reasons in patients in whom surgery is not indicated. In these specific cases, clinical follow-up for at least 6 months with repeated imaging

procedures (EUS and CT) use in our study although not ideal is a well-accepted reference standard.

Safety of EUS-FNA is well established (43) and complication rates range between 1% and 2.5% (44). Small cases series have reported complications rates from EUS-guided Quick-Core® biopsy to range from 2% to 4%, with the largest study showing a complication rate of 2.4% (35). In our present series of 114 cases there were no complications associated to the procedure. Therefore, the use of EUS-FNB needle seems as safe as the standard FNA or Quick-Core® needle.

In conclusion, performing a EUS-guided biopsy with the new histology needle is feasible and safe for histopathology diagnosis of intraintestinal and extraintestinal mass lesions in this consecutive series of patients. It offers the possibility to obtain a core sample for histological evaluation in the majority of cases, with an overall diagnostic accuracy over 85%. From the limited data available, with all the reservations taking into account the design of this study, the observation emerges that a dedicated expert pathologist is likely to have significant impact on final accuracy.

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6

Interobserver agreement among pathologists regarding core tissue specimens obtained with a new endoscopic ultrasound histology needle; a prospective multicentre study in 50 cases

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ABSTRACT

Aim

To evaluate the interobserver agreement among pathologists in grading the quality of specimens obtained with a new 19-gauge endoscopic ultrasound histology needle.

Methods

This multicentre prospective study involved 50 slides prepared using material obtained with the new needle. Five experienced pathologists independently reviewed all of the samples, and made assessments of the following features: the presence of a core, the adequacy of the specimen, the interpretability of the specimen, and the possibility of performing additional analyses using the material. Interobserver agreement, determined by Fleiss' kappa statistic and 95% confidence intervals (CIs), was used as the primary outcome measure.

Results

Overall, the presence of a core was reported in 88% of cases with good agreement among the pathologists (κ= 0.61; 95% CI 0.52–0.70). The specimens were adequate in 91.2% of cases, and Fleiss' κ was 0.73 (95% CI 0.61–0.81). The interpretation of the specimens was reported to be 'easy' in approximately 87% of cases, with moderate agreement among the pathologists (κ = 0.44; 95% CI 0.35–0.53). The possibility of performing additional analyses from the same sample was rated as positive in approximately 91%, with good agreement (κ = 0.66; 95% CI 0.58–0.75).

Conclusions

There was excellent interobserver agreement among pathologists in the assessment of the histological material, especially with regard to sample adequacy.

INTRODUCTION

Endoscopic ultrasound (EUS) is an established method for detecting intraintestinal and extraintestinal mass lesions and peri-intestinal lymphadenopathy.[1–4]

The diagnostic yield of EUS-guided biopsies depends on the characteristics of target tissues and technical factors, such as type of needle used, biopsy technique, and sample processing method. Other important factors include expertise and clinical interaction among endosonographers and pathologists; this is particularly facilitated by on-site interpretation, which significantly increases the diagnostic yield of EUS-guided fine needle aspiration (FNA).[5, 6] However, depending on logistics and costs, rapid on-site cytopathology is not universally available, and, in addition, the yield of cytology in certain tumours, such as lymphoma, well-differentiated adenocarcinoma, and stromal tumours, is limited, because in these cases the diagnostic workup frequently requires immunophenotypic and molecular studies.[7–10]

Because of these inherent limitations of cytology, there has been increasing interest in histological sampling using needles of a larger calibre. Various EUS- guided techniques have been explored for the retrieval of tissue specimens, including FNA and Tru-Cut needles, with variable rates of success and complications.[11–16]

A new 19-gauge fine needle biopsy (FNB) device has recently become available (EchoTip ProCore nee- dle; Cook Endoscopy Inc, Limerick, Ireland). We have recently published a multicentre study assessing the feasibility and diagnostic accuracy of this newly developed EUS 19-gauge histology needle. The study found that this was an easy and reliable method for obtaining histological samples of both pancreatic and non-pancreatic lesions, with an overall accuracy of 86% with only one needle pass.[17]

One of the key factors in obtaining consistent diagnostic accuracy using this technique is the involvement of a dedicated gastrointestinal pathologist with experience in handling and dealing with materials obtained by FNA.[15] However, the reproducibility of these results and the interobserver variation among pathologists remain unclear.

The aim of this study was to evaluate the interobserver agreement among gastrointestinal pathologists in grading the quality of specimens obtained using the new EUS histology needle. Samples from intraintestinal and extraintestinal mass lesions and peri-intestinal lymphadenopathy were eligible for this study.

MATERIALS AND METHODS

For this multicentre study, 50 histological slides obtained with the ProCore needle from five centres (Marseille, Milan, Rome, Rotterdam, and Santiago de Compostela) were pooled. The study was approved by each local institutional review board. Be-

cause no direct intervention was made in these patients, informed consent was not mandatory.

Between September and December 2010, the ProCore needle was used in consecutive patients referred for EUS-guided tissue acquisition to evaluate intraintestinal or extraintestinal mass lesions and/or peri-intestinal lymph nodes.

EUS technique and specimen processing

EUS-guided FNB was performed using a convex array echoendoscope (Pentax EG-3870UTK or Olympus UCT-140/180). All procedures were performed by experienced endosonographers, and only one pass was performed.

Tissue acquisition was performed according to a standard protocol, so that each centre used the same technique: after the target lesion had been endosonographically visualized, and the region had been scanned for vessels by the use of colour and pulsed Doppler, FNB with the 19-gauge ProCore needle was performed, from the duodenum, stomach, oesophagus, or rectum, depending on lesion location. The FNB needle was advanced into the target tissue under endosonographic guidance. Once the lesion had been penetrated, the stylet was removed, and suction was applied with a 10-ml

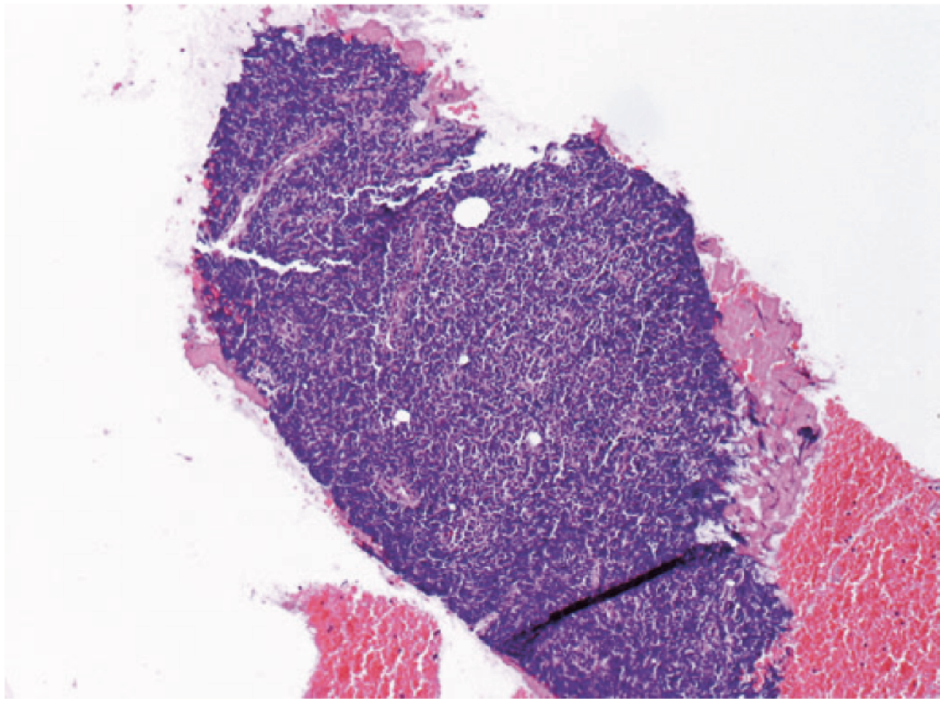

Figure 1. A tissue core fragment obtained using the ProCore 19-gauge needle, with a dense lymphoid infiltrate. This fragment allowed complete immunophenotypic and molecular evaluation, with a final diagnosis of T-cell lymphoma.

syringe. The needle was kept still for approximately 10 s, and was then moved to and fro within the lesion three times. Suction was released before removal of the needle. Tissue samples were recovered in CytoLyt and/or formalin by flushing the needle with 5 ml of saline solution. All samples were processed at the pathology departments for histological analysis, and in each centre were assessed by one dedicated pathologist with a particular interest in evaluating tissue materials obtained via EUS; all of the pathologists worked in academic referral centres. Samples were embedded in paraffin following arrival at the pathology laboratory, and tissue sections of 3–4 micrometers were stained with haematoxylin and eosin for morphological evaluation.

Study definition

To assess interobserver agreement in analysing specimen quality, the pathologists from the five European centres met together (C.D., K.B., G.M., I.A., and G.R.), each of them bringing the slides from 10 consecutive cases performed in his or her own centre. Each pathologist, independently and blinded to the final diagnosis, made assessments for the following features: the presence of a tissue core, the adequacy and interpretability of the specimen, and the possibility of performing additional analyses on the acquired material, such as immunohistochemistry and fluorescence in-situ hybridization. For each specimen, each pathologist received a structured, predefined worksheet to record all relevant data.

The adequacy of the specimen for diagnosis was defined as the clear presence of target organ cells that allowed the pathologist to obtain an accurate diagnosis. The interpretation of the specimen was judged as easy or not easy, taking into account the percentage of pathological tissue as compared with the rest of the material on each slide. To quantify this, we considered three different classes: < 50% of pathological tissue (class 0), between 50% and exactly 70% (class 1), and >70% (class 2).

Each pathologist, in turn, showed his or her own specimens at the microscope (10 non-selected cases from each centre, numbered from 1 to 10). The microscope room was equipped to allow simultaneous visualization of each slide from different observer positions by multiple investigators, to allow independent reviewing and scoring. Each reviewer was provided with the target organ site, but no other clinical information was given. The histological slides were then independently reviewed by five pathologists who were blinded to the identity of the patient and the final diagnosis.

After all worksheets had been completed, the data were collected and analysed by an endosonographer and a statistician not involved in the evaluation of the slides (M.C.P. and M.B.).

Statistics

Results obtained from different pathologists and different centres were compared by use of Pearson's chi-square test, in order to evaluate possible systematic differences (Table 1).

Interobserver agreement was determined by the use of kappa statistics [Fleiss' κ-statistic and 95% confidence intervals (CIs)]. κ -Statistics are widely used and accepted coefficients that provide a measure of observer agreement, accounting for agreement other than that which occurs by chance alone. κ -Statistics were interpreted according to the convention of Landis and Koch[18]: <0, no agreement; 0–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.0, almost perfect agreement. Statistical significance was established as $P < 0.05$ (two-tailed). All analyses were carried out using STATA version 11.0 (Stata Corp., Austin, TX, USA).

Table 1. Rates for tissue cores, sample adequacy and interpretation analysed separately for each of five pathologists, with *p*-values and κ-statistics.

	Pathologist						
	A	B	C	D	E	*p*-value	Agreement κ (95% CI)
Presence of core (%)	92	88	90	76	92	0.08	0.61 (0.52-0.70)
Slide adequacy (%)	94	92	92	88	90	0.86	0.73 (0.61-0.81)
Interpretation easy (%)	94	86	84	80	90	0.27	0.44 (0.35-0.53)
Further techniques (%)	88	94	86	96	90	0.39	0.66 (0.58-0.75)

CI, confidence interval

RESULTS

A total of 50 cases were reviewed by five experienced pathologists: 23 samples were from the pancreas, 15 from lymph nodes, seven from submucosal lesions, two from abdominal masses, one from the adrenal gland, one from a mediastinal mass, and one from a peritoneal nodule.

Overall, the presence of a tissue core (Figure 1) was reported in 88% of cases, with good agreement among the pathologists ($\kappa = 0.61$; 95% CI 0.52– 0.70). We considered whether the percentage of slides with a core differed across observers, but we did not find a significant difference ($P = 0.08$).

The specimens were adequate in 91.2% of cases. Specimen adequacy did not significantly differ among pathologists ($P = 0.86$), and Fleiss' κ was 0.73 (95% CI 0.61–0.81).

For pancreatic specimens, the presence of the core and the sample adequacy were significantly better for masses obtained from the stomach and the bulb than for lesions obtained from the second part of the duodenum (95.6% versus 71%, $P = 0.003$, and

100% versus 65.5%, P = 0.001, respectively). Agreement among pathologists for pancreatic specimens was almost perfect (κ = 0.81; 95% CI 0.68–0.94).

When pancreatic specimens were compared with all other specimens (mostly lymph nodes and submucosal lesions), there was no significant difference regarding the presence of a tissue core (P = 0.09), but the sample adequacy of non-pancreatic lesions was significantly better (P = 0.001). The interpretation of the specimens was reported as 'easy' in approximately 87% of cases, with moderate agreement among the pathologists (κ = 0.44; 95% CI 0.35–0.53). The interpretation of pancreatic specimens was judged as 'easy' in approximately 84% of cases, and there was no significant difference among the observers (P = 0.6).

Rates for tissue cores, sample adequacy and interpretation, analysed separately for each of five pathologists, with P-values and κ -statistics, are reported in Table 1.

Overall, the possibility of performing additional analyses from the same sample, such as immunohis- tochemistry or fluorescence in-situ hybridization, was rated as positive in approximately 91% of samples, with good agreement among pathologists (κ = 0.66; 95% CI 0.58–0.75).

In analysis of the percentage of pathological tissue reported by the observers, 69% of samples were in class 2 (>70% of pathological tissue), 27% were in class 0 (<50%), and 4% were in class 1 (between 50% and 70%). The relationship between pathological tissue percentage and specimen adequacy is reported in Table 2. We observed a significant correlation between the amount of tissue and the percentage of specimens judged as adequate for diagnosis (P = 0.001).

Table 2. Relationships between different classes of pathological tissue and specimen adequacy (1, adequate; 0, not adequate).

Pathological tissue class	Adequacy		
	0	1	Total
0 (≤ 50%)	19 (90.48)	48 (21.24)	67 (27.13)
1 (>50% and ≤ 70%)	0 (0.00)	10 (4.42)	10 (4.05)
2 (>70%)	2 (9.52)	168 (74.34)	170 (68.83)
Total	21 (100)	226 (100)	247 (100)

Data are given as n (%)

DISCUSSION

To our knowledge, this is the first study reporting on interobserver reproducibility among pathologists in evaluating the quality of specimens obtained through EUS with a needle of large calibre. We found that this new EUS histology needle provides histological samples that are adequate for diagnosis in the majority of cases (91.2%). The

reproducibility among five expert pathologists in the assessment of the adequacy was good (κ = 0.73), regardless of the characteristics of the target lesion sampled.

In a recently published multicentre study, we assessed the feasibility and diagnostic accuracy of this newly developed EUS 19-gauge histology needle, and reported an easy and reliable way of obtaining histological samples of both pancreatic and non-pancreatic lesions with an overall accuracy of 86% with only one needle pass.[17] In a multivariate analysis of our data, the only variable associated with obtaining an optimal sample for histological analysis and making a correct final diagnosis was the intervention of an experienced dedicated pathologist to evaluate the sample as compared with a general pathologist. Since the role of the pathologist appears to be pivotal in the interpretation and usability of this tissue acquisition method, the goal of the current study was to evaluate the reproducibility of interpretation and perceived adequacy of the specimens obtained using the newly designed needle. Only two studies in the literature have analysed the reproducibility of cytopathological diagnosis of specimens obtained with EUS-guided FNA, and both documented good diagnostic agreement between experienced cytopathologists for samples from mediastinal lymph nodes and mass lesions.[19,20]

For this study, each pathologist contributed slides of 10 consecutive patients. Consequently, we cannot completely exclude the possibility that pathologists could recall their own slides, thereby introducing a potential bias. The effect of this theoretical bias on overall agreement should have been towards the null value (decreasing overall interobserver agreement: in fact, a pathologist not completely blinded with respect to his or her own slides could have a lower level of agreement with all other colleagues). A sensitivity analysis repeating the κ calculation, excluding data given by each pathologist when analysing his or her own slides, was performed, and the results did not change significantly (data shown in Table 3).

Our study included a large percentage of pancreatic lesions (44%), followed by lymph nodes (30%) and submucosal lesions (14%). This is of interest, because the differential diagnosis of pancreatic masses is a frequent clinical dilemma, and the cytopathological

Table 3. Rates for tissue cores, sample adequacy and interpretation analysed separately for each of five pathologists, with *p*-values and κ-statistics, excluding data given by each pathologist when analysing his or her own slides (total number in the table = 200).

	Pathologist						
	A	B	C	D	E	*p*-value	Agreement κ (95% CI)
Presence of core (%)	90	92	90	75	90	0.06	0.59 (0.48-0.70)
Slide adequacy (%)	92	100	90	85	87	0.16	0.67 (0.56-0.79)
Interpretation easy	92	90	82	75	92	0.09	0.40 (0.29-0.51)
Further techniques	85	97	82	95	90	0.12	0.70 (0.59-0.82)

CI, confidence interval

interpretation of pancreatic lesions is considered by pathologists to be challenging, especially for well-differentiated carcinoma and those with extensive necrosis. Moreover, there are lesions that can show features of both reactive and malignant conditions, and, although ductal adenocarcinoma is the most frequent cause of pancreatic masses, other neoplasms with different prognoses and treatment options can arise not infrequently within the pancreas. For this reason, we separately analysed pancreatic samples, but we did not find any significant difference among pathologists in grading adequacy ($P = 0.92$), the presence of a core ($P = 0.2$), or interpretation ($P = 0.6$); perhaps even more importantly, the evaluation of the adequacy of pancreatic specimens showed the best agreement among observers ($\kappa = 0.81$), proving that the needle provided reliable tissue sampling even in pancreatic masses.

In our study, the adequacy of the specimens significantly improved when the percentage of pathological tissue increased, and although this is not synonymous with obtaining more material, it seems very likely that, for the evaluation of histological material, more is actually better.

The ability to routinely apply additional techniques, such as immunohistochemistry or fluorescence in-situ hybridization, on the same material will very likely become increasingly important in the near future. Recent advances in molecular diagnostic techniques have made it possible to carry out various types of immunostaining and gene analysis with a small amount of specimen obtained by EUS-guided FNB.[21] It seems very likely that medical oncologists will demand a histological specimen of a tumour, especially in the era of neoadjuvant treatment, to further tailor and individualize therapy for a specific patient.

The results of our study are based on the judgement of five highly experienced pathologists in the assessment of this type of sample: this is a potential limitation of this study, because this does not necessarily represent everyday clinical practice in many community hospitals. In the future, it would be of interest to evaluate the interobserver agreement among more generally oriented pathologists.

In conclusion, this study shows that the new EchoTip ProCore needle not only consistently provides endosonographers and pathologists with adequate histological material, but also guarantees excellent interobserver agreement between pathologists regarding sample adequacy. These results are particularly encouraging, given that samples were largely obtained from lesions in challenging locations, including pancreatic head tumours, with only one needle pass.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Rate of tissue cores, sample adequacy and interpretation analyzed separately for each of 5 pathologists with p value and K statistic, excluding data given by each pathologist when analyzing their own slides (total number in the table = 200).

7

Therapeutic endosonography

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INTRODUCTION

Indications to perform endoscopic ultrasonography (EUS) have changed dramatically with the introduction of curvilinear-array echoendoscopes. From a solely observational diagnostic tool, EUS has turned into an advanced interventional technique offering the possibility to not only acquire tissue samples by means of fine needle aspiration (FNA), but also to introduce for example drugs by fine needle injection (FNI). In addition, various accessories such as radio-opaque fiducials or guidewires can be advanced through a needle into a target structure or lesion. Using such guidewires placed under EUS guidance, advanced types of cyst, biliary, and pancreatic drainage procedures can be carried out. In this chapter, indications and techniques of advanced interventional therapeutic endosonography will be discussed.

EQUIPMENT

Therapeutic endosonography became possible by the introduction of curvilinear-array echoendoscopes in which the EUS image is parallel to the working channel, allowing instruments to be passed in the same plane under real-time ultrasonographic (US) guidance. Table 1 provides an overview of the presently available curvilinear-array echoendoscopes along with some of their most important features. To facilitate manipulation of FNA needles or other devices, curvilinear array echoendoscopes, alike side-viewing ERCP endoscopes, have an elevator. The working channels of curvilinear-array echoendoscopes are as large as 3,8 mm to allow passage of accessories up to 10 Fr. Image resolution and penetration depth of the US image are inversely related and depended on the frequency; the higher the frequency, the higher the image resolution, but the lower the penetration depth (approximately 2 cm), the lower the frequency,

Table 1. Presently commercially available electronic curvilinear array echoendoscopes

Instrument	US scan angle	Frequency (MHz)	Tip diameter (mm)	Insertion tube (mm)	Channel (mm)	Video: Field of view / direction	Tip deflection: up/down
Olympus							
GF-UC140(P)-AL5	180°	5, 6, 7.5, 10	14.6 (14.2)	12.8 (11.8)	3.7 (2.8)	100° / 55° forward oblique	130° / 90°
GF-UC160(P)-OL5	150°	7.5	14.6 (14.2)	12.6 (11.8)	3.7 (2.8)	100° / 55° forward oblique	130° / 90°
Pentax Medical							
EG-3870UTK	120°	5, 7.5, 10	12.8	12.8	3.8	120° / 50° forward oblique	130° / 130°

the lower the image resolution, but the higher the penetration depth (approximately 7 cm). With the exception of a prototype forward scanning curvilinear-array echoendoscopes (XGiF-UCT160) [1], all devices have endoscopic video imaging oblique to the shaft. Curvilinear-array echoendoscopes, alike radial devices, have a separate channel to allow for water inflation of a disposable balloon mounted on the tip of the instrument. This water-filled balloon improves acoustic coupling for transmission of US waves through the gastrointestinal wall. However, because acoustic coupling can also be achieved by gently maneuvering the transducer onto the mucosa, many endosonographists do not use a balloon when using a curvilinear-array echoendoscopes. There is a variety of EUS accessories including FNA needles in three different sizes (25, 22, and 19-gauge). For interventional EUS purposes a 22-gauge needle may suffice in cases in which non-viscous fluids are to be injected. In other cases, and more in particular in circumstances in which a guidewire or fiducials are to be introduced, a 19-gauge needle is mandatory. For EUS-guided celiac plexus neurolysis a special 20-gauge needle device has been developed (Cook Endoscopy, Winston-Salem, USA).

EUS-GUIDED CELIAC PLEXUS NEUROLYSIS

In a recent meta-analysis by Yan and co-workers of five randomized controlled studies with a total of 302 patients, a disappointing effect of percutaneous or intraoperative celiac plexus neurolysis (CPN) on pain management was shown [2]. There was a statistically significant difference in pain scores in favor of CPN, albeit with minimal clinical significance. The weighted mean difference in pain scores between both conventional treatment (analgesics) and CPN was only 6%. In light of this disappointing clinical effect, it has been suggested that the limited efficacy of percutaneous CPN may be caused by inadequate targeting of alcohol injection at the site of the celiac plexus. In 1996, Wiersema and co-workers introduced a new and possibly more effective technique to carry out a celiac plexus neurolysis (CPN) under EUS-guidance [3]. In this technique, a puncture needle is inserted through the dorsal stomach wall under real-time EUS guidance, immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk (figure 1). Once the needle is positioned 3 to 5 ml of bupivacaine (0.25%) is injected for local anaesthesia followed by 10 ml pure alcohol (96%). This is then repeated at the opposite site. Some prefer not to inject bilaterally, but inject in the midline anteriorly to the celiac trunk. There are no data available showing that either one of these techniques is superior. The EUS-guided approach is considered safer than the traditional percutaneous approach because of its close approximation to the celiac trunk avoiding puncturing a needle alongside the spine or through intra-abdominal organs.

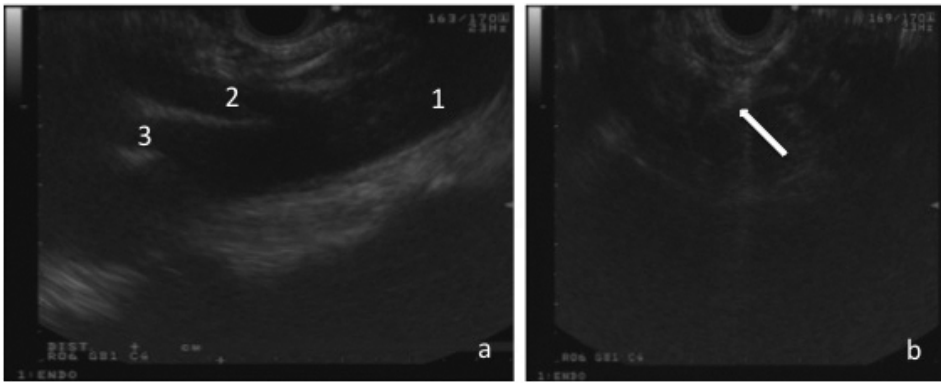

Figure 1. EUS- guided celiac plexus neurolysis.
1a 1. abdominal aorta, 2: celiac trunk, 3: superior mesenteric artery. The celiac trunk is visualized by tracing the aorta as the first vessel that braches of the vessel below the diaphragm. The needle (white arrow) is advanced just above the celiac trunk. **1b.** Scope is torqued a few degrees laterally and the needle (white arrow) is advanced further alongside the celiac trunk. Once alcohol injection starts, the image gets blurred. This procedure is repeated at the other side.

No studies have been published comparing percutaneous CPN with EUS-guided CPN, nor any controlled randomized trials comparing EUS-guided CPN with conventional opioid treatment. EUS-guided CPN has been utilized in patients with painful chronic pancreatitis and patients with oncologic type pain due to inoperable pancreatic carcinoma. For the latter indication, two prospective cohort studies have been published. Gunaratnam and co-workers performed a study in 58 patients of whom 78% experienced a decline in pain scores after the EUS-guided CPN [4]. This effect lasted for 24 weeks when adjusted for morphine use and adjuvant therapy. Five patients experienced procedure-related transient abdominal pain. No major complications were seen. In the second prospective study performed by Wiersema and co-workers, 30 patients (pancreatic carcinoma n=25, intra-abdominal metastases n=5) underwent EUS-guided CPN [3]. Pain scores were significantly lower compared with baseline scores at 2, 4, 8, and 12 weeks after EUS-CPN. At these follow-up intervals, 82% to 91% of patients required the same or less pain medication than at baseline and 79% to 88% of patients had persistent improvement in their pain score. Complications were minor and consisted of transient diarrhea in four patients. Recently, Levy and co-workers showed that celiac ganglia can be visualized at EUS [5]. Ganglia were typically seen between the celiac trunk and the left adrenal being hypoechoic, oblong or common shaped, often with an irregular edge, and often containing a hyperechoic focus or strands. There size ranged from 2 by 3 mm to 7 by 20 mm. The total number of ganglia in patients ranged between 1 and 4 and more than 1 ganglion was seen in 5 out of 9 patients. The authors speculated that direct targeting of these ganglia might improve the efficacy of the EUS-guided CPN. Whether such an approach would be feasible and leads to an improved outcome with respect

to pain control remains to be proved. Recently, Gleeson and co-workers prospectively showed that in a series of 200 patients celiac ganglia were identified in 81% of cases, typically located to the left of the celiac artery, anterior to the aorta [6]. Future studies should address questions such as whether EUS-guided CPN is superior to conventional medical treatment and percutaneous CPN and whether direct EUS-guided targeting of celiac ganglia has additional treatment benefits.

EUS GUIDED FNI IN TREATMENT OF PANCREATIC CANCER

Based up on the safety and feasibility profile of FNA and experiences with EUS-guided CPN, FNI has gradually matured and expanded the indication for interventional EUS even further. At present, EUS FNI for intratumoral pancreatic cancer therapy involves antitumoral agents, immunotherapy, and ablative techniques. In the past years a number of studies have been published with different agents injected by EUS-FNI in pancreatic tumors including lymphocyte cultures (Cytoimplant) [7], viral vectors (TNFerade) [8, 9], and oncolytic viruses (ONYX-015) [10].

Chang and co-workers performed a phase 1 trial in which EUS-FNI intratumoral injections of activated alogenic mixed lymphocyte culture (Cytoimplant) were given in 8 patients with unresectable pancreatic cancer [7]. Various doses were given by a single injection. There were no procedure related complications, but grade 3 and 4 toxicities occurred in 7 patients, the most frequent one being fever. All toxicities were reversible. On follow-up investigations by computed tomography there was a partial response in two, minimal response in 1, stable disease in 3, and progression of disease in 2 patients. A randomized trial comparing Cytoimplant with gemcitabine was started, but is currently not recruiting patients. Apparently, the study was stopped prematurely due to a worse outcome in the Cytoimplant group, but results have not been published yet.

TNFerade is a replication deficient adenovirus vector that incorporates the human tumor necrosis factor alpha gene which is regulated by a radiation inducible promoter (Egr-1). Animal data in mice provide rational for local delivery of human tumor necrosis factor alpha in which a host dependant response(s) for TNFerade was found on primary lesion as well as lymph node metastasis [11]. Farrell and co-workers conducted a phase I/II multicenter trial in which TNFerade is injected intratumorally by EUS-FNI, computed tomography, or percutaneous ultrasound guidance (PUG) in combination with continuous intravenous infusion of 5-fluorouracil (200 mg/m^2/day, 5 days per week) and radiotherapy (50 Gy) [8]. Preliminary data on 50 patients of which 27 had delivery by EUS-FNI and 23 had delivery by PUG did not show significant differences in treatment response based on the route of delivery. A partial response was seen in 13% versus 10% and stabilization in 73% versus 75% of patients, respectively. Dose limiting toxicity was

seen in 3 patients after EUS-FNI, with pancreatitis in two and biliary obstruction in one. Meanwhile a multicenter phase II/III trial is carried out in which patients with unresectable pancreatic adenocarcinoma are randomized to be treated according Standard Of Care (SOC) therapy alone or TNFerade with SOC. Final results are eagerly awaited with an interim analysis showing a trend towards an improvement of one-year and overall survival with TNFerade [9].

ONYX-015 (Onyx Pharmaceuticals,USA) is an oncolytic attenuated adenovirus modified selectively to replicate in and kill cells that harbor p53 mutations. Hecht and co-workers undertook a trial of the feasibility, tolerability, and efficacy of EUS injection of ONYX-015 into unresectable pancreatic carcinomas [10]. Twenty-one patients with locally advanced adenocarcinoma of the pancreas or with metastatic disease, but minimal or absent liver metastases, underwent eight sessions of ONYX-015 delivered by EUS injection into the primary pancreatic tumor over 8 weeks. The final four treatments were given in combination with gemcitabine. After combination therapy, 2 patients had partial regressions of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease or had to go off study because of treatment toxicity. No clinical pancreatitis occurred despite mild, transient elevations in lipase in a minority of patients. Two patients had sepsis before the institution of prophylactic oral antibiotics. Two patients had duodenal perforations from the rigid endoscope tip. No perforations occurred after the protocol was changed to transgastric injections only.

There are two orphan techniques which are not so much 'fine needle injection' procedures but comprise of 'fine needle introduction' of an accessory device aimed to destroy the tumor mass. One of these techniques is EUS guided radiofrequency ablation which has been tested some years ago in a pig model [12]. Although complications were relatively mild and pathology showed a well demarcated acute coagulation zone of 8 to 10 mm in all specimens, no subsequent (human) trials have been undertaken to further explore the use of this technique. The same holds true for yet another experimental technique, EUS guided photodynamic therapy, in which tumor damage is induced by photochemical tissue necrosis after intravenous administration of a photodynamic agent. This was also tested in a pig model [13]. Three pigs were pretreated with porfimer sodium. Next, a laser fiber with a 1 cm cylindrical light diffuser was passed through a 19 G needle into the liver, kidney, spleen, and pancreas. Energy was delivered to a total of 50 joules of 630 nm over 125 sec. There were no procedure related complications. Pathology review showed areas of necrosis of approximately 3.5 mm2 with some hemorrhage and granulation tissue.

Despite initial excitement about the technical feasibility of EUS-guided FNI to treat pancreatic cancer, this technique has not yet become a mainstream indication for EUS. This is primarily due to difficulties in developing effective drugs for intratumoral injections, but progress in this area is eagerly awaited and expected the coming years.

EUS-GUIDED IMPLANTATION OF RADIO-OPAQUE MARKERS (FIDUCIALS)

With the ongoing developments of radiotherapy, and more in particular the utility of multiple narrow beams stereotactic radiosurgery to deliver very high single radiation doses to treat tumors more effectively, the issue of safety in relation to accurate targeting of the radiation beam has become an important issue. For this purpose these radiotherapy delivery systems use real time imaging guidance [14]. In some instances, like for example brain tumors, anatomical landmarks such as bony structures in the skull serve as a reference point, but for soft tissue tumors in areas like the chest or the abdomen this does not suffice. In these cases the implantation of radiographic markers, or so-called fiducials, has shown to be a valuable alternative [15]. Traditionally these fiducials were implanted surgically or percutaneously under ultrasonographic or CT guidance X [16]. Since surgery is invasive and some lesions are difficult to access per-

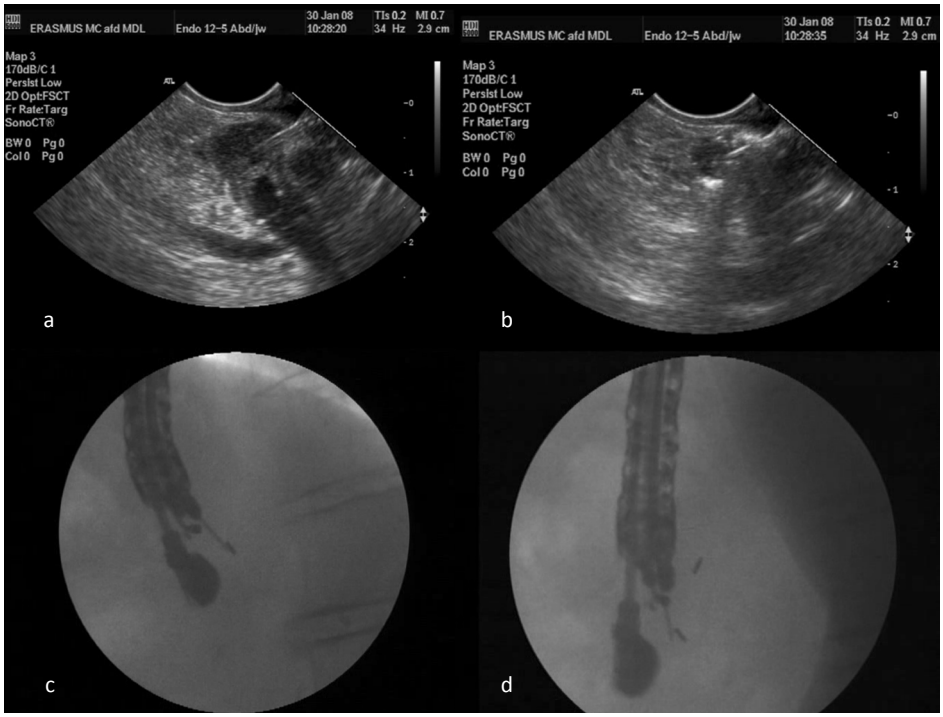

Figure 2. EUS-guided placement of fiducials to guide cyberknife radiation in a patient with a small, cytologically proven, local recurrence of gastric cancer after surgical resection.
2a. EUS-guided puncture of malignant mass lesion close to splenic artery with 19 G needle (white arrow). **2b.** EUS guided advancement of fiducial through a 19 G needle with pusher rod. De fiducial has just disengaged from the needle tip and is visualized as a hyperechoic structure with an acoustic shadow. **2c.** X-ray image showing a fiducial just being pushed out the 19 G needle. **2d.** X-ray image showing the tip of the 19 G needle and 2 fiducials that have already been place inside the mass lesion

cutaneously, EUS has been proposed as an attractive alternative implant modality [17, 18] (figure 2).

Pishvaian and co-workers performed a prospective study to evaluate the safety and feasibility of placing fiducials in mediastinal and intra-abdominal tumors under EUS guidance in 13 patients scheduled for high precision CyberKnife frameless image-guided stereotactic radiosurgery [18]. The fiducials used were cylindrical gold seeds with a length of 3 or 5 mm and a diameter of 0.8 mm customized to fit in a 19-gauge needle. Under curvilinear array EUS-guidance a 19-gauge fine needle was positioned in the target area and fiducials were placed through the needle lumen. The position of the fiducials was verified by EUS and by fluoroscopy. For accurate fiducial tracking by the CyberKnife system, a minimum of 3 fiducials were inserted around the tumor area or at the edges of the tumor itself, there was an angle of at least 15 degrees between any 2 fiducials, and the minimum distance between 2 fiducials was aimed to be 2 cm. EUS-guided fiducial placement was successful in 11 out of 13 patients (84.6%) with tumors in different locations such as the retrocrural area at the dome of the diaphragm, porta hepatis, gastro-esophageal junction, mediastinum, thoracic paraspinal area, and pancreas. A total of 3 to 6 fiducials were placed in each patient. In the first 8 patients no prophylactic antibiotics were given. After one patient developed an infectious complication possibly related to the procedure, the following 5 patients received prophylactic antibiotic at the time of the procedure (ciprofloxacin 400 mg intravenously) followed by a 3-days course of oral ciprofloxacin (500 mg twice a day). Forward-loading the fiducials and pushing them through the needle can be problematic. First, in cases when the echo-endoscope tip is angulated, as is commonly the case for pancreatic head tumors, it is often difficult to advance the fiducials through a standard 19G FNA needle. Second, the use of the stylet often introduces air into the tumor, which obscures EUS visualization and may hamper proper delivery of fiducials. To overcome these problems Owens and Savides introduced a new technique in which the fiducial is back-loaded into the 19G needle and held in place with sterile bone wax that allows for easy fiducial delivery and elimination of air introduction [19].

EUS GUIDED DRAINAGE OF PANCREATIC FLUID COLLECTIONS, ABSCESSES AND INFECTED NECROSIS

The first endoscopic cyst-gastrostomy and cyst-duodenostomy were performed by Sahel and co-workers and Cremer and co-workers in 1982 [20, 21]. Endoscopic drainage of pseudocysts became an increasingly popular technique because of the relatively low complication rate compared to surgical and percutaneous treatment and comparable success rates. Soon in the development of the technique it was shown that routine

radial EUS undertaken before endoscopic cyst drainage increases the safety of the procedure by determining the most optimal site for access and avoiding accidental puncture of interposing vessels between the stomach wall and the cyst [22, 23]. Of equal importance, EUS prior to attempted cyst drainage can be helpful in identifying cystic neoplasms in 3 to 5% of cases [22, 24]. Nevertheless, despite the use of radial EUS and marking the optimal site of puncture, endoscopists were still dependent on the bulge of cyst into the lumen of stomach or duodenum. One of the most important steps in the development of interventional EUS was taken by Grimm and co-workers in 1992[25]. They created a fistula between stomach and cyst with the aid of a linear echoendoscope. Due to the small working channel of only 2.0 mm, the endoscope had to be exchanged for a regular side-viewing endoscope after puncture and guidewire placement in the pseudocyst under EUS guidance. This procedure was further developed by Giovannini, Wiersema and Chak[26-28]. With the introduction of therapeutic linear echoendoscopes with working channels of 3.7 mm (Olympus, Japan) or 3.8 mm (Pentax, Japan) it is now possible to achieve adequate drainage with placement of multiple large-bore stents and a nasocystic catheter without changing the endoscope. Because of these developments the endoscopist is no longer dependent on a visible bulge to puncture the cyst and is able to choose the safest and shortest puncture route avoiding blood vessels and other organs under real-time EUS vision.

Several non-randomized case series suggest that EUS guided pseudocyst drainage is more safe than traditional "blind" techniques [29, 30]. To date, only one randomized trial has been published comparing the two methods[24]. In a series of 30 patients with both bulging and non-bulging cysts, patients randomized to EUS guided drainage could all be treated successfully (100%), whereas this was the possible in only 5 of 15 patients (33%) assigned to conventional drainage. All remaining 10 patients subsequently underwent successful EUS guided drainage. There were no differences in the occurrence of complications. Given the study design, potential bias favoring EUS guided drainage cannot be excluded, but it does show a 100% success rate, including failed "blind" cases. To date, in most centers with an interventional endoscopy unit, EUS guided drainage is the preferred treatment for most pseudocysts. Only cases that are not amenable for endoscopic treatment because of a location too distant from the stomach or duodenum wall or failures of endoscopic treatment are referred for surgical or percutaneous intervention. In our institution, as in other centers, the attention has shifted to endoscopic treatment of patients with more complicated diseases, e.g. infected pseudocysts, pancreatic abscesses and walled-off pancreatic necrosis [31, 32]. Despite the fact that no randomized trials exist comparing either surgical, percutaneous or endoscopic treatment, some recent retrospective series have shown that endoscopic treatment of infected necrosis in acute pancreatitis patients might be a viable alternative to surgery [33-35].

Definitions and indications for intervention

Considerable controversies exist about the nomenclature of peri-pancreatic fluid collection despite the attempt to unify terms with the Atlanta classification system [36]. Most authors agree to divide peri-pancreatic fluid collections in three categories: 1 acute fluid collections, 2 pseudocysts, and 3 walled off pancreatic necrosis (WOPN) [33]. Acute fluid collections occur early in the course of acute pancreatitis, have no defined wall and usually disappear after several weeks although they can become very large. Endoscopic interventions are hardly ever necessary. Acute pseudocysts, defined as well-circumscribed homogenous with a well-defined wall require intervention only when symptomatic, i.e. pain, infection or obstruction of the gastrointestinal tract or bile duct. Size in itself is not an indication for drainage since spontaneous regression or disappearance is frequently observed. Pseudocysts can also occur in the setting of chronic pancreatitis and have the same radiological appearance as acute pseudocysts. Indications for drainage are driven by either symptoms (pain, infection and obstruction) or size. Most experts advise drainage if the size of the pseudocyst is larger than 6 cm since this might increase the risk of complications, mainly bleeding and infection [37]. Walled-off pancreatic necrosis (WOPN) is also described as organized pancreatic necrosis. As long as no infection occurs treatment is usually conservative. If infection occurs drainage is mandatory.

Procedure and Technique

Antibiotic prophylaxis is generally applied to decrease the risks of infectious complications after failed drainage or incomplete drainage of septated or communicating cysts. It is mandatory to have adequate surgical backup. Drainage can be performed under conscious sedation although it can be helpful to do the procedure under general anesthesia, especially if multiple cysts need to be drained or the drainage procedure needs to be combined with ERCP. Usually the procedure is started in the left-lateral position. Depending on local anatomy it can sometimes be helpful to turn the patient to the prone position. Fluoroscopy is mandatory even though it is technically feasible to drain a pseudocyst with a single stent using only EUS guidance. While the transgastric or transduodenal drainage of fluid collections has become an established technique, the procedure is quite demanding and usually requires more ERCP than EUS skills. In fact, EUS is required only for the first part of the procedure to get safe access into the fluid collection. There are several different techniques to perform EUS-guided drainage of a pancreatic fluid collection. Application is largely based on personal preference and experience. Nevertheless, some general considerations can be made with respect to the technical procedure.

The procedure is started with a therapeutic linear echoendoscope. The optimal site for puncture is chosen based on distance from the gastric wall and interposing blood vessels. Generally a distance of 1 cm (or less) is considered safe although even when the

distance between gastric wall and pseudocyst is much larger, up to 2,5 cm, it is often possible to create an endoscopic cyst-gastrostomy. Access can be gained with either a specially designed cystotome or with a regular 19G needle. A potential disadvantage of the cystotome is that the EUS visibility of the inner part, which is basically a needle-knife sphincterotome, is sometimes not so clear and that the inner catheter is rather floppy (figure 3).

These characteristics make it sometimes more difficult to use. To avoid such problems, a regular 19G needle can be used to gain access (figure 4). Once the needle is inside the fluid collection, 10 cc's of the cyst fluid are aspirated for culture, cytology and biochemical markers (amylase, CEA) and subsequently 10 to 20 cc's of contrast are

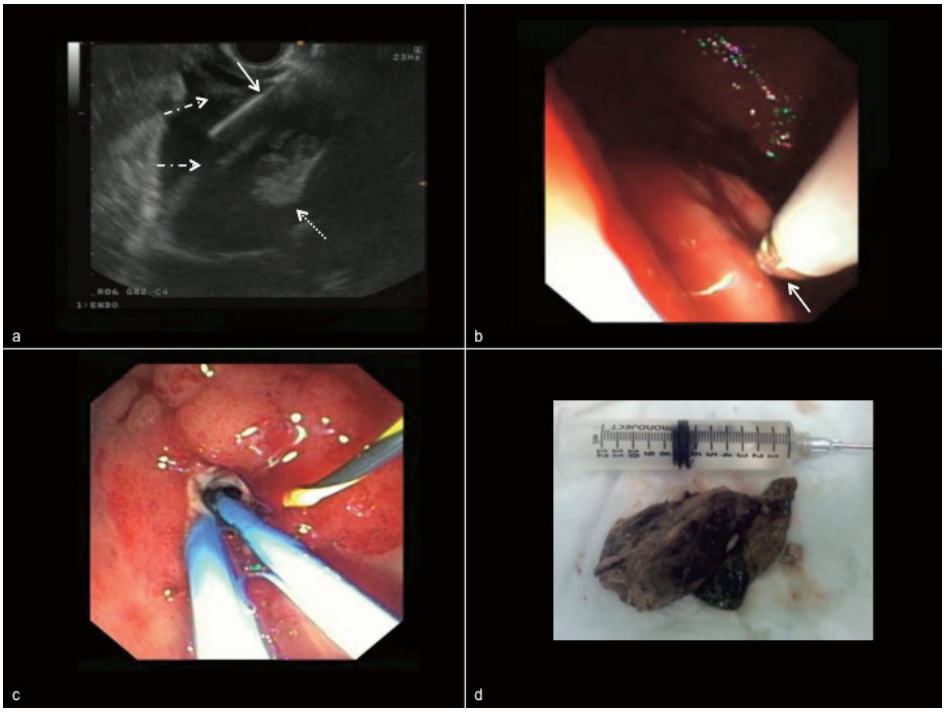

Figure 3. EUS guided puncture and drainage of large pseudocyst using the cystotome.
3a. The inner 5 Fr catheter (white arrow) with a metal tip of the cystotome is advanced through the stomach wall into the pseudocyst using electrocautery under EUS guidance. Some electrocautery artifacts are visible (broken white arrows). There is also some blood (dotted white arrow) twirling to the bottom of the pseudocyst. **3b.** Using electrocautery on the metal tip (white arrow), the 10 Fr outer catheter of the cystotome is advanced over the inner catheter into the pseudocyst. **3c.** The fistelous tract through the stomach and cyst wall created by the 10 Fr electrocautery tip of the outer cystotome catheter is nicely visible. Two pigtail stents have already been positioned. The guidewire is advanced into the cyst to place a nasocystic catheter for irrigation. **3d.** 48 hours after the initial EUS-guided pseudocyst drainage, the fistula was dilated up to 18 mm and endoscopic debridement was commenced removing large chunks of necrotic tissue.

injected. This sometimes delineates communication with the pancreatic duct, but more importantly it shows the size and shape of the cyst making it easier to interpret the position of guidewires later in the procedure. After puncture a stiff long ERCP guidewire is left in place and dilation of the cyst-gastrostomy fistula is mandatory. If however a dilation balloon cannot be passed successfully into the cyst, the outer part of the cystotome can be advanced over the guidewire into the cyst using electrocautery. The use of a regular sphincterotome is associated with an increased risk of bleeding.

It is generally accepted that placement of multiple stents reduces the chance of clogging and improves eventual outcome. Through the outer part of a cystotome or via an 8.5 Fr stent introduction system (OASIS; Cook Endoscopy, Winston-Salem, USA) a second

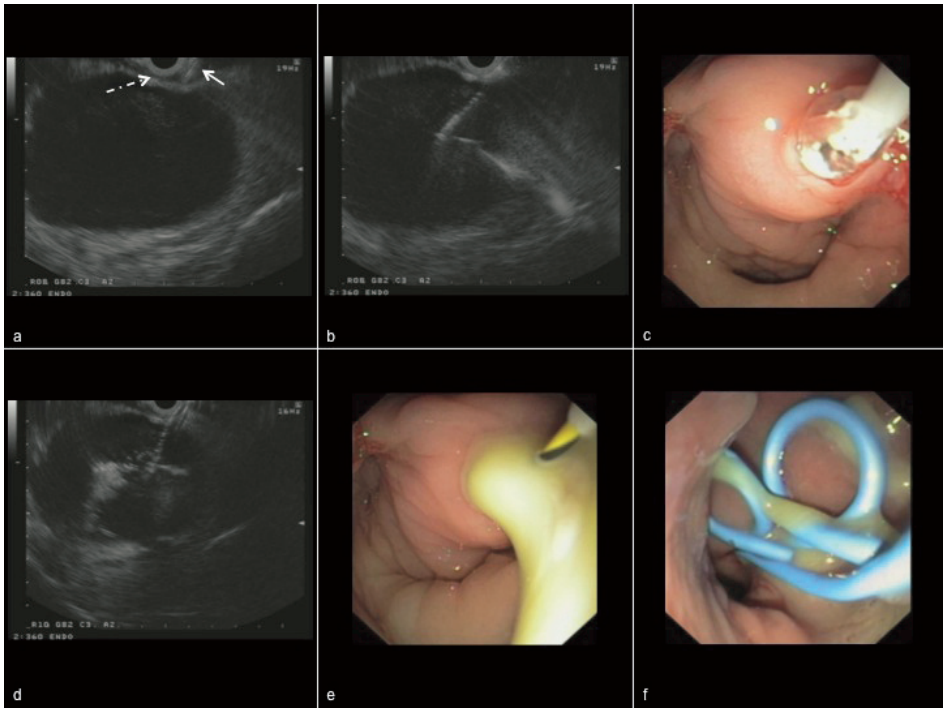

Figure 4. EUS-guided puncture and drainage of large infected pseudocyst using a 19 G needle.
4a. A 19 G needle (white arrow) is positioned using EUS guidance for transgastric puncture (stomach wall: broken arrow) of a large pseudocyst. **4b.** The 19 G needle is advanced into the pseudocyst under EUS guidance. The acoustic shadow of the needle is well visible. **4c.** A guidewire has been advanced into the pseudocyst through the 19 G needle. The needle has been removed and a 8 mm dilation balloon has been introduced over the guidewire into the cyst. Using endoscopy and fluoroscopy the balloon is adequately positioned to dilate the fistulous tract. **4d.** The guidewire is still safely positioned within the pseudocyst after the balloon has been removed. Some blood can be seen twirling within the cyst cavity after balloon dilation. **4e.** Immediately after the balloon is deflated, pus is gushing from the pseudocyst into the stomach. **4f.** Two 7 fr pigtail stents have already been positioned and a third stent is being pushed into the pseudocyst.

wire can be placed inside the cyst and 2 stents can be placed easily [38]. It is advisable to use double pigtail stents (7 Fr) for drainage because compared to straight stents, they are less traumatic to the cyst wall, thereby reducing the chance of bleeding [39]. If there is a clinical suspicion of infection it is advisable to place a 6 Fr nasocystic catheter and start cyst irrigation with 1 liter of water or saline per 24 hr with manual boluses of 100 – 200 ml every 4 to 6 hours depending on cyst size and aspect. If the cyst contains debris and solid or necrotic material an endoscopic re-intervention should be considered after 1 to 2 days with further dilation of the fistulous tract up to 18 mm and endoscopic debridement using a regular forward viewing endoscope. Necrosectomy is usually best done with a dormia basket or a Roth net. Occasionally a grasping forceps can be useful. Usually several repeat procedures are necessary until viable tissue of the wall of the cyst is clearly visible. In between these procedures cyst irrigation is maintained using a nasocystic catheter.

Complications

The main complications of endoscopic drainage of pancreatic fluid collections are infection, bleeding, perforation, stent migration, and stent dysfunction. Reported frequencies in the literature vary markedly, between 11 and 37%, at least partly due to different patient populations investigated [29, 31, 39, 40]. In general, complication risk increases with increased complexity of the procedure, especially when underlying pancreatic necrosis is present. Infection is probably the most frequent complication after endoscopic drainage. The use of prophylactic antibiotics might decrease this risk. The most important risk factor is incomplete drainage. This can be due to stent clogging or migration, non-communicating cyst compartments, and, most importantly, the presence of pancreatic necrosis. Most cases with infectious complications can be managed endoscopically by transmural necrosectomy [34, 41]. Bleeding is less frequently encountered when using EUS guided drainage. If bleeding occurs from the site of the cyst-gastrostomy, it can usually be managed endoscopically. Presence of a pseudoaneurysm must be excluded. Overt perforation is rather uncommon with most series reporting perforation rates below 5%, although in earlier series this percentage was somewhat higher [32, 39, 40, 42, 43]. Experience is therefore likely to be of influence. Most cases of perforation involve leakage of pancreatic juice in the peritoneum. When the drainage procedure was technically successful and adequate positioning of stents in the cysts cavity is confirmed on CT scan, this can usually be managed conservatively. The fistula will mature in 1 to 3 days and leakage will stop.

Outcome and results

Results in general are best for uncomplicated cysts in chronic pancreatitis. The efficacy of transmural endoscopic drainage in these patients is more than 90% and has therefore

become treatment of choice in centers where this expertise is available, although no prospective controlled series are available in which percutaneous, surgical and endoscopic treatment are compared. A small retrospective case-controlled study in which surgical cyst-gastrostomy was compared with EUS-guided endoscopic drainage showed comparable success, re-intervention and complication rates [44]. However, due to a shorter mean hospital stay the endoscopic treatment was more cost-effective. Success rates in infected WOPN are considerably lower at around 70%, even in centers with considerable experience [31, 34].

Drainage of pelvic abscesses

In three published case series of 12, 4 and 4 patients it was shown that it is possible to drain pelvic abscesses with the aid of a linear therapeutic echoendoscope [45-47]. In the first study stent placement was successful in 75% of patients whereas a 100% technical success rate was achieved in the latter two. With the aid of basically the same techniques as described above an overall success rate was achieved of approximately 75% when combined with short-term irrigation of the abscesses. This approach is a promising technique in patients that are sometimes very difficult to manage surgically or radiologically.

Future developments

Some of the difficulties of EUS guided drainage procedures, especially those related to the sometimes awkward maneuverability and to the oblique direction in which force is exerted, might be overcome by the use of a prototype forward viewing linear echoendoscope. Initial clinical experience in a small case series did suggest that endoscope control compares favorably to traditional linear echoendoscopes [1]. More trials are awaited to demonstrate this and perhaps it will be possible to drain previously inaccessible fluid collections with the aid of this endoscope. With the increasing use of transmural endoscopic necrosectomy more effective instruments and accessories to evacuate necrotic tissue from the drained cavities are eagerly awaited.

EUS GUIDED DRAINAGE OF THE BILIARY SYSTEM

The majority of the biliary system can be visualized with EUS. Only visualization of the right hepatic lobe is limited but common bile duct, gall bladder and left hepatic duct can easily be identified with a linear echoendoscope. This opened up the way for EUS guided biliary drainage and rendezvous type procedures. Although endoscopic treatment of biliary obstruction through ERCP is successful in approximately 90% of patients, cannulation of the major papilla fails in selected cases because of local tumor infiltration or (surgically) altered anatomy. Nowadays almost every patient in whom ERCP fails can be

managed by percutaneous transhepatic drainage. However, percutaneous biliary drainage is associated with considerable morbidity due to bleeding, cholangitis and bile leakage in 10–30% of patients [48]. The search for an endoscopic alternative for percutaneous interventions therefore seems logical and with the ability of linear EUS to gain access to transmural structures development of transgastric and transduodenal EUS-guided biliary drainage was inevitable. Most papers on this subject have focused on the transmural placement of plastic or self-expandable stents, but rendezvous type procedures have also been described. In the next part of this chapter we will describe indications, procedural technique, complications and outcomes of EUS-guided hepaticogastrostomy, EUS-guided choledochoduodenostomy and EUS-guided cholecystostomy.

EUS guided hepaticogastrostomy

Given the excellent visualization of the left liver lobe from the stomach it is not difficult to identify dilated bile ducts. Since the right liver lobe is much more difficult to examine, patients with unilateral dilation of the right biliary system are no candidates for this procedure. In theory, all patients with malignant obstruction after failed ERCP are potential candidates to undergo EUS-guided hepaticogastrostomy. Several case series have shown that the procedure of transgastric stenting is technically feasible and promising. However, due to the lack of comparative studies with for example percutaneous approaches and the small number of patients included, this technique should still be regarded an experimental procedure only to be performed in a clinical research setting [49-55].

Procedure

All patients in published series received pre-procedural antibiotic prophylaxis. The biliary system is identified from the stomach at the lesser curvature and a dilated bile duct is punctured with a 19G or 22G needle. A 22G needle is more flexible and easier to handle, but will only pass a soft and floppy 0.018" guidewire making subsequent interventions more difficult. After the stylet is removed from the needle, contrast is injected and a cholangiogram is obtained. The next step is passing a long (480 cm) guidewire through the needle deep into the biliary system or preferably through the stenosis in the duodenum. In case of the latter, a rendezvous procedure could be considered provided that the papilla can be reached. One of the main concerns in these kind of procedures is shearing of the guidewire on the sharp tip of the needle. Modern guidewires are nearly always hybrid type wires with a coating and a core. Stripping of the coating can occur with the risk of loss of part of the guidewire and subsequent failure to exchange accessories over the damaged guidewire. The risk of shearing increases with stiffness of the wire and increased angulation of the needle. In both circumstances more force is exerted at the tip of the needle. Obviously, repeated in and out movements of the wire when multiple

attempts at reaching the desired position also increases the chance of shearing. Some form of dilation is necessary to deploy either a plastic stent or a self-expanding metal stent (SEMS) through the fistula. For this, a sharp tip ERCP cannula (4.0 Fr) followed by biliary dilation catheters up to 8.5 Fr can be used and avoid the use of electrocautery. However, in the previously mentioned studies, also small caliber cystotomes (6 or 8.5 Fr) and needle-knifes have been used with success. After dilation deployment of a stent is the final step. Both straight and double pigtail plastic stents have been used and covered and uncovered SEMS. At present it is not known which type (or combination of stents) is the optimal choice with regard to outcome and occurrence of complications, mainly obstruction with subsequent cholangitis, bile leakage and migration. Once the fistula has been created and a stent has been in place for several days it is generally easy to perform a subsequent procedure and exchange or de-obstruct previously placed stents.

Complications

Overall complication risk in the 20 patients published was 25% without mortality. Complications ranged from cholangitis due to stent migration or obstruction, ileus due to migrated stents and biloma. Contrary to expectations bile leakage and subsequent localized peritonitis was not a major clinical problem, although some post-procedural pain was not uncommon.

Outcome

Outcome and results have been generally good in the published patients although one should acknowledge that publication bias may be considerable. Re-intervention rates were approximately 20%. Before any definite recommendations and conclusions can be drawn about this procedure more data are needed.

EUS guided choledochoduodenostomy

In general, indications for EUS-guided choledochoduodenostomy are the same as for the hepaticogastrostomy. For this procedure however, the duodenal bulb must be preserved and accessible as it is the point of access thereby limiting the patients in whom this procedure can be performed. Results of a total of 25 patients have been published in several small case series.

Procedure

As with hepaticogastrostomy it is common practice to give pre-procedural antibiotic prophylaxis. For transduodenal rendezvous procedures the therapeutic echoendoscope should be introduced into the duodenum and after obtaining a straight position as in ERCP the echoendoscope should be slowly withdrawn until the usually dilated bile duct comes into view from the duodenal bulb. The directional view is then towards the

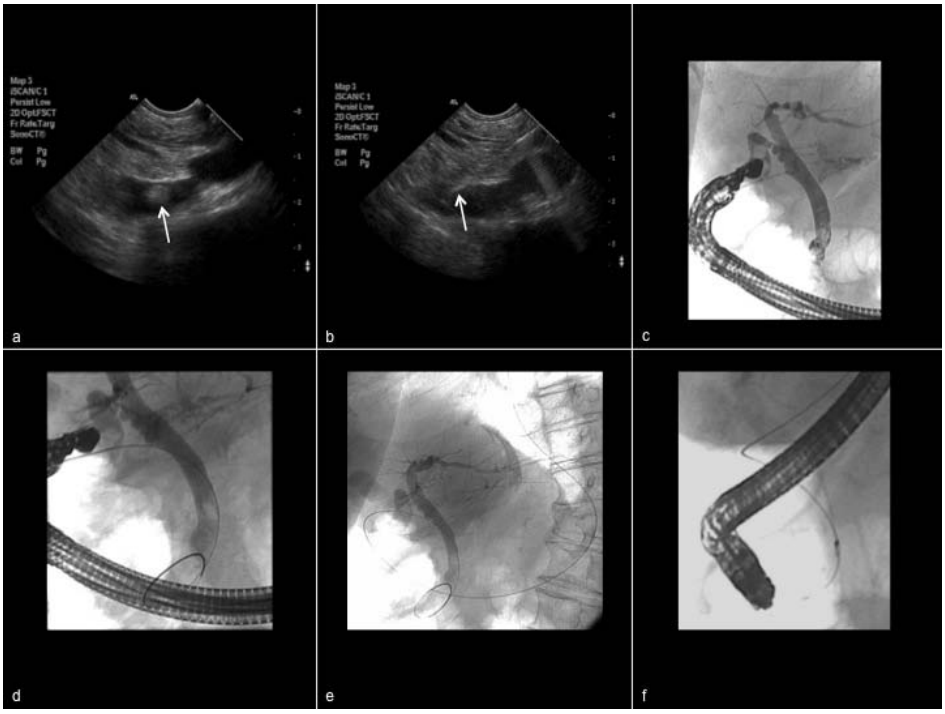

Figure 5. EUS-guided rendez-vous procedure to enable endoscopic retrograde cholangiography after failed attempt to cannulate the papilla of Vater.
5a. Linear EUS image showing the common bile duct from the duodenal bulb with a bile stone causing an acoustic shadow (white arrow) **5b.** EUS-guided needle puncture (white arrow) of the common bile duct. **5c.** Cholangiogram with contrast injection through the EUS puncture needle. **5d.** Advancement of guidewire through EUS puncture needle into the common bile duct across the papilla of Vater into the duodenum. **5e.** Guidewire position after removal of EUS scoop. **5f.** Advancement of side-viewing ERCP scope into the duodenum in front of the papilla. The guidewire has been retrieved through the working channel using a snare. Over the guidewire a cannula is advanced into the common bile duct.

ampulla of Vater, enabling passing of the guidewire after puncture of the common bile duct (figure 5). For EUS-guided choledochoduodenostomy it is mandatory to introduce the echoendoscope into the duodenal bulb in a long position. From this position the ultrasound view is directed towards the liver hilum, enabling stent placement transduodenally. In this position either a needle-knife or a 19G needle is introduced into the bile duct after which a cholangiogram is obtained. Although hepatic artery and portal vein are close by, avoiding them should not be difficult with the aid of Doppler sonography. A long guidewire is then left in situ after which, like in performing a hepaticogastrostomy, dilation of the fistula is performed with a biliary dilation catheter. Next a plastic stent, most authors have used straight stents, or a SEMS can be placed. Subsequent procedures can be performed with a regular duodenoscope.

Complications

In the 25 patients published thus far the complication rate was 19% (5 patients). Two cases of biliary leakage led to a localized bile peritonitis and 3 patients had a pneumoperitoneum after the procedure. Although all cases could be managed conservatively and no procedure-related mortality was observed this complication rate is rather high, especially when considering that these procedures were performed at tertiary referral institutes by expert endoscopists.

Outcome

Procedural success was achieved in 92% of cases (23 out of 25). All patients had relieve of jaundice and cholestasis. Only one study describes long-term follow-up [56]. In this paper average stent patency of plastic 8.5 Fr stents was an impressive 211 days. Although this procedure, as the EUS-guided hepaticogastrostomy, seems a promising and exciting alternative to percutaneous drainage in patients that fail ERCP, it is at present too early to make any definitive conclusions. Further research is awaited, especially comparative randomized trials between EUS-guided choledochoduodenostomy and percutaneous approaches.

EUS-guided cholecystostomy

The cornerstone in the management of patients with acute cholecystitis is surgical intervention. In patients deemed unfit for surgery the most commonly used alternative treatment is percutaneous drainage. Since it is usually easy to identify the gallbladder from the gastric antrum and/or the duodenal bulb and it is in close proximity to the enteral wall, the concept of transmural drainage of the gallbladder is a logical extension from other biliary and pancreatic drainage procedures. Internal drainage has potential advantages as indwelling percutaneous catheters cause considerable patient discomfort. The procedure of EUS-guided cholecystostomy has been described in two case series[57, 58], including 12 patients in total. All patients were deemed unfit for surgery, usually because of severe co-morbidities. The shortest distance to the distended gallbladder was chosen from either gastric antrum or duodenal bulb and the gallbladder was then punctured with a 19G needle. After contrast injection a 0.035" guidewire was placed in the gallbladder. In the Korean series (9 patients) drainage was performed with a 5 Fr nasocholecystic catheter after dilation of the tract to 6 Fr. This catheter was left in situ until elective cholecystectomy in most cases. Surgery was not hampered by the indwelling catheter. In the Belgian series the dilation of the tract was performed with either a 6 or 10 Fr cystotome with subsequent placement of a nasocholecystic catheter and in one case combined with placement of a double pigtail stent. In the other 2 patients the nasocholecystic catheter was replaced endoscopically with a double pigtail stents several days after initial drainage. All patients did well and had clinical resolu-

tion of their cholecystitis within 72 hours after the EUS-guided cholecystostomy. There was one case of small bile leakage and one pneumoperitoneum, both complications could be managed conservatively and were without clinical consequences. Although these results are quite promising, obviously prospective randomized trials comparing EUS-guided cholecystostomy and percutaneous drainage must be performed before any recommendations can be made with regard to the clinical utility of EUS-guided cholecystostomy.

EUS-GUIDED PANCREATIC DUCT DRAINAGE AND RENDEZVOUS

The main principle of endoscopic treatment in chronic pancreatitis is decompression of the duct. It is thought that ductal hypertension, due to stones or strictures, is one of the key causes of pain in chronic pancreatitis. Endoscopic treatment, if necessary combined with extracorporeal shock wave lithotripsy (ESWL), through ERCP is quite successful in experienced hands. It can lead to a major relief of pain in up to 60% - 80% of patients if decompression is achieved [59-62]. Although a recent prospectively conducted randomized trial clearly favored surgery over endoscopic treatment [63] in many institutions endoscopy is still first-line treatment and surgery only considered when endoscopic treatment fails. Although in expert hands successful cannulation of the pancreatic duct is achieved in over 90% of cases selective cannulation sometimes fails [64]. Either due to altered surgical anatomy, very tight strictures, severe inflammation or pancreas divisum with orificial stenosis access can sometimes be impossible. After surgical treatment for chronic pancreatitis recurrent disease and complaints are not infrequent. In some series drainage is inadequate in up to 20% of patients [65]. Depending on the type of surgical intervention it can be impossible to continue with endoscopic treatment. Especially after duodenum preserving pancreatic head resection according to Beger or a Whipple procedure it can be impossible to gain access to the pancreatic duct via ERCP. Recurrence after surgery can be caused by recurrent disease or stenosis of the pancreaticojejunostomy. In both cases this can lead to dilation of the pancreatic duct. Since, even after surgery, the body and tail of the pancreas can be easily identified from the stomach and duodenal bulb this enables puncture and subsequent drainage, or a rendezvous procedure if the papilla can be reached, of the pancreatic duct via linear EUS. Four papers (cases series, retrospective data and 1 prospective study) have been published that evaluated EUS-guided drainage or rendezvous of the pancreatic duct [66-69]. Transluminal drainage was attempted in the two papers by Kahaleh and co-workers and Tessier and co-workers , whereas Mallery and co-workers describe attempted rendezvous procedures. Both techniques were evaluated by Will and co-workers. A total of 65 patients were described in these papers.

Procedure

All patients described did receive pre-procedure prophylactic antibiotics. With the therapeutic linear echoendoscope the pancreas is examined from stomach and duodenal bulb (figure 6). The site for puncture must be chosen taking different parameters into account. Distance to the gastric or duodenal wall is important, but it is also very important to obtain a view of the pancreatic duct in a longitudinal way. This enables the endoscopist to look "into" the pancreatic duct and makes subsequent interventions over a guidewire much easier. Especially in severe calcifying chronic pancreatitis the duct may be hard to visualize due to the many acoustic shadows. This is another consideration when determining the puncture site. Finally, every effort should be taken to guide the wire towards the pancreatic head and, if at all possible, pass into the duodenum or jejunum. This gives the endoscopist more wire "to work with" and reduces the chance

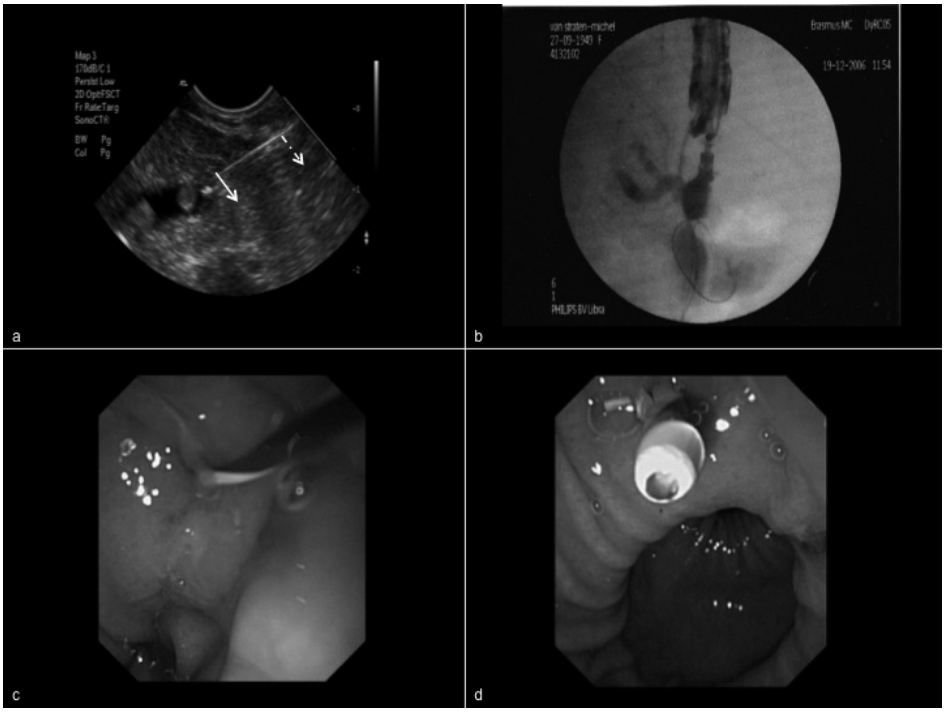

Figure 6. EUS-guided pancreatic duct – gastrostomy in a patient with pain due to a stricture and duct obstruction after surgical pancreaticojejunostomy.
6a. EUS-guided puncture of the dilated pancreatic duct (white arrow) with a 19 G needle (broken arrow). **6b.** Contrast injection through the puncture needle with filling of the dilated pancreatic duct and the jejunal loop. The anastomotic stricture is nicely visible (white arrow). A 6 fr. cystotome is advanced over a guidewire through the stricture into the jejunal loop. **6c.** Puncture hole in the stomach with a guidewire in position. **6d.** Final situation with distal 7 Fr stent tip positioned in the stomach. The stent has been advanced through the stomach wall, pancreatic duct, and stricture and its proximal tip is located in the jejunal loop.

of losing access when exchanging accessories. After successful puncture of the duct a pancreatogram is obtained after removal of the stylet. As in biliary drainage procedures it is preferable to use a 19G needle since an 0.035" guidewire due to its inherent stiffness will facilitate the further procedure. Especially with repeated maneuvers when trying to pass a stenosis the risk of shearing of the guidewire increases as described in the section on biliary drainage procedures. The EUS part of the procedure ends when the endoscopist succeeds in passing the guidewire into the duodenum via the major or minor papilla. It is advisable to put plenty of guidewire in the duodenum to increase the stability of the position when advancing the duodenoscope into position. When attempting a transmural drainage the next step is dilating the fistula trajectory. Several methods have been described using either a small tip ERCP cannula followed by a biliary dilation catheter and/or a biliary balloon dilation catheter or electrocautery with a cystotome. It is our personal preference to use the small caliber (6 Fr) cystotome since it is sometimes very hard, especially when the position of the echoendoscope is not ideal, to advance any accessory into the pancreatic duct due to severe fibrosis and scarring that occurs with chronic pancreatitis. When a combined cutting/coagulation current is applied to the cystotome passage into the duct is usually successful. If necessary intraductal or anastomotic strictures can be dilated with either a biliary balloon dilation catheter or the cystotome. The procedure ends with placement of a 7 Fr straight endoprosthesis. Several weeks later this can be exchanged for 2 stents, usually without problems with the aid of a regular duodenoscope.

Complications

Complication risk of EUS-guided pancreatic duct drainage appears to be quite high and can be procedure-related or occur later in time. In two series stent migration and occlusions occurred in 20 to 55% of cases [67, 69] whereas also stent induced strictures were observed on follow-up in one series [69]. Procedure-related complications varied between 5% and 44%. Most common was post-procedure pain but severe pancreatitis, perforations, bleeding and hematoma have been described. The numbers of patients are too small to judge whether the type of procedure, especially the dilation modality, is of influence on the occurrence of complications. No procedure related mortality has been described.

Outcome

Long-term outcome data are not available. As was to be expected just like after successful ERCP in obstructive chronic pancreatitis approximately 65% of patients experienced pain relief immediately after the procedure. The numbers are too small to judge whether a drainage procedure or a rendezvous procedure is more effective in pain relief. EUS guided drainage of the pancreatic duct at present is a technically challenging procedure with a relatively high complication rate, both procedure related and stent related.

Although there is a subset of patients that can definitely benefit from these techniques at present there is insufficient evidence to recommend this procedure on a routine basis. It should be further explored as part of a research program.

FUTURE INDICATIONS FOR THERAPEUTIC EUS

As we have shown in the previous paragraphs the indications to perform EUS have shifted and continue to evolve, as many other endoscopic interventions, from being a purely diagnostic procedure towards an advanced therapeutic technique. In this last section we will discuss some developments on possible future applications of interventional EUS focusing on vascular interventions and the possible role of EUS in NOTES.

EUS and vascular interventions

EUS may have a possible role in both detection and treatment of various lesions resulting in gastro-intestinal bleeding. Due to the detailed images EUS provides it can potentially be of great value in both determining the source of bleeding as in directing treatment specifically through detailed visualization of local vascular anatomy. This first shown to be an effective approach in the localization and treatment of Dieulafoy lesions [70]. Another more recent paper described the use of EUS in the management of 5 patients with refractory bleeds of different sources despite intensive endoscopic and radiological treatment attempts [71]. Real-time EUS visualization was used to inject 99% alcohol into small (1–2 mm) feeding vessels of pseudo-aneurysms and Dieulafoy lesions in three patients. In the 2 other patients cyanoacrylate was injected into bleeding vessels in patients with a duodenal ulcer and a bleeding GIST. Interestingly, it was possible to monitor the efficacy of treatment directly by use of Doppler ultrasound. During severe gastrointestinal bleeding it can occasionally be very difficult to adequate visualize the exact source of bleeding. Since imaging with EUS is not hindered by blood EUS guided therapy might be a useful adjunct to the endoscopic armentarium. The development of the forward-viewing linear echoendoscope might overcome problems related to the sometimes awkward handling of the oblique-viewing linear echoendoscope.

EUS has also been used in transmural endovascular interventions. One case report describes the successful insertion of endovascular microcoils through a regular 22G needle in a patient with ectopic varices refractory to conventional therapy [72]. Several animal porcine studies have been performed in which angiography of the major abdominal vessels [73], portal vein angiography and pressure monitoring [74-77] and even cardiac catheterization were performed [78]. Although apparently safe in a porcine model obvious issues of sterility and bleeding risk need to be assessed before any of these techniques can be used in humans.

EUS and NOTES

Apart from safe and effective closure, obtaining a reliable and safe access to the (retro) peritoneal cavity is also very important for the further development of NOTES. EUS might be useful for this since it adequately visualizes surrounding structures, organs and major blood vessels. In a porcine model it was shown that through the use of EUS NOTES incisions, especially in locations other than the anterior gastric wall, are potentially more safe and therefore more versatile [79]. Through the use of t-tags that can be applied through a regular 19G needle porcine studies have shown that it is possible to effectively perform transmural lymphadenectomy [80], gastropexy [81] and tissue approximation [82]. To date, the most important addition of EUS to NOTES procedures is the identification of the best access point for specific procedures [83].

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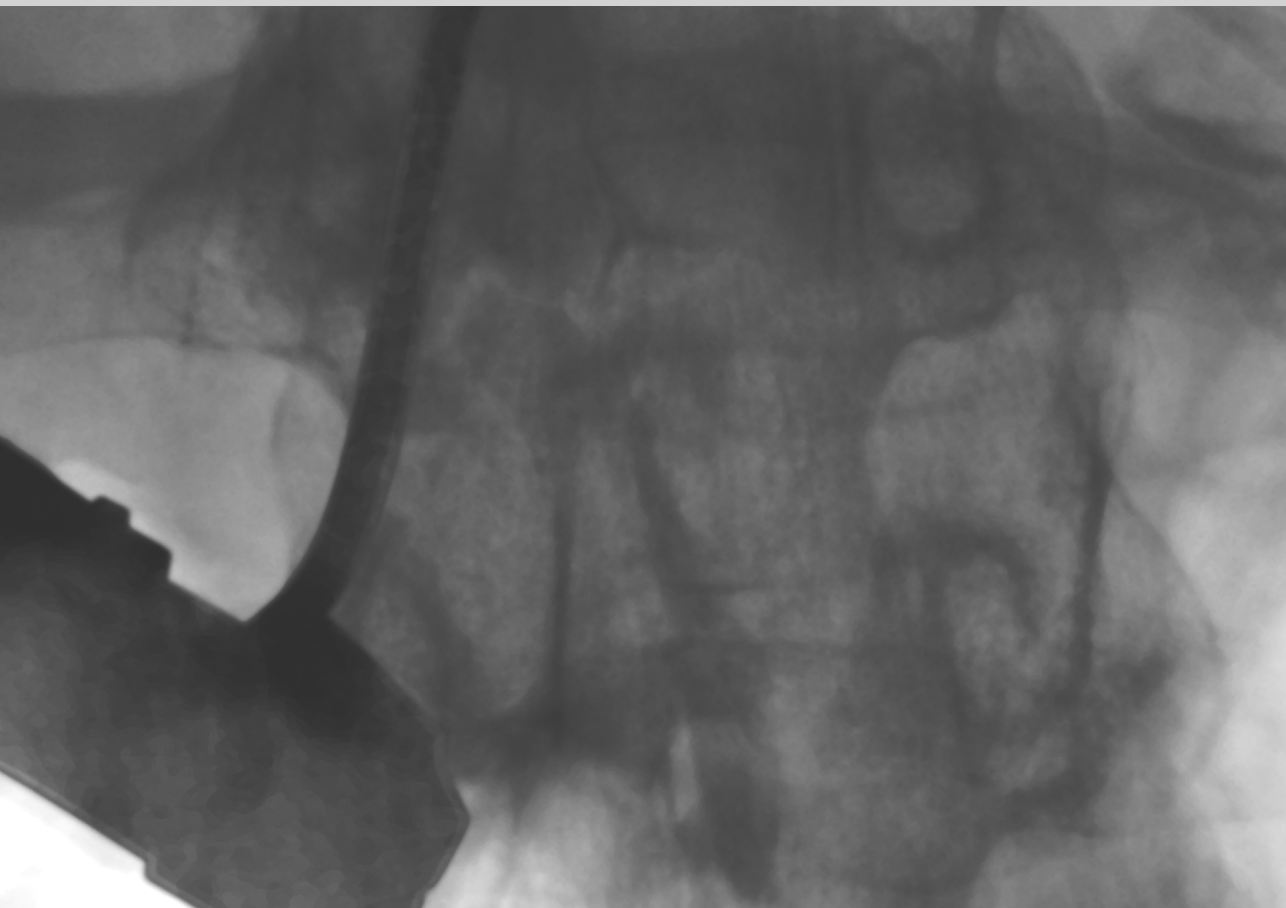
Section 3



Novel developments in the endoscopic treatment of benign biliary and pancreatic disease

8

Endoscopic treatment of chronic pancreatitis

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ABSTRACT

In chronic pancreatitis, therapeutic endoscopy can be considered in three settings; drainage of the pancreatic duct, pseudocyst drainage, and treatment of biliary obstruction. In this chapter these techniques are extensively discussed with a focus on patient selection, the drainage techniques and the optimal duration of drainage. The available evidence regarding morbidity and mortality and long-term outcomes are summarized. Subsequently, an effort is made to establish the future role of endoscopic treatment in chronic pancreatitis.

In chronic pancreatitis, therapeutic endoscopy can be considered in different settings: drainage of the pancreatic duct to alleviate pain, pseudocyst drainage, and treatment of biliary obstruction. These techniques have become increasingly popular over the past decades, even though high-quality studies were lacking and the evidence for their efficacy was mainly based on retrospective studies. Just recently, more information from prospective studies has become available.

PANCREATIC DUCT DRAINAGE

Introduction

Chronic pancreatitis is a disease characterized by an ongoing inflammatory process with severe pain as the predominant symptom. Although the origin of pain is likely to be multifactorial, pancreatic duct obstruction is considered an important etiologic factor. Therefore, ductal decompression became standard treatment for patients with painful obstructive pancreatitis [1, 2]. Obstruction of the pancreatic duct can be caused by strictures, intraductal stones or, in the majority of cases, by a combination of both. Nowadays, improved imaging modalities (high-resolution abdominal computed tomography and a 3-Tesla magnetic resonance cholangiopancreatography (MRCP)) provide accurate information regarding the pancreatic ductal system to allow patient selection for endoscopic treatment without performing a retrograde pancreatogram. The aim of endoscopic drainage is to decompress the pancreatic duct and restore the outflow of pancreatic juice to the duodenum. It involves sphincterotomy, extracorporeal shock-wave lithotripsy (ESWL), removal of stones, and dilatation of strictures by means of temporary stent insertion.

Procedural Aspects

Pancreatic Duct Stones

Since the introduction in 1987, ESWL has become a cornerstone of endoscopic drainage in chronic pancreatitis. ESWL not only improved the results but also expanded the indications of endoscopic treatment; floating stones <5–6 mm in diameter can be extracted transpapillary with a balloon or small-caliber Dormia basket, but the majority of pancreatic stones are impacted and too large to be removed without fragmentation [3]. It is important to emphasize that ESWL of pancreatic stones is not a simple technique because it requires considerable experience and specialized equipment consisting of a forceful electromagnetic lithotripter with a fluoroscopic two-directional targeting system (the most commonly used being the Dornier Compact Delta lithotripter, Dornier Med-Tech, Wessling, Germany), it is generally executed in expert centers. As treatment is painful and time-consuming (a single session takes about 1–2 h), it is best carried out with the patient under general anesthesia. Most ESWL sessions are immediately followed by an endoscopic procedure to clear the pancreatic duct from stones and evaluate the presence of strictures [4–7]. In the largest retrospective study, a mean of 5 sessions was necessary to achieve complete fragmentation [8]. Consecutive treatment sessions are usually carried out within a few days, during which time the patient remains admitted to the hospital. In between sessions an endoprosthesis or nasopancreatic drain can be used to prohibit pancreatic duct obstruction by stone fragments and to facilitate complete duct clearance.

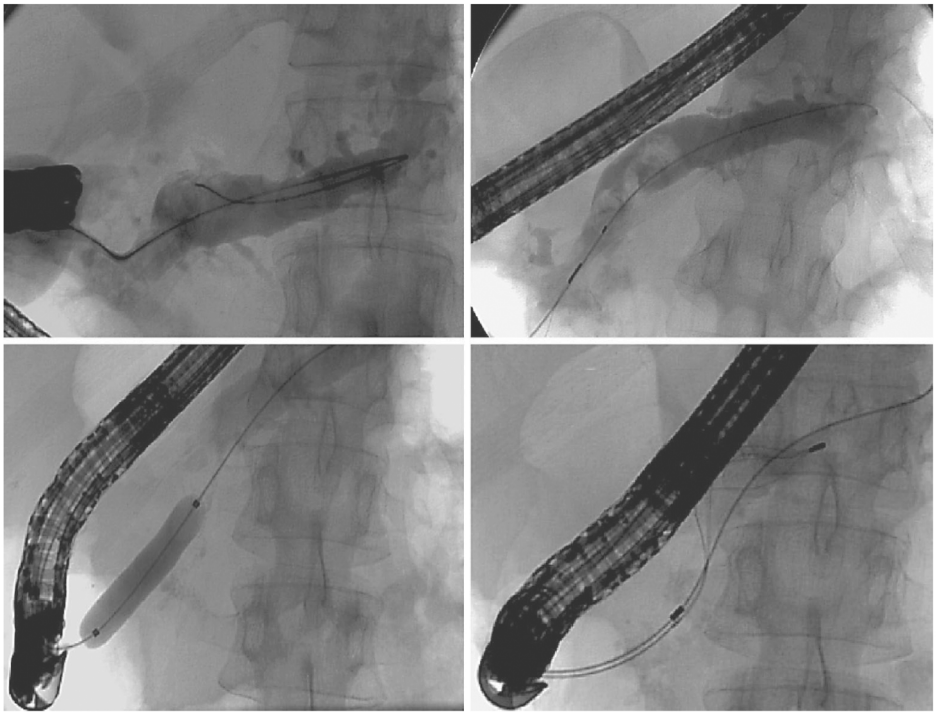

Figure 1: treatment of pancreatic stones
1a: Initial cannulation of severely dilated pancreatic duct with distal stricture via minor papilla with tapered tip cannula and hydrophilic wire.
1b: Minor sphincterotomy and filling defects compatible with pancreaticolithiasis
1c: Balloon dilation of distal stricture
1d: Removal of stones with dormia basket

ESWL is considered a low-risk procedure with a 5–10% morbidity, acute pancreatitis being the most frequent complication [8, 9]. In the past, no mortality was observed, but in a recently published prospective study, 1 patient died of a perforated duodenal ulcer in which ESWL might have played a causative role [10]. ESWL is effective in experienced hands; stone fragmentation is achieved in more than 90% of cases and complete duct clearance in 44–74% of patients [3, 5, 6, 8–18]. The best results are reported for solitary distal stones in absence of a stricture but multiple, large, and impacted stones are no contraindication because the newer lithotripters are able to pulverize these stones completely [4, 19].

Pancreatic Duct Strictures

In chronic pancreatitis, fibrotic pancreatic duct strictures require dilatation and temporary insertion of an endoprosthesis. Many questions remain regarding the technical aspects of this technique. At present, prospective studies comparing different endoscopic treat-

ment protocols are lacking. Moreover, in retrospective reports, technical details are rarely discussed. As a consequence, evidence-based guidelines regarding the need for sphincterotomy and dilation, the choice of stents, or the duration of treatment do not exist.

Despite this lack of evidence, a selective pancreatic sphincterotomy is advocated to provide optimal access to the pancreatic duct and facilitate stone extraction. The sphincterotomy is performed towards the 1-o'clock position and can be extended safely until the first duodenal fold. It should be large enough to allow easy access of instruments and prevent post-papillotomy stenosis. Either the needle-knife technique over a stent, or a pull-sphincterotomy can be performed, with similar complication rates of 4% in retrospective studies [20, 21]. A recent prospective study reported that the needle-knife technique was safer resulting in less post-ERCP pancreatitis [22]. In case a distal stricture is present, a short-nosed small-bore sphincterotome can also be useful.

Balloon dilatation of the pancreatic sphincter, as applied by Sasahira et al. [12], seems an interesting alternative technique but needs further evaluation. One study evaluated the benefits of sphincterotomy alone in obstructive pancreatitis (pain improvement in 60% of patients), but the size, retrospective nature, and patient population prohibit drawing any definite conclusions [23]. There is no evidence to support routine biliary sphincterotomy in these patients, unless signs of biliary obstruction are present [24].

Cannulation of the pancreatic duct is usually straight forward although in patients with active inflammation identification and cannulation of the papilla can be difficult due to edema. Furthermore, in 5–10% of patients access can only be obtained via the minor papilla either due to a devised pancreas or because of an impassable stenosis of the Wirsung's duct.

Most strictures can be passed by a regular or hydrophilic 0.035-inch guidewire although sometimes the use of a thin 0.018- or 0.021-guidewire is necessary. Tight strictures, which cannot be passed by a 5- or 6-Fr guiding catheter, require dilatation, either with a 4- to 6-mm balloon or a graduated dilating catheter. Extremely tight strictures can also be dilated with a Soehendra stent retriever which is passed through the stricture over a non-metallic wire as a corkscrew.

Subsequently, stent placement can generally be performed with relative ease. For pancreatic drainage, a range of stents are available. At first, polyethylene biliary endoprostheses were used. Later, stents with multiple side holes were specifically developed for pancreatic use, to allow optimal drainage from the side branches. However, the benefit of these pancreatic stents was never studied and therefore both stent types are used in this setting. Recently, two new model stents have been introduced: these so-called S-shaped and wing-shaped stents are presumed to have a longer patency and less chance of migration, but this needs to be proven prospectively [25–27]. Stents have a wide variety in diameters from 3 to 12 Fr. Laugier and Renou [28] were the first to suggest that a larger stent circumference results in a better outcome. The current trend

is to use a stent with the largest possible diameter, and to insert an increasing number of stents with each consecutive procedure to further dilate the stricture in analogy with the treatment of benign biliary strictures [29–31].

Perhaps the most interesting question regarding endoscopic dilatation of the pancreatic duct is how long a stent should be left in place. So far, the effect of stent duration on treatment outcome was never properly investigated and the two possible stent exchange protocols (either to change the stent at prescheduled intervals or to exchange 'on demand' meaning when symptoms of obstruction recur) have not been compared.

Exchanging the stent on a regular basis has the advantage of preventing recurrent symptoms due to stent obstruction [32, 33]. Furthermore, this will limit treatment duration because stricture resolution is frequently evaluated and treatment may be terminated as soon as the obstruction has resolved. Shorter treatment duration might be important in the light of two findings. First, some studies suggest that the presence of a stent leads to progression of duct damage in patients with chronic pancreatitis, but most of these changes seem reversible [34–37]. A more important reason to limit the treatment duration is the prospective observation that many patients experienced considerable pain during stent therapy, a finding that might even be aggravated if multiple stents are used [10]. The single argument in favor of a long stenting period is the belief that this will improve the efficacy of stricture dilation and reduce the chance of recurrence, although evidence to support this assumption is lacking. In published series the stent duration ranged from 5.5 to 28 months, but the reported efficacy and recurrence rate did not vary accordingly [10, 19, 28, 29, 38–45]. Only three studies have evaluated prognostic factors of outcome in pancreatic stenting, but none found a significant benefit of a longer treatment duration [10, 28, 38]. Furthermore, even when assuming that clinical success is achieved only after years of treatment, it is impossible to know whether pain relief was accomplished by the endoscopic intervention or if it was a consequence of the natural course of the disease [16, 46].

Outcome

There is sufficient data to conclude that endoscopic pancreatic drainage in chronic pancreatitis is technically feasible and safe. Morbidity is observed in 6–58%, but most complications are stent-related and easy to treat [10, 19, 28, 38, 39, 41–44]. However, since the introduction of endoscopic treatment, surgical techniques have evolved too, and the high complication rates of a decade ago are no longer applicable [47–49]. Therefore, the central argument in comparing endoscopic and surgical drainage has shifted from safety to efficacy. This comparison is complicated by the lack of high-quality reports on endoscopic drainage; most studies were retrospective, had a heterogeneous patient population, did not use well-defined treatment protocols and most importantly, they failed to use uniform and validated outcome measures [19, 28, 38, 39, 42, 43].

Despite the above-mentioned limitations, some conclusions regarding the role of endoscopic drainage of the pancreatic duct in chronic pancreatitis can be drawn. Surgical drainage (by a pancreaticojejunostomy according to Partington-Rochele [50], or in the presence of an inflammatory mass, by a Beger or Frey procedure, achieves long-term pain relief in 65–85% of patients [51–58]. After endoscopic drainage, retrospective studies report a highly variable complete pain relief of 15–84% [19, 28, 29, 38, 39, 42–44]. Only two randomized trials have been published that compare endoscopic and surgical drainage in a prospective manner and both report a clear-cut benefit of surgery [10, 41]. A possible pathophysiological explanation for this finding is offered by Reber et al. [59] who showed in an animal study that surgery is more effective in alleviating the parenchymal pressure due to the opening of the pancreatic capsule. Moreover, in both randomized trials the outcome of endoscopic treatment was disappointing and much worse than would have been expected based on the available retrospective data.

In the first study, Dite et al. [41] observed complete pain relief in 14% of patients only. However, the general opinion regarding this study is that it cannot be considered a fair comparison between the two treatment options because surgery on the one hand encompassed more than just a drainage procedure, and endoscopic drainage techniques did not meet the current standards. In the second randomized trial, which was published last year by our group in the New England Journal of Medicine, complete or partial pain relief was observed in 32% of patients assigned to endoscopic drainage as compared with 75% of patients who underwent surgical drainage [10]. Moreover, surgery resulted in a more rapid (within 6 weeks) and sustained pain relief during the 2 years of follow-up. For patients in the surgical group treatment consisted of a single intervention (the surgical procedure), while patients assigned to endoscopic treatment underwent a median of 5 therapeutic interventions and suffered considerable pain during this treatment period, even with a patent stent in situ. A possible limitation of this study is that the patients suffered from extensive disease and therefore, results might be different for a population with less complex pathology.

Recently a renowned center for ESWL treatment performed a third prospective randomized trial in which they compared conventional endoscopic treatment consisting of ESWL combined with endotherapy (stone clearance and stent placement in case of a pancreatic duct stricture) with ESWL alone. After 2 years, pain relief was observed in 25 of the 48 patients that were analyzed (52%) with an advantage of the ESWL alone treatment (58 vs. 46%) [14].

As prospective data suggest that the long-term success rate of endoscopic treatment is limited, the question remains if there is a role for endoscopic treatment of pancreatic duct obstructions in chronic pancreatitis. First, further development of endoscopic techniques might improve results. To date, studies that focus on the technical aspects of endoscopic treatment are rare and conflicting. On the one hand, some authors advocate

a more aggressive approach: Costamagna et al. [29] have reported promising results of cumulative stenting with a success rate of 84%. Others are investigating less elaborate techniques. For instance, as mentioned above, Dumonceau et al. [14] achieved better results after ESWL treatment alone than in combination with endoscopic treatment. Future prospective studies are needed to solve these issues. Second, a better patient selection might improve the outcome. Now that in patients with complex pathology (with multiple strictures and stones) endoscopic drainage seems to be inferior to surgery, the interest shifts to patients with less extensive disease. There is evidence that in symptomatic patients with a single obstruction or stone, the course of the disease may be favorably altered by an early intervention.

Farnbacher et al. [9] found that the only parameter predictive of long-term pain relief after endoscopic pancreatic duct drainage was a short duration of disease [10, 41]. Also, animal studies have shown that pancreatic insufficiency develops early in the course of obstructive pancreatitis and becomes permanent within several weeks [60]. Therefore, the best way to prevent irreversible damage and pancreatic function loss may be to decompress the duct at a very early stage. Moreover, even patients without symptoms may benefit from endoscopic drainage. At present, in this third category of patients, duct decompression is postponed until symptoms of pain or recurrent flareups of pancreatitis develop. Future studies should evaluate if early duct decompression may prevent a course of intractable pain in such patients.

Summary

In conclusion, recent evidence suggests that surgery offers a better chance of success in patients with extensive obstructive pancreatitis and a combination of strictures and multiple stones. However, this does not write off endoscopic pancreatic duct drainage in chronic pancreatitis. It may well be that patients with less complex pathology will benefit from endoscopic treatment at an early stage of the disease, but this needs to be proven. Moreover, endoscopic therapy may still be justifiable in selected patients with extensive disease who show a favorable pain response within the first 8 weeks of stent treatment. If not, or when stricture resolution is not accomplished after a treatment period of 1–2 months, patients should be referred for surgery.

PSEUDOCYST DRAINAGE

Introduction

Pseudocyst formation is a frequent complication of chronic pancreatitis with a reported incidence of 20–40% [61–63] and in contrast to acute pancreatitis, spontaneous resolution is rare [64–68]. Two mechanisms of cyst formation have been postulated. First,

cysts may follow an acute exacerbation of the disease ('acute on chronic pancreatitis') when peripancreatic fluid becomes organized in a walled-off collection. The second mechanism suggests an obstruction of a side branch of the pancreatic duct that results in a saccular dilatation. Pancreatic duct disruption and obstruction often accompany pseudocysts in chronic pancreatitis and if a communication between the duct and the pseudocyst is present, cyst drainage requires addressing these duct abnormalities because otherwise they will maintain filling of the cyst [69–71].

In chronic pancreatitis, indications for pseudocyst drainage are persistent symptoms and cyst-related complications. Pancreatic pseudocysts may lead to compression of the gastrointestinal tract, the biliary system or major vessels. Furthermore, spontaneous rupturing, bleeding and secondary infection of the cyst may occur.

Whether asymptomatic pseudocysts should be treated is debatable. The decision to drain is made based on the estimated chance of spontaneous resolution on the one hand, and the chance of developing complications on the other. Both figures are not exactly known for patients with chronic pancreatitis, but they are likely to be less than 10% [64–68, 72]. Available data suggests that for cysts <6 cm in diameter, the resolution rate is even higher and because complications are rare in these small cysts, a wait-and-see policy is defendable [65, 73, 74]. Moreover, also for larger asymptomatic cysts, a conservative follow-up has become more common, although a rapid increase in size is still considered an indication for drainage.

Imaging Studies

Prior to drainage, imaging studies are performed. Computed tomography has long been the key investigation in this setting. However, MRCP has evolved and provides excellent imaging of the pancreas and pancreatic region, comparable with computed tomography [75–77]. Furthermore, MRCP has additional value because it can be used to evaluate the pancreatic duct and therefore has become the first choice imaging modality when pseudocysts are suspected. Further prospective studies are necessary to assess if a MRCP can annul the need of a retrograde pancreatogram. Secretin-stimulated MRCP is able to visualize the pancreatic duct in 97% of patients but an endoscopic retrograde cholangiopancreatography is superior in depicting subtle pancreatic duct abnormalities [78]. At present, it has not been ascertained that MRCP is able to diagnose all clinically relevant duct abnormalities, in particular ductal communication with the pseudocyst [79].

Alternative drainage Modalities

Historically, surgical pseudocyst drainage was associated with significant morbidity (7–37%) and mortality (0–6%) [80–82] with a recurrence rate of 10% [81, 83–85] and therefore less invasive techniques were welcomed. However, in the future, evolvement of laparoscopic techniques might expand the role of surgical drainage again [86–88].

Percutaneous drainage is generally dismissed because it requires the presence of an external drain for an extended period of time and because it frequently leads to fistula formation [89–91]. At present, endoscopic pseudocyst drainage is the only feasible alternative to surgery and can be performed either through the gastrointestinal wall of the stomach or duodenum (transmural approach), or transpapillary if a connection of the cyst with the pancreatic duct is present.

Procedural Aspects

General Aspects

Prior to the procedure a broad-spectrum antibiotic prophylaxis should be administered to decrease the risk of infectious complications [92]. The procedure is generally carried out under conscious sedation but it can be helpful to perform the procedure under general anesthesia, especially if multiple cysts need to be drained or the procedure is combined with an ERCP.

Transpapillary Drainage

Transpapillary drainage is the most straightforward and probably the safest drainage route [39, 87, 93, 94]. It requires communication of the cyst with the pancreatic duct and is performed by inserting an endoprosthesis in the pancreatic duct over a guidewire. Whether the endoprosthesis should be advanced all the way into the cyst cavity is unknown. Placement of the stent into the cyst may optimize drainage. A possible disadvantage may be that the outflow from the pancreatic duct located upstream from the cyst is compromised.

Transpapillary drainage is indicated when duct abnormalities (strictures and/or disruptions) are present because they will maintain filling of the cyst. Therefore, imaging of the pancreatic duct system (by MRCP or ERCP) is recommended prior to drainage. Because duct strictures require prolonged dilation treatment, stent therapy is generally continued well after cyst resolution has been accomplished. The disadvantage of transpapillary drainage is that it will often not suffice if a pseudocyst is large or contains debris, because a single small-diameter stent cannot provide sufficient drainage. In that case, a combination of transpapillary and a transmural drainage is recommended [93]. In our practice we consider cysts >6 cm an indication for drainage by multiple routes.

Transmural Drainage

Transmural pseudocyst drainage is achieved by placing stents through the wall of the stomach or duodenum. Traditionally, a side-viewing endoscope was used to puncture the gastrointestinal wall at the site of most the prominent bulge. With the introduction of endosonography (EUS), cyst drainage techniques have greatly evolved. At first,

a radial echoendoscope was used in a step-by-step procedure to identify the optimal drainage site [86, 95, 96]. Subsequently, a side-viewing duodenoscope was introduced to perform the drainage procedure.

Later, the single-step technique was developed using a therapeutic linear echoendoscope, with a number of potential advantages; it is likely to shorten the procedure time and does not carry the risk that the identified drainage site will be lost when the endoscopes are switched. Furthermore, real-time vision of the puncture allows better identification of the safest and shortest drainage route [97]. In addition, EUS guided drainage expanded the indications of pseudocyst drainage because it allows drainage of non-bulging cysts. Finally, it allows a better definition of the amount of debris and necrosis within the cyst.

Retrospective studies reported conflicting results of this technique and the single prospective cohort study did not find a clear difference in safety or efficacy compared to the conventional two-step approach. Only one prospective randomized trial compared the two drainage procedures and reports a 100% success rate of EUS guided drainage as compared to a 33% success rate of the conventional drainage technique, with a similar complication rate. At present, the 'EUS-guided' technique has been adopted as the preferred drainage method by most expert centers [98].

There are several techniques to perform EUS-guided drainage utilizing a range of different accessories. Application is largely based on personal preference and experience. Nevertheless, some general remarks can be made with respect to their implementation.

The procedure is started by determining the optimal puncture site, either in the stomach or in the duodenum. The site is selected based on the presence of interposing blood vessels and the distance between the cyst and the gastrointestinal wall. Generally, a distance up to 1 cm is considered safe; however, drainage is possible up to a distance of 2.5 cm.

To enter the cyst, a regular sphincterotome is not recommended as it is associated with an increased risk of bleeding. Access can be gained with a regular 19-gauge needle, or electrocoagulation may be used to burn a hole with a specially designed cystotome. An advantage of the latter is that it is relatively easy to introduce a catheter once the inner part of the cystotome is inside the cyst. A disadvantage is that the inner part of the cystotome is floppy and that its EUS visibility is poor. Furthermore, Monkemuller observed less bleeding when puncturing was performed without electrocoagulation [99, 100]. Therefore, we prefer to use a regular 19-gauge needle. It is important to puncture the cyst as tangentially as possible to decrease the distance that needs to be traversed. Once the needle is inside, cyst fluid is aspirated for culture, cytology and analysis of biochemical markers and 10–20 cc of contrast is injected to delineate the cyst. A stiff, long (480-cm) ERCP guidewire is then advanced into the cyst to secure access and the most difficult part of the procedure, dilation of the cyst-gastrostomy tract, begins. It is almost

always possible to follow the wire with an 8-mm biliary dilation balloon. If the dilation balloon cannot be passed into the cyst, the outer part of the cystotome can be advanced over the guidewire into the cyst using electrocoagulation. Other options include the use of a narrow tip ERCP cannula, a biliary dilation catheter, or a 6-Fr cystotome. At this stage it is important to use the ultrasound image to keep the optimal position and only convert to the endoscopic image after the dilation balloon has entered the cyst cavity.

Insertion of multiple (mostly three) endoprosthesis is recommended to prevent clogging and secondary infection of the cyst [101]. After placement of the first stent, one needs to regain access into the cyst for subsequent stent placement. This can be difficult due to a change in the position of the endoscope once the cyst is decompressed. Therefore, it is best to introduce a second guidewire before placing the first stent. If a cystotome was used to gain access, it is easy to introduce 2 guidewires through the outer catheter. Another option is to use an 8.5-Fr stent introduction system (Oasis®; Cook Endoscopy, Inc.) which makes it quite easy to place a second wire inside the cyst [19]. Generally, 7-Fr stents with a length of 4–6 cm suffice. Stents with a double pigtail configuration are advocated because they are safer, with less chance of migration, perforation, and bleeding due to erosion of the stent though the cyst wall [87, 96] (fig. 2).

If there is a clinical suspicion of infection it is advisable to place a 6-Fr nasocystic catheter and start cyst irrigation with 1 liters of water or saline per 24 h with manual boluses of 100–200 ml every 4–6 h depending on cyst size and aspect. When the cyst contains debris and solid or necrotic material, an endoscopic reintervention should be performed after 1 or 2 days with further dilation of the fistulous tract up to 18 mm

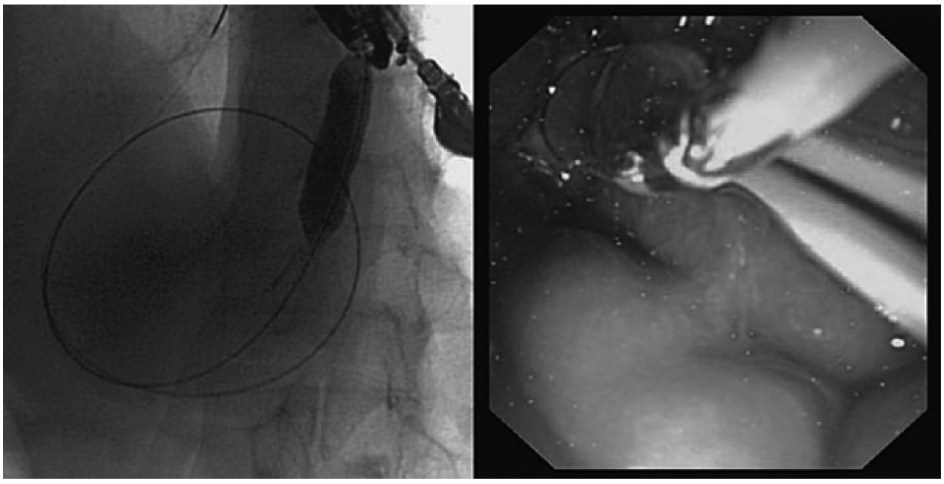

Figure 2: Transgastric pseudocyst drainage.
2a Fluoroscopic image of the dilation of the cystenterostomy opening with balloon.
2b Endoscopic image of the dilation procedure after the first two pig-tail stents have already been inserted.

to allow endoscopic debridement with a forward viewing endoscope. A therapeutic gastroscope has a better suctioning capability, but is less flexible. Necrosectomy is best done with a Dormia basket or a Roth net and occasionally a grasping forceps can be useful. If stents are removed during the necrosectomy, it is important to leave at least one stent in place to reduce the chance of a blow-out of the cyst due to hyperinflation. Usually several repeat procedures are necessary until viable tissue of the wall of the cyst is clearly visible. In between these procedures cyst irrigation is maintained using a nasocystic catheter.

Before stents are endoscopically removed, cyst resolution is affirmed by an abdominal ultrasound, computed tomography or MRCP. The optimal duration of drainage is unknown, but generally the stents are left in place for at least several weeks [87, 102]. In our retrospective study, we observed superior outcome after a drainage period of at least 6 weeks, and therefore have adapted our drainage protocol accordingly [86].

Under specific circumstances it is probably safe to leave the stents in situ for an indefinite period, e.g. in older patients and in patients that are not able to undergo any further interventions. An interesting topic for future research is the use of covered metal stents or biodegradable stents instead of plastic stents to maintain the fistulous tract between the cyst and gastrointestinal lumen [103, 104].

Outcome

A systematic review of 25 published series regarding endoscopic pseudocyst drainage in a total of 569 patients reported an overall success rate of 81% (range 50–100%), a complication rate of 12%, a mortality rate of less than 1%, and a recurrence rate of 14% [87]. However, these studies encompassed patients suffering from both acute and chronic pancreatitis, which is relevant because the outcome seems to be more favorable for patients with chronic pancreatitis.

Beckingham was the first to observe that the success rate varied according to the nature of the underlying disease (75% in chronic pancreatitis as opposed to 25% in acute pancreatitis) [105]. Baron et al. confirmed this finding when he differentiated outcome according to acute, necrotizing and chronic pancreatitis and reported that pseudocyst drainage was the most effective and the safest for patients with chronic pancreatic with a success rate of 92% and a complication rate of 17% [95].

Retrospective studies have suggested a more favorable outcome in patients with a cyst located in the pancreatic head [106]. Furthermore, although the transgastric route is most often performed, some studies report a slight advantage of the transduodenal-route [69, 87, 93, 107].

Summary

For patients with chronic pancreatitis, endoscopic pseudocyst drainage is an effective and safe therapeutic modality and should be the treatment of first choice when available. However, pseudocyst drainage is a challenging procedure and requires an experienced interventional endoscopist. Surgery and percutaneous drainage should be reserved for patients in whom endoscopic drainage failed.

BILIARY DRAINAGE

Introduction

Approximately 10–30% of patients with chronic pancreatitis will develop a common bile duct obstruction during the course of their disease [105]. This biliary obstruction may arise from two distinct mechanisms; compression of the duct as a result of periductal swelling of the pancreas caused by acute inflammation, or fibrotic structuring caused by ductal damage due to the chronic inflammatory process. Biliary strictures are associated with a broad spectrum of presentations, from mildly elevated liver enzymes to complete biliary obstruction. Cholangitis is a life-threatening complication and an obvious indication for drainage, but subclinical cholestasis requires drainage too, as it may lead to secondary biliary cirrhosis. Therefore, biliary drainage is indicated regardless of the presenting symptoms [108, 109]. Traditionally, a surgical bypass (i.e., choledochojejunostomy or hepatojejunostomy) was the only treatment option. Although surgery provides a definite solution, the associated morbidity and mortality lead to the investigation of alternative drainage techniques. At present, endoscopic stenting is often chosen as the initial therapy, in analogy with postoperative biliary strictures for which endoscopic treatment was reported to be successful in 43–83% of patients [108, 110–113].

Procedural Aspects

When a biliary obstruction is suspected, imaging studies (computed tomography or MRCP) are necessary to affirm the diagnosis, to rule out malignancy, and to evaluate the presence of other pancreatitis associated complications. Subsequently, an endoscopic retrograde cholangiogram is performed. A common bile duct stricture is identified as a distal narrowing of the duct with prestenotic dilatation and/or delayed runoff of the contrast agent. At the start of stent treatment a biliary sphincterotomy is performed to facilitate repeat access to the biliary tree and enable insertion of multiple stents later in the course of treatment. In case of a tight stricture (which cannot be passed by a regular 5- to 6-Fr ERCP catheter), dilatation is indicated, either with a balloon or graduated dilating catheter. Finally, a polyethylene Amsterdam-type stent (10-Fr) is inserted over a guiding catheter, long enough to bridge the stricture (usually 7 or 9 cm between the flaps).

Generally, after 3 months a cholangiogram is repeated. The stricture is considered sufficiently dilated when the stricture-waist and the proximal dilatation have disappeared. Furthermore, duct patency can be affirmed with a regular ERCP catheter, which should pass the stricture without resistance. In addition, observing a rapid runoff of the injected contrast agent (within 1–2 min) is proof of sufficient stricture resolution. When the stricture is resolved the stent treatment is terminated, but if the stricture persists, treatment needs to be continued. The aim of further stenting should be to maximize the dilation force. This is accomplished by inserting multiple stents in a cumulative fashion. With each procedure the stricture is first further dilated, followed by the insertion of an increasing number of endoprostheses. When stricture resolution is not accomplished within a 1-year period (after 3 stent exchange procedures), a successful outcome is highly unlikely and surgery should be considered [114].

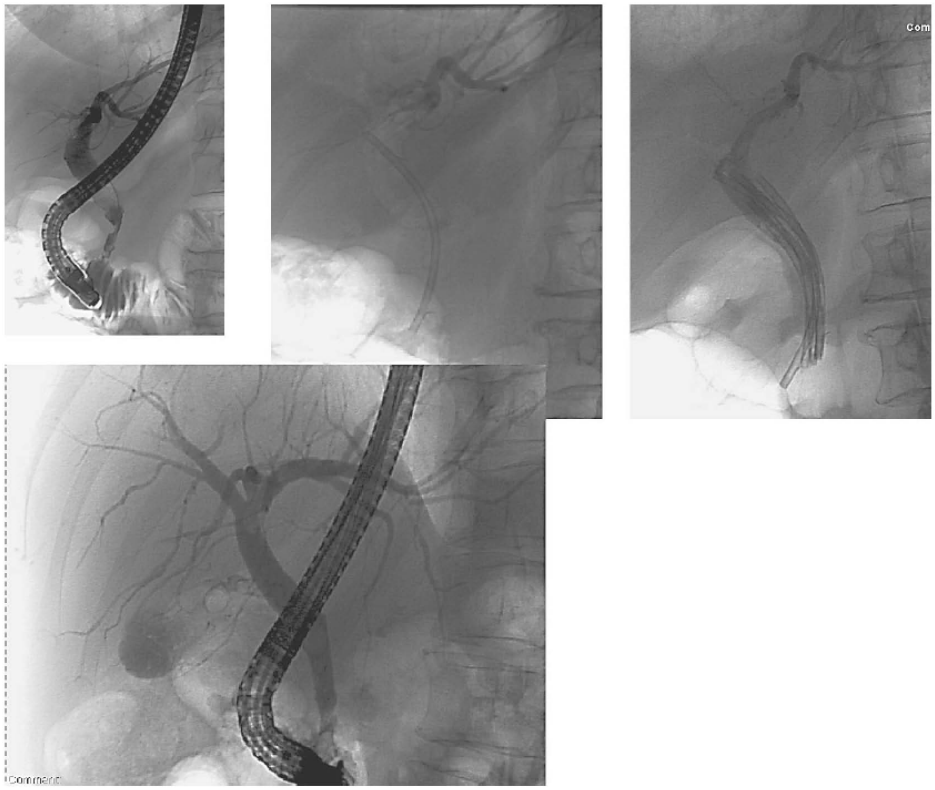

Figure 3: treatment of benign biliary stricture in chronic pancreatitis via progressive plastic stenting
3a. Short distal stricture at level of pancreatic head with upstream dilation.
3b. Initial placement of single plastic stent.
3c. Over 9 months period placement of 5 10 fr stents.
3d. Result after 1 year treatment.

An interesting development is the use of self-expandable metal stents as an alternative treatment. A number of small series showed metal stents to be effective in treating biliary strictures due to chronic pancreatitis, but their irremovable nature makes them unsuitable for use in this benign disease [104, 115–118]. To overcome this problem, removable metal stents were developed, equipped with a covering and extraction lasso to enable stent extraction. At present, experience with these stents is limited to several positive case reports [103, 119]. Future studies should aim at further improving this technique, because the larger stent diameter makes them an attractive alternative to dilatation with plastic stents; stent occlusion occurs less often and frequent stent exchanges are unnecessary [120]. Furthermore, treatment may be more efficient because the maximal dilatation force is effective from the very beginning of endoscopic treatment, in contrast to cumulative insertion of plastic stents in which case the dilatation force is gradually increased with each procedure.

Outcome

Obviously, biliary stents are able to resolve cholestasis temporarily, but they are less likely to achieve long-term dilatation in patients with chronic pancreatitis. Published series reported disappointing long-term success rates of 10–38% using single stents [114, 121–124]. Despite the overall poor results of endoscopic treatment, a subset of patients might benefit from biliary drainage. Kahl et al. [124] evaluated prognostic factors of outcome in biliary stenting and showed that the presence of calcifications in the pancreatic head was a strong predictor of a more negative outcome. In the 39 patients with calcifications, long-term success was achieved in 8% only, whereas in the 22 patients without calcifications a successful long-term outcome was observed in 59%. The explanation for this finding may be found in the different mechanisms of biliary obstruction in chronic pancreatitis. Because calcifications are a sign of long-standing chronic pancreatitis, one might hypothesize that the strictures in these patients are typically of fibrotic nature and therefore difficult to dilate. The patients without calcifications are more likely to have developed an obstruction secondary to edema, which subsides over time and only requires temporary bridging of the stricture.

For this purpose, stent placement is most appropriate. Results from our recently published series endorse this theory with the presence of concomitant acute pancreatitis resulting in a 95% chance of a successful treatment as opposed to a 24% success rate in its absence [114]. This phenomenon might also explain the unusually high 80% success rate observed by Vitale et al. [125] after balloon dilatation and stenting of biliary strictures; calcifications were present in only 4 out of the 20 patients that were studied.

An obvious way to improve outcome is a more vigorous dilatation of strictures by placing multiple stents. In the treatment of postoperative biliary strictures, this has been proven highly effective, and Draganov et al. [126] was the first to apply this method to

patients with chronic pancreatitis. By inserting a cumulative number of stents with each procedure, stricture resolution was achieved in 4 of 9 patients (44%). However, in the subgroup of patients with calcifications, the results remained disappointing; stricture resolution was accomplished in 1 of 6 patients. Pozsár et al. [127] later placed the maximal number of stents that the stricture would allow (with a median of 2), which resulted in a 60% stricture resolution. Catalano et al. [31] even achieved a 100% success rate in 12 patients by inserting at least 4 stents.

Serious adverse events of biliary stenting are rare. Stent occlusion is the only complication that is frequently encountered (in most studies in approximately 35%), even when stents are exchanged on a regular basis [114, 123, 127–130]. Mostly, this complication is easily treated by stent exchange. However, in patients with pancreatitis caused by alcohol abuse, noncompliance is a considerable risk. Not showing for the arranged stent exchange can result in severe cholangitis, sepsis and even death[127, 128].

Summary

At present, endoscopy has become the first-line approach for the treatment of postoperative biliary strictures, but strictures related to chronic pancreatitis are much more difficult to treat, especially fibrotic strictures, and patients should be informed about the limited efficacy. If, nevertheless, endoscopic therapy is chosen, an aggressive approach is preferred, with the insertion of a cumulative number of stents earlyin the course of treatment. In this respect, the use of removable fully covered selfexpandable metal stents is promising because they immediately provide a dilation diameter of 30 Fr which is equivalent to seven 10-Fr plastic stents. When the stricture has not resolved within a 1-year period, the patient should be referred for surgery.

GENERAL CONCLUSIONS

In chronic pancreatitis, the lack of well-defined clinical trials combined with an evolving endoscopic technology has created a strong need for prospective studies to further clarify the indications, methods and duration of endoscopic interventions.

Overall, the future of endoscopic treatment in chronic pancreatitis seems to lie in a pro-active approach; treating pancreatic duct strictures at an early stage of the disease, extensive debridement of pseudocysts, and a fierce dilatation of biliary strictures.

Most importantly, surgery and endoscopic treatment should not be regarded as competing strategies but as complimentary treatments. Therefore, during the course of endoscopic treatment, patients should be carefully monitored and regularly discussed by a multidisciplinary team and when relief of symptoms and/or progression is not satisfactory, surgery must not be postponed. Moreover, when more than one complication

is simultaneously diagnosed in a patient, (i.e. a pancreatic duct stricture and a common bile duct stricture) surgery might be considered at an earlier stage, because the overall chance of long-term endoscopic success decreases with each additional complication.

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9

Clinical outcome of progressive stenting in patients with anastomotic strictures after orthotopic liver transplantation

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ABSTRACT

Background and study aims

Anastomotic strictures are an important cause of morbidity after orthotopic liver transplantation (OLT). Endoscopic treatment is the primary treatment modality for biliary complications after OLT. The outcome and complications of a progressive stenting protocol are largely unknown.

Patients and methods

A longitudinal cohort study of OLTs was conducted. Only patients with late strictures were included. Treatment success was defined as cholangiographic stricture resolution and liver enzymes returning to normal with follow-up of at least 12 months.

Results

Between May 2000 and June 2009, 375 OLTs were performed. A duct-to-duct anastomosis was created in 304 cases (81%). In 63 patients (21%; 95% confidence interval [CI] 16.5%–25.6%) an anastomotic stricture developed and progressive stenting was started in 35. During treatment two patients died of a non-treatment-related cause and two patients underwent a second OLT during stent therapy. Therefore 31 patients were available for analysis (male:female 21:10; median age 61 years, range 28–75 years). Progressive stenting required a median number of 5 endoscopic retrograde cholangiopancreatography (ERCP) procedures (range 4–11). A median maximum of 4 stents (range 2–8) were inserted. A total of 21 patients (67.7%; 95%CI 50.1%–81.4%) developed a treatment-related complication. In 33 out of a total of 155 ERCPs (21.3%) a complication occurred: cholangitis (n = 12), transient cholestasis (n = 11), post-ERCP pancreatitis (n = 7), and treatment-related pain (n = 3). The median follow-up time after stent removal was 28 months (range 12–92). Treatment was successful in 25 patients (80.6%; 95%CI 63.7%–90.8%).

Conclusion

Progressive stenting for anastomotic strictures after OLT is demanding and burdensome, necessitating a median of 5 ERCP procedures with complications occurring in one out of five procedures. Its success rate however is high (81%), avoiding surgery in the large majority of patients.

INTRODUCTION

After orthotopic liver transplantation (OLT) a considerable proportion of patients develop biliary complications. The incidence, including leakage, strictures, and stone and cast formation, is approximately 30% and complications are therefore one of the most important causes of OLT-related morbidity [1–5]. At present, endoscopic retrograde cholangiopancreatography (ERCP) is considered to be the cornerstone of treatment of these complications. Alternative options such as percutaneous balloon dilation of the stricture or surgical hepaticojejunostomy are considered to be less efficacious or more invasive [6,7].

Strictures after OLT can be located at the biliary anastomosis or can be non-anastomotic. Non-anastomotic strictures typically involve the hepatic ducts of the donor liver and are thought to be caused by ischemia or donation after cardiac death [8,9]. These strictures tend to respond less favorably to therapy and often require a re-transplant, although aggressive endoscopic therapy may slightly improve outcome [10,11]. The vast majority of biliary strictures after OLT are at the anastomosis and multiple case series have shown a favorable response to various methods of endoscopic therapy including balloon dilation, stenting (single or multiple stents), or a combination of both, with success rates between 65% and 94% [12–16].

The drawback of these series is that they either do not contain original data or report on a small number of patients [12–15]. The largest series published to date (n = 69) also included a significant number of patients with early anastomotic strictures, usually defined as strictures occurring within the first month after OLT. Due to the particular nature of these early strictures, likely being caused by postoperative edema rather than ischemia and fibrosis, they tend to respond better to therapy. For this reason the results of that series regarding the outcome of endoscopic therapy are probably too optimistic for true fibrotic anastomotic strictures [17].

Nowadays, in most institutions a "progressive stenting" protocol is followed whereby an increasing number of plastic endoprotheses, tailored to the diameter of the duct, are inserted at intervals of 3 months over a 1-year period [18]. However, there are several drawbacks to this approach, of which multiple procedures for one treatment cycle is the most important one. This results in a considerable burden for both patients and endoscopy units. Furthermore, the duration of therapy increases the risk of stent dysfunction and ensuing cholangitis necessitating stent exchange, although this risk probably decreases with the number of stents placed. For these reasons several case series have been published describing the use of fully covered self-expandable metal stents (fcSEMS) in patients with anastomotic strictures after OLT [19–24]. When evaluating a new treatment methodology such as fcSEMS, it is of particular importance to compare its merits with the standard treatment of which outcome and complication risks should

be well known. However, there is still a paucity of data on efficacy and complications of progressive plastic stenting in patients with OLT and existing data are based on either small or non-representative series. We therefore aimed to explore the outcome of a progressive plastic stenting protocol in patients with an anastomotic stricture after OLT.

PATIENTS AND METHODS

A longitudinal cohort study was conducted based on data recorded in a prospectively maintained registry of all adult patients who underwent a deceased donor OLT between May 2000 and June 2009. Analysis of these data was done with local institutional review board approval. T-tubes were not routinely used during this period. During the study a progressive stenting protocol was followed for the treatment of anastomotic stricture. Before the inclusion period usually one or two stents were placed and after the end of the period most patients with anastomotic strictures were treated with fcSEMS as part of a study protocol. In the progressive stenting protocol used during the study period, a single 10-Fr endoprothesis was initially inserted. After improvement of clinical and biochemical parameters, progressively more stents were placed at 3-monthly intervals over a period of 1 year. The goal was to insert as many stents as the diameter of the donor hepatic duct allowed for.

Inclusion criteria were the presence of a duct-to-duct anastomosis and signs of cholestasis, jaundice or cholangitis. Strictures were defined as relevant when significant narrowing or tapering was seen at cholangiography and improvement of cholestatic liver enzymes occurred after initial stent placement. With this strategy patients with any other cause of liver enzyme disturbances (recurrence of the underlying liver disease, rejection) could reliably be excluded and did not undergo progressive stenting.

Exclusion criteria were a presumed dominant stricture at a level other than the anastomosis, a hepaticojejunostomy as primary anastomosis, and early strictures, defined as occurring within the first month after OLT and disappearance of stricture after initial single stent therapy.

ERCPs were performed under conscious sedation by experienced pancreaticobiliary endoscopists. Intravenous antibiotic prophylaxis was routinely given shortly before the start of the procedure and continued for 24 hours. In all cases a sphincterotomy was performed if not done previously. Balloon dilation of the stricture was performed at the discretion of the endoscopist to facilitate stent placement and was never used as a sole treatment modality, although virtually all patients (29/31; 93.5%) underwent at least one balloon dilation during one or more of the ERCPs.

Statistical analysis was performed with SPSS v 15.0 (Chicago, Illinois, USA). Treatment success was defined as absence of a stricture during cholangiography at the end of the

protocol, as confirmed by easy passage of an inflated balloon through the anastomosis, adequate run-off of contrast, and no recurrence of cholestasis, jaundice, or cholangitis due to a recurrent stricture during follow-up. Re-admission to the hospital within 1 week or prolonged stay after the procedure was considered a serious adverse event.

RESULTS

During the inclusion period a total of 375 OLTs were performed (Fig. 1). Of the 304 patients in whom a duct-to-duct anastomosis was created, 63 developed an anastomotic stricture (21%; 95% confidence interval [CI] 16.5%–25.6%). The reasons for not entering the progressive stenting protocol in 28 patients were diverse: early anastomotic stricture that responded well to short-term stenting in 16 patients, treatment with fcSEMS

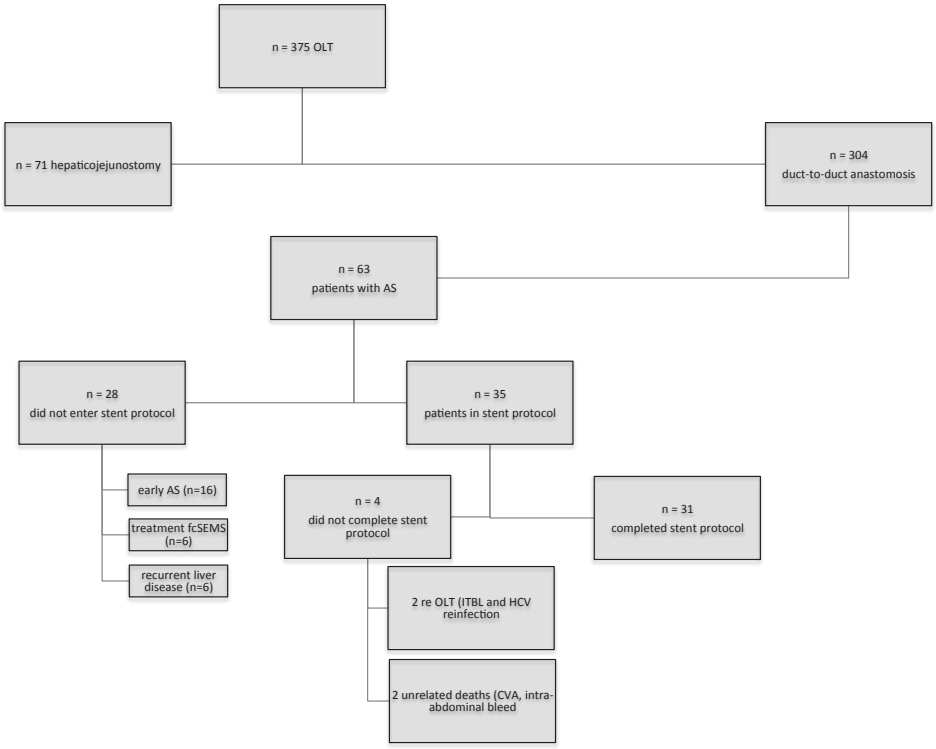

Figure 1: Flowchart of patients through the study
CVA: Cerebrovascular accident
fcSEMS: fully covered self-expandable metal stent
HCV: Hepatitis C
ITBL: Ischaemic type biliary lesions
OLT: orthotopic liver transplantation

Table 1: Patient characteristics

Patient characteristics	
Patients in progressive stenting protocol	31
Gender (male/female)	21 / 10
Median age (years)	61 (28 – 75)
Median follow-up (months)	28 (12 – 92)

in 6 patients, and in 6 patients cholestasis was not caused by a dominant anastomotic stricture but by recurrence of the underlying liver disease. Four patients did not complete the protocol: two underwent a second OLT (one because of ischemic type biliary lesions, the other because of acute liver failure due to re-infection with hepatitis C), and two patients died of unrelated causes (one intra-abdominal bleed, one cerebrovascular accident). These four patients were excluded from the analysis.

The characteristics of the remaining 31 patients are shown in Table 1. Patients required a median number of 5 ERCPs (range 4–11). The median maximum number of 10-Fr stents was 4 (range 2–8). Complications requiring hospital admission or a prolonged stay after the procedure occurred in 21 patients (67.7%; 95%CI 50.1%–81.4%). Calculated per procedure the complication risk was lower: 22 serious complications were noted in a total of 155 procedures (14.2%; 95%CI 9.6%–20.6%). Complications were cholangitis (n = 12; three occurring immediately after ERCP and treated with prolonged antibiotics), post-ERCP pancreatitis (all mild, n = 7), and treatment-related pain that responded to the use of temporary analgesics (n = 3). Although not uncommon, transient cholestasis (n = 11) was not classified as a serious complication. No mortality was observed.

Overall treatment success, defined by absence of recurrence of cholestasis, jaundice, or cholangitis due to a recurrent stricture, was achieved in 25 out of the 31 patients who completed the protocol (80.6%; 95%CI 63.7%–90.8%). Median follow-up after stent removal was 28 months (range 12–96 months).

The six patients in whom the progressive stenting protocol failed were treated either with hepaticojejunostomy (n = 5) or placement of a fcSEMS (n = 1).

DISCUSSION

The majority of patients who completed the progressive stenting protocol were successfully treated endoscopically. As the study was based on a prospectively maintained registry of a rigidly performed protocol and all transplant patients are closely followed at our hospital for the remainder of their lifetime the quality of the treatment and follow-up data is ensured.

Although patients with anastomotic stricture after OLT are increasingly treated with fcSEMS, the evidence for this strategy is scarce given the lack of comparative studies and the quality of published data with regard to the outcome of treatment with plastic stenting. The introduction of any new technique or method should, preferentially, be compared with a standard treatment. This is particularly true for the use of fcSEMS in benign biliary strictures, including those occurring after OLT, given the non-negligible chance of complications including migration, cholangitis, and secondary strictures [19–24]. To truly evaluate and subsequently compare techniques, patient populations investigated should be as homogeneous as possible. We therefore took care to include only patients with true anastomotic stricture after OLT and excluded all patients with early and non-anastomotic strictures. This is of great importance because including patients with early strictures of edematous nature, overestimates the true virtues of any dilation therapy. This is true for both progressive plastic stenting as well as fcSEMS treatment. All patients included in this series had true fibrotic anastomotic strictures. Therefore, the current results can be regarded as truly representative for the effect of treatment with progressive plastic stenting, and the risk of selection bias by including patients with early anastomotic strictures and non-anastomotic strictures is reduced.

The quality of the data and interpretability of results of the present series are also substantiated by the length of follow-up, as it is likely that any benign biliary stricture will show immediate cholangiographic improvement after a period of (aggressive) stenting, whether progressive with plastic or with temporary placement of fcSEMS. The true value of outcome data can therefore only be interpreted after significant length of clinical follow-up and laboratory evaluation. The minimum follow-up period of 12 months and median follow-up of 26 months further increases the strength of the current data.

The overall success rate in this series was 81% which is in line with previously published studies [12–16]. This should be regarded as the gold standard success rate of a progressive plastic stenting protocol in anastomotic stricture and is the benchmark for future studies, for example with fcSEMS. However, the efficacy of this, and other, progressive stenting protocols comes at a price. The number of procedures required to achieve this efficacy was high and the related costs of procedures, equipment, and hospital admissions would be considerable. Furthermore, although these procedures are technically not very complicated, the burden for patients should not be underestimated. This is illustrated by the considerable complication risk. The risk of complications, mainly cholangitis and pancreatitis, as calculated per patient when available in previously published studies, is usually lower than in the current study but varies between 1.4% and 24.3% [12,14,16,17,25]. These differences are more likely to be caused by the retrospective nature of previously published studies on this subject than by inherent differences in patient care, technique, or differences in patient populations. Nevertheless, a per procedure risk of 14.2% for serious complications is substantial.

In summary, although the endoscopic treatment of biliary anastomotic strictures by means of a progressive plastic stenting protocol is demanding for patients and labor intensive for healthcare providers, it is highly efficacious and saves 80% of patients from undergoing complicated surgical repair or even a re-transplantation.

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Comparative Cost Effectiveness Analysis of Progressive Plastic Stenting versus Covered Metal Stenting in patients with anastomotic strictures after orthotopic liver transplantation

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ABSTRACT

Background

Treatment of patients with anastomotic strictures (AS) after orthotopic liver transplantation (OLT) by progressive plastic stenting (PPS) is effective, but expensive and burdensome given the necessity for multiple ERCPs. Recently several case series have been published describing the use of fully covered self-expandable metal stents (fcSEMS). It is not known whether this approach decreases costs besides potentially reducing the number of procedures. We therefore modelled the costs of various fcSEMS scenarios in relation to the costs of PPS.

Methods

PPS costs were obtained from a longitudinal cohort of 31 AS patients who were treated in our hospital with a success rate of 80%. For PPS a median of 5 ERCPs were required and resulted in a median of 1 complication per patient. We performed a top-down cost-analysis of PPS and compared this with the cost of six hypothetical models of fcSEMS treatment. Treatment costs were calculated using source data from the financial department of our hospital. For this analysis we assumed that the efficacy of fcSEMS treatment, i.e. stricture resolution, was equal or greater than PPS and complication rates would be equal. The most optimistic scenario assumes that only 2 ERCPs and 1 fcSEMS would be required in all patients. We calculated the maximal cost reduction with a stent prize of € 1000 (fcSEMS A) or € 1500 (fcSEMS B). We also performed a break-even calculation by determining the maximum allowed number of ERCPs with fcSEMS placement per patient assuming that the total treatment costs are equal to PPS, with a stent prize of € 1000 (fcSEMS C) or € 1500 (fcSEMS D). Finally, a clinical scenario was modeled assuming that a second ERCP with fcSEMS placement was needed in 30% of cases and a third ERCP with fcSEMS placement in 10% of cases, with a stent prize of € 1000 (fcSEMS E) or € 1500 (fcSEMS F) and calculated the cost reduction compared to PPS. ERCP costs without stent placement were € 750 and costs of plastic stents € 51 a piece.

RESULTS

Per patient costs for PPS were calculated at €4196. The use of fcSEMS reduced costs in all scenarios. The highest reduction was achieved in scenarios A and B, respectively €1696 (40%) and €1196 (29%). In scenarios E and F, allowing for 2nd and 3rd fcSEMS placement in a subset of patients the cost reduction was less pronounced but still considerable at €996 (24%) and €296 (7%). Finally, in scenarios C and D the mean number of fcSEMS that were allowed according to a break-even cost analysis was 1.97 and 1.53 respectively.

Conclusions

Treatment of AS after OLT with fcSEMS compared to PPS potentially saves costs in all calculated clinical scenarios and is largely dependent on the price of fcSEMS. Even when allowing for 2nd fcSEMS placement in 30% of the patients and 10% a 3rd ERCP with fcSEMS placement, total treatment costs are lower. Importantly, this scenario would also result in a 50% reduction in the number of ERCPs which should be considered a major benefit from the patient's perspective.

INTRODUCTION

The incidence of biliary complications, including leakage, strictures and stone and cast formation, is approximately 30% and therefore one of the most important causes of OLT related morbidity[1-5]. While the treatment of both stones and leakage is usually straightforward, the treatment of biliary strictures after OLT can be challenging and demanding for both physicians and patients. Biliary strictures after OLT are in most instances located at the site of the anastomosis[6]. The preferred treatment for anastomotic strictures (AS) nowadays is endoscopic since it is superior to percutaneous alternatives and less invasive than surgical options[7, 8]. Until recently in virtually all institutions a protocol consisting of progressive plastic stenting was used to treat AS. During successive ERCP's at three monthly intervals an increasing number of plastic stents is used to dilate the stricture over the course of one year[9]. In the series published thusfar the efficacy of this treatment is between 65% and 85%[4, 10-15].

Recently several case series have been published describing the use of temporary, removable partially and fully covered self expandable metal stents (pcSEMS and fcSEMS) in benign biliary strictures (BBS) including AS after OLT[16-23]. Efficacy with regards to stent resolution and complication rate are roughly similar or better compared to PPS but at the prospect of fewer ERCP procedures and hospital admittances the use of fcSEMS is emerging as an attractive treatment option for OLT patients with AS.

There are however no data available with regards to the cost-effectiveness of this approach. Since trials comparing PPS and fcSEMS in BBS have not yet been published and efficacy and complication rates in the published case series are equivalent cost-effectiveness becomes even more important before this new treatment modality can be recommended as standard care especially given the rising costs of healthcare. In cost-effectiveness analysis it is conventional to distinguish between the **direct costs** and **indirect** or **productivity costs** associated with the intervention, as well as what are termed **intangibles,** which, although they may be difficult to quantify, are often consequences of the intervention and should be included in the cost profile.

Examples of direct costs are both medical, e.g. drugs; staff time and costs of equipment and patient related such as transport and out-of pocket expenses.

Examples of productivity costs are production losses and other uses of time.

Intangibles are for example pain, suffering and adverse effects.

It is essential to specify which costs are included in a cost-effectiveness analysis and which are not, to ensure that the findings are not subject to misinterpretation.

It is unknown whether the use of fcSEMS decreases costs compared to PPS. A potential benefit of fcSEMS is that ideally only 2 ERCP's are necessary during treatment. A potential disadvantage of fcSEMS is their high cost. To answer the question of cost-effectiveness on the use of fcSEMS we undertook an analysis on our own cohort of patients that were treated in our institution with PPS.

METHODS

We performed a cost-analysis where in which we modeled the costs of various fcSEMS scenarios and compared those with the costs of PPS. The data from PPS were obtained from a longitudinal cohort of 31 patients with AS after OLT that were treated in our institution (Endoscopy 2013). The success rate at 12 months of PPS in this cohort was 80%. To achieve this a median of 5 ERCP's were required with a median maximum number of four 10 fr. stents at the end of treatment. The rate of major complications was considerable, per procedure the complication risk (cholangitis, pancreatitis and post procedural pain) was 14% and in total 21 of 31 patients (68%) encountered some kind of complication during the course of treatment.

In this cost-analysis, costs were calculated top-down meaning that direct costs were retrieved from the source data of the financial department of our institution. With this method all costs of the procedure, including used accessories and costs of admittance are included in the analysis. Thus calculated we compared the costs of PPS with six different hypothetical scenarios of fcSEMS treatment.

To perform the analysis we made several assumptions. Firstly, we presumed that the efficacy of fcSEMS treatment is equal or better than PPS. Secondly, we assumed that complication rates of both treatment options are equal.

The cost of an ERCP without stentplacement was calculated at €750. Costs of plastic stent placement were €51 a piece. For the analysis two prices of fcSEMS were used, initially a price of €1500 was chosen but since the price of fcSEMS is decreasing, scenarios with a price of €1000 per fcSEMS were also calculated.

Six scenarios were calculated. Scenarios A and B are the most optimistic in assuming that only two ERCP's and one fcSEMS would be necessary at respectively €1000 en €1500 per fcSEMS. In scenarios E and F it was assumed that a second ERCP with fcSEMS placement would be necessary in 30% of patients and a third ERCP with fcSEMS placement in 10% of treated patients. Finally, in scenario C and D a break-even calculation was performed to determine the mean number of ERCP's with fcSEMS per patient at what point the costs of fcSEMS and PPS are equal.

RESULTS

The results of the analysis are depicted in table 1. The total costs of PPS were calculated at €4196. The use of fcSEMS contributed to lower costs in all scenarios. Not surprisingly the highest reduction was achieved in the most optimistic scenarios A (cost of fcSEMS €1000) and B (cost of fcSEMS €1500) when assuming that only 2 ERCP's were needed in the fcSEMS scenario. If this would be the case a cost reduction of €1696 (scenario A) or €1196 (scenario B) can be achieved, reducing costs of treatment by 40% and 29% respectively.

In scenarios E (cost of fcSEMS €1000) and F (cost of fcSEMS €1500), assuming perhaps more realistically that 30% of patients would need placement of a second fcSEMS and

Table 1: cost analysis of different scenarios.

Scenario	Treatment costs	Mean ERCPs with fcSEMS placement	Total ERCPs per patient	Cost reduction compared to PPS
PPS	€ 4196	0	5.0	
fcSEMS A	€ 2500	1.0	2.0	€ 1696 (40%)
fcSEMS B	€ 3000	1.0	2.0	€ 1196 (29%)
fcSEMS C	€ 4196	1.97	2.97	
fcSEMS D	€ 4196	1.53	2.53	
fcSEMS E	€ 3200	1.4	2.4	€ 996 (24%)
fcSEMS F	€ 3900	1.4	2.4	€ 296 (7%)

PPS: progressive plastic stenting
fcSEMS: fully covered self expandable metal stent

10% placement of a third fcSEMS, the use of fcSEMS also would lead to significant cost reduction compared to PPS. In scenario E costs would be reduced by €996 (24%) and in scenario F still by €296 (7%).

Finally, in scenarios C and D, once again with assumed prices of fcSEMS of €1000 and €1500 respectively, the break-even point was calculated. This results in the maximum mean number of ERCP's with fcSEMS placement allowed to achieve equal costs for fcSEMS placement compared with PPS. In scenario C this number is 1.97 meaning that if, on average, 1.97 ERCP's with fcSEMS placement per patient are performed costs are equal. If this number is lower, the use of fcSEMS leads to cost reduction. Inversely, for higher averages, the use of fcSEMS becomes more expensive. For scenario D this number is 1.53.

DISCUSSION

To our knowledge this is the first study investigating the cost-effectiveness of the use of fcSEMS in the treatment of patients with AS after OLT. We clearly show that the use of fcSEMS not only leads to a decrease in patient burden by reducing the number of ERCP's needed but also leads to a significant cost reduction in all clinical scenarios we investigated despite the high prices of fcSEMS in comparison to plastic stents.

For a new technique or method to become accepted efficacy, safety and cost-effectiveness are equally important. Since no comparative studies have been performed, we need to rely on, mainly retrospective, case-series. These have been published on both PPS and fcSEMS treatment [4, 10-24]. When both approaches are compared based on these data, the treatment of post OLT anastomotic strictures with fcSEMS appears to be at least as efficacious as the treatment with PPS. With regards to complications per procedure the data are more varying for both methods and difficult to interpret. General ERCP risks as post-ERCP pancreatitis and sphincterotomy related complications as bleeding and perforation are likely to be similar. Placement of fcSEMS in benign biliary strictures, including AS after OLT, however introduces "new" and potentially serious complications such as proximal and distal migration and removal difficulties[16-18, 20, 22].

Nevertheless, this study has several weaknesses. First, the method chosen, a top-down analysis, potentially misses costs that are not directly handled by the financial department. Second, the scenarios chosen were calculated under the assumption that both success and complication rates are equal for both scenarios. Given the lack of a trial comparing both strategies and the relatively small number of patients in published papers this assumption had to be made, especially since the reported complication rates for PPS vary between 1.4% and 24%.[11-15, 24] For the case series published describing the use of fcSEMS specifically in OLT patients, the complication rate, including migration,

varies between 27% and 47%[19, 21, 22, 25]. Since most migrations in these studies were without clinical consequences, the premise of an equal complication rate seems justified. Efficacy rates in the same series vary between 53% and 94%. It seems likely that these differences are at least partially explained by differences in types of fcSEMS and the duration of treatment.

Strengths of this study are that the used method of cost calculating is robust, especially since data from the financial department were used, and reflect true costs. Furthermore, it seems likely that our results, although calculated only for OLT patients with AS, can be extrapolated to other patients with BBS. AS after OLT are, in common daily practice, rarely encountered and other causes of BBS such as chronic pancreatitis and after cholecystectomy are much more common. Since costs of treatment in BBS are, as our study shows, largely determined by the number of ERCP's needed and the costs of fcSEMS, the principles and the outcome with regards to costs are likely to be interchangeable. However, as in OLT patients, to definitely answer these questions, comparative trials are needed.

In summary, our study clearly shows that, when complication and efficacy rates of both treatment arms are the same, the use of fcSEMS in the treatment of patients with AS after OLT, leads to a substantial cost reduction compared to PPS.

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A prospective group sequential study evaluating a new type of fully covered self-expandable metal stent for the treatment of benign biliary strictures (with video)

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ABSTRACT

Background

Fully-covered self expandable metal stents (fcSEMS) are an alternative to progressive plastic stenting for the treatment of benign biliary strictures (BBS) with the prospect of a higher treatment efficacy and the need for fewer ERCPs, thereby reducing the burden for patients and possibly costs. Key to this novel treatment is safe stent removal.

Aim

We investigated the feasibility and safety of stent removal of a fcSEMS (MITech, Korea) with a proximal retrieval lasso: a long wire thread integrated in the proximal ends of the wire mesh that hangs freely in the stent lumen. Pulling it enables gradual removal of the stent inside-out. Secondary aim was success of stricture resolution.

Methods

Non-randomized, prospective follow-up study with 3 sequential groups of 8 patients with BBS. Patients had strictures either postsurgical (post-cholecystectomy (LCx) or liver transplantation (OLT)), due to chronic pancreatitis (CP), or papillary stenosis (PF). Strictures had to be located at least 2 cm below the liver hilum. All patients had one plastic stent in situ across the stricture and had not undergone previous treatment with either multiple plastic stents or fcSEMS. The first cohort of patients underwent stent placement for 2 months, followed by 3 months if the stricture had not resolved. The second and third cohort started with 3 months and 4 months, respectively, both followed by another 4 months if indicated. Treatment success was defined by stricture resolution at cholangiography, the ability to pass an inflated extraction balloon and clinical follow-up (at least 6 months).

Results

23 patients (11 female; 20–67 yrs) were eligible for final analysis. One patient developed a malignant neuroendocrine tumor in the setting of CP. Strictures were caused by CP (13), OLT (6), LCx (3) and PF(1). In total 39 fcSEMS were placed and removed. Removals were easy and without complications. Transient pain after insertion was common (13 of 23/56%) but was easily managed by analgesics in all patients. Other complications were cholecystitis (1), cholangitis due to stent migration (1, stent replaced) or stent clogging (2, managed endoscopically) and worsening of CP (2). In these patients, the fcSEMS was removed and replaced after pancreatic sphincterotomy and PD stent placement. Median follow-up was 15 months (range 11 – 25). Overall treatment success was 61% (14/23); in the CP group 46%, in the remaining patients 80% (p=0.11). Patients with stricture resolution after removal of the first stent (n=7; success 6/7) showed a trent towards a more

sustained treatment success than patients who needed a 2nd stent placement (n=16; success 8/16); p=0.12).

Conclusions

Removal of a new type of fcSEMS with a proximal retrieval lasso in patients with BBS proved easy and uncomplicated. Treatment success for CP strictures was higher compared to what is known from results of progressive plastic stenting protocols. For other indications treatment success was comparable to progressive plastic stenting, but with the prospect of fewer ERCP procedures.

INTRODUCTION

Benign biliary strictures (BBS) can be caused by a number of conditions, e.g. primary sclerosing cholangitis, papillary stenosis, autoimmune pancreatico-cholangitis or bile duct stones[1]. The most commonly occurring causes of BBS are however chronic pancreatitis and postoperative bile duct injuries, either due to cholecystectomy or anastomotic after liver transplantation[2-5]. Adequate and definite treatment is essential since persistence of biliary strictures ultimately can lead to secondary biliary cirrhosis apart from jaundice and cholangitis[6]. Although surgery is still considered to be the most definitive treatment for BBS, an initial attempt by endoscopic means is usually undertaken given the invasive nature of surgical treatment and the relatively low morbidity and mortality of endoscopic treatment. The success of endoscopic intervention is highly dependent on the underlying cause of the stricture. Whereas in post-surgical strictures success rates of endoscopic treatment of up to 80% have been published, strictures due to chronic pancreatitis in general respond less favorably to conventional endoscopic treatment with success rates of approximately 25%[7-10]. The initial endoscopic treatment protocol generally consisted of placement of a single large bore plastic endoprosthesis. This has evolved into a more aggressive approach where during a year of endotherapy elective stent exchanges every 3 months with placement of an incremental number of stents lead to a 89% success rate in a retrospective cohort series of postoperative bile duct strictures[11]. Results of this strategy in chronic pancreatic induced biliary strictures, especially in calcifying disease, are less impressive although only small case series have been published with limited follow-up[12, 13]. However, even under ideal circumstances and a favourable outcome, this strategy requires multiple ERCPs with associated risks, costs and patient burden. Therefore the use of self expanding metal stents has been investigated in BBS. Uncovered SEMS are not usable in BBS since, despite their larger diameter, stent clogging occurs almost invariably due to epithelial / mucosal hyperplasia[14-16]. Furthermore removal is extremely hard or impossible. The use of partially

covered SEMS has been hampered by increased rates of migration, stent clogging when in place indefinitely and removal difficulties [17-20].

For this reason the use of fully covered SEMS (fcSEMS) has been investigated in a number of studies, after removal was shown to be possible[21-26]. The main concerns of fcSEMS use in BBS are migration and complicated removal due to unraveling of the stent.

Several techniques for removal of fully covered stents are available. Firstly the distal end can be grasped with a snare and subsequently the entire stent is pulled out. A potential disadvantage of this technique is that the whole surface area of the stent inside the common bile duct must detach at the same. A considerable force is sometimes needed, especially when deployed across a tight stricture. This increases the chance of distortion and disintegration of the stent. Secondly a distal lasso can be used, both for stents that have been deployed across the papilla and stents that are placed fully inside the common bile duct and use the distal lasso as an anchor[26]. Although the use of a distal lasso causes lengthening of the stent thereby facilitating stent removal still the entire surface area of the stent must detach from the mucosa of the common bile duct at the same time.

For this reason we conducted a prospective, non-randomized sequential group study in patients with benign biliary strictures with the aim to investigate feasibility, safety and effectiveness of a new type of fully covered SEMS with a proximal lasso. We hypothesized that the use of a proximal lasso would enable removal of the stent inside-out in a more controlled way with less force since the proximal end of the stent would be slowly pulled into the lumen. This would enable gradual inversion and detachment of the stent. Also the direction of force would be in a straight line with the orientation of the stent.

Another possible advantage of a proximal lasso could be that in the case of inward migration the long proximal lasso can be maneuvered into the duodenum with the aid of a grasping forceps or extraction balloon thereby providing an easy and safe way to complete stent retrieval in these cases.

PATIENTS AND METHODS

Design

This was a non-randomized prospective follow-up study with a sequential group design. Because safety of stent removal was defined as the primary outcome parameter, the cohort of 24 patients with BBS was divided into 3 subgroups A, B and C of 8 patients. In group A the first stent was removed after 2 months and, depending on the cholangiographic result, a second stent could be deployed and left in situ for 3 months. If in this

group stent removal after 2 months proved safe these periods were extended to 3 and 4 months respectively in group B whereas in group C a maximum of two stents could be deployed for two periods of 4 months. Therefore the maximum duration of therapy was 5 months in group A, 7 months in group B and 8 months in group C.

The primary outcome parameter of the study was successful removal of the stent using the proximal lasso. Secondary outcome parameters were stricture resolution, complications, ease of stent removal, stent patency, migration rate, integrity of the covering membrane and the number of endoscopic procedures.

Stent design, insertion and removal

For this study a novel nitinol prototype fully covered SEMS was used (Hanaro, M.I. Tech, Seoul, Korea; figure 1). The stent is double flared as an antimigration feature. The introduction system is 8.5 french and available in 50, 60, 70, 80 and 90 mm total length. The diameter once fully deployed is 10 mm. Gold radiopaque markers are on both proximal and distal end of the stent to facilitate accurate deployment and positioning. Recapturing and redeployment of the stent is possible. Both a distal and proximal lasso are attached to the stent. Traction on the proximal lasso causes inversion of the proximal part of the stent into the lumen (figure 2a and 2b; video of fluoroscopy at time of removal).

Stents were placed and removed at ERCP by experienced biliary endoscopists (JWP, MB) after biliary sphincterotomy. In patients with an intact gallbladder it was attempted

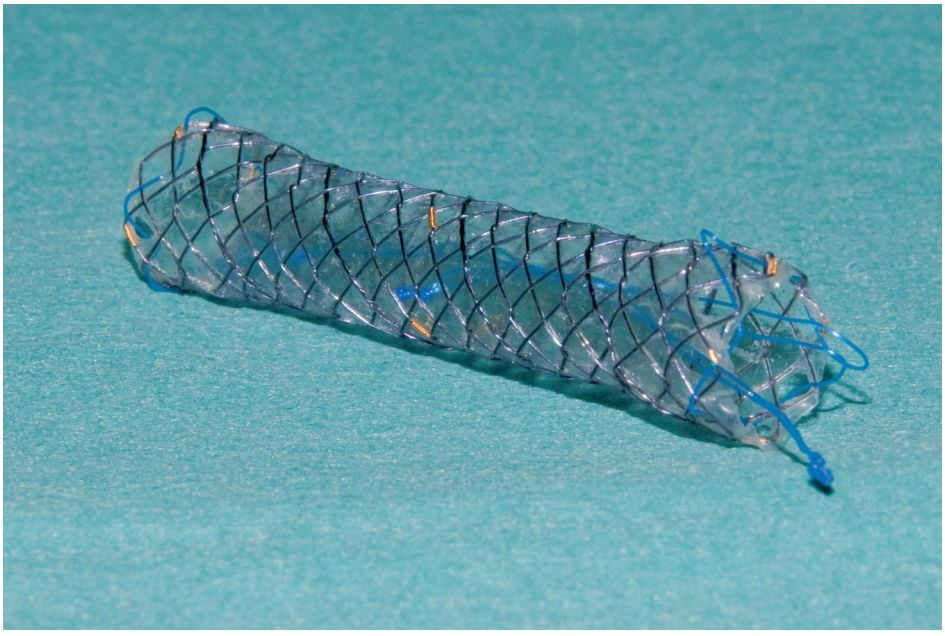

Figure 1: Prototype Hanaro fully covered stent with proximal and distal lasso

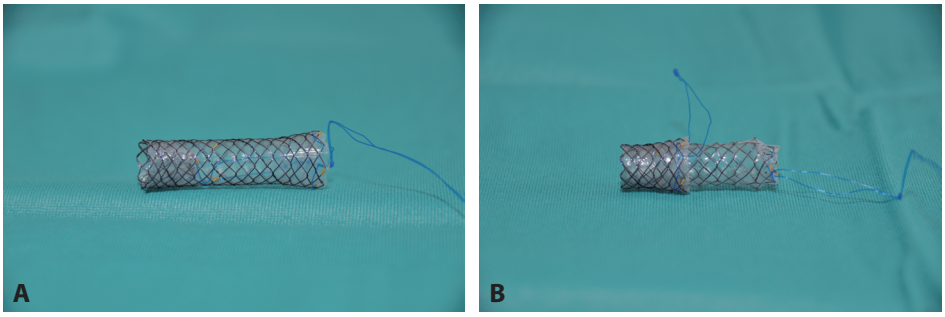

Figure 2 a and b: Traction on the proximal lasso enables inside-out removal of the stent

to position the proximal end of the stent below the level of the cystic duct insertion whenever possible.

Removal of the stent firstly was attempted by grasping the proximal lasso with grasping forceps or snare. If the lasso could not be identified the stent was swept with an extraction balloon in an attempt to pull the lasso into the duodenum. If this failed then the distal lasso was used to remove the stent.

All patients with gallbladders and those after livertransplantation received antibiotics periprocedurally during 24 hours.

Patients

Inclusion and exclusion criteria are listed in table 1. The study was approved by our institutional review board and all patients gave written informed consent.

In all patients with non-surgical causes of the stricture both cross-sectional imaging (CT or MRI) and endoscopic ultrasonography were performed to rule out a malignant cause of the stricture. Patients had one plastic stent in situ across the stricture before enrollment. Previous treatment with either multiple plastic stents or fcSEMS was not allowed.

Table 1: Inclusion and exclusion criteria.

Inclusion criteria
BBS due to a post surgical injury
BBS due to chronic pancreatitis
BBS due to ampullary stenosis
Age above 18 years
Exclusion criteria
Proximal extend of the stricture less than 2 cm below the liver hilum Non-anastomotic stricture (post OLT)
Previous treatment with SEMS or more than 1 plastic stent
Refusal to sign informed consent

BBS = benign biliary stricture

Table 2: patient characteristics

Characteristics	No.
Total no. of patients	23
Mean age (y; range)	57 (29 – 74)
Etiology of BBS	
Chronic pancreatitis	13
Post LTx	6
Post cholecystectomy	3
Papillary stenosis	1

Between September 2008 and December 2009 24 patients were enrolled into the study. One patient, included in group B, was removed from the analysis because his presumed benign biliary stricture eventually proved to be caused by a malignant pancreatic neuro-endocrine tumor (table 2).

Follow up

Patients were followed at the outpatient clinic. Both laboratory parameters and imaging methods were used to assess clinical outcome with regards to cholestasis and stricture resolution. Treatment success was defined as resolution or improvement of the stricture on the cholangiogram, the ability to pass an inflated extraction balloon easily through the stricture and the absence of cholestasis during follow up of at least 6 months.

Descriptive statistics were performed and data are presented as numbers with subsequent percentages. All statistical analyses were performed using SPSS version 16.0 (SPSS Chicago Illinois, USA).

RESULTS

Outcome

All 23 patients completed the study protocol. All stent placements were technically successful (figure 3). Median follow up was 15 months (range 11 - 25). Results with regards to overall treatment success are shown in figure 4. Overall success rate was 65% (15 / 23). The chance of an overall treatment success was lower in patients with a BBS due to chronic pancreatitis (success rate 46%; 6/13) compared to any other cause of BBS (success rate 80%; 8/10) although this difference did not reach statistical significance (p=0.11). Those patients that had resolution of their stricture after removal of the first stent, 6 out of 7 (86%) apparently had a better outcome than those patients that required placement of a second stent, 8 out of 16 (50%), although this difference also did not reach statistical significance (p=0.12).

The average stent time for treated patients was 5.5 months.

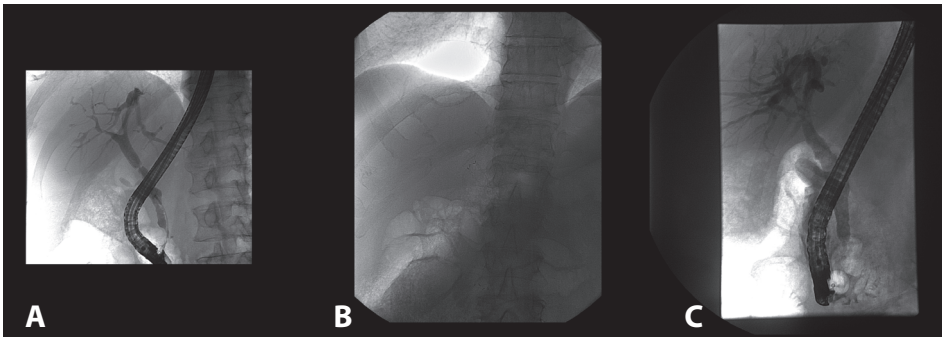

Figure 3. A: Narrow stricture of the common bile duct after laparoscopic cholecystectomy.
B: Deployment of an 8 cm fully covered self-expandable metal stent with a proximal lasso.
C: Cholangiogram after 3 months with a stent in place.

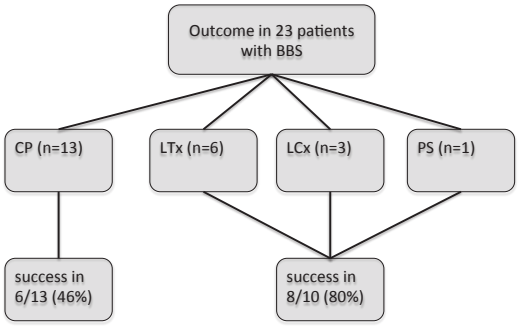

Figure 4: Overall outcome in 23 patients with benign biliary strictures (BBS). CP, chronic pancreatitis; LTx, liver transplantation; LCx, laparoscopic cholecystectomy; PS, papillary stenosis.

Removals

In total 39 stents were deployed and removed without complications. In one patient with chronic pancreatitis and a very tight stricture the wire mesh appeared to broken at the time of removal. Despite this the stent could be removed easily and replaced according to protocol. Removal was judged to be easy by the endoscopists in all other cases. The proximal lasso was hanging in the duodenal lumen in 37 of 39 removals (95%). In the other two cases it was possible to retrieve the proximal lasso by sweeping the stent with an extraction balloon. Removals were performed with removal of the endoscope.

Complications

Several complications occurred (table 3). We observed one case of cholecystitis 1 week after placement of the first fcSEMS that was managed conservatively with antibiotics and percutaneous gallbladder drainage. Two patients with chronic pancreatitis developed worsening of their chronic pancreatitis within one month after the stent placement. Both cases were managed with subsequent pancreatic sphincterotomy and insertion

Table 3: complications

Complications	No.
Cholecystitis	1 (4%)
Worsening of chronic pancreatitis	2 (9%)
Cholangitis	
Migration	1 (4%)
Clogging	2 (9%)
Pain	13 (57%)

of a temporary plastic stent in the pancreatic duct. Despite the antimigratory features of the stent used in this study, outward migration three weeks after stent placement induced cholangitis in one patient. At repeat ERCP a persistent stricture was observed and a second study stent was inserted. Two other cases of cholangitis were caused by clogging of the stent and were managed by cleaning the stent with an extraction balloon at 5 and 8 weeks following stent placement.

The most frequently encountered complication was pain immediately after deployment of the stent. In all cases the pain subsided within 1 week and could be managed by temporary analgesics.

DISCUSSION

In this first prospective group sequential study on the use of fcSEMS in patients with BBS this novel type of SEMS proved to be effective and both easy and safe to remove. The proximal lasso, which is the main new feature of this stent, proved to be advantageous and easy to use. In the vast majority of cases the proximal lasso was hanging freely in the duodenal lumen and could be easily grasped with either a grasping forceps or a snare. When grasped the stent was easily removed inside out without exerting much force. This potentially could reduce the chance of complications associated with stent removal such as unraveling and bleeding. Furthermore, in a recent paper concerning patients with biliary leaks after liver transplantation clinically significant biliary strictures developed at the level of the deployed fcSEMS with extensive mucosal ulcerations visualized during choledochoscopy[27]. It is conceivable that this is at least partly due to the trauma associated with removal of the fcSEMS.

The outcome with regard to stricture resolution in this study on patients with non chronic pancreatitis induced BBS is comparable to the literature[11, 13, 28]. The number of procedures needed in a fcSEMS based strategy is expected to be lower than in a progressive stenting protocol. However, since no comparative studies exist, care must be taken to compare results between studies. Although the difference between chronic

pancreatitis induced BBS and other types of BBS in this study, that was not powered to do so, did not reach statistical significance, the results were still less favourable in the chronic pancreatitis group. This is in concordance with previously published papers as is the final success rate of 46% in our series with a median follow up of 15 months (range 11 – 25 months) [10, 12, 13, 18, 19, 22, 29]. We also observed a trend towards a higher success rate when the stricture had improved significantly after removal of the first stent versus those that needed a second stent (success rate 86% vs 50%; p=0.12), but evidently the study was not designed and powered to investigate these effects. Furthermore it is important to emphasize that duration of stent therapy in our series was relatively short since the primary endpoint of the study was a safe stent removal. Given the fact that the majority of patients needed a second stent period and that the average time of stenting was 5.5 months, outcome might even improve further when patients would get treated with a longer indwelling stent time.

A major concern with the use of fcSEMS is the relatively high complication rate. The most frequently observed complication in our series was transient pain after deployment of the stent. This is probably explained by the relatively rapid dilation of the stent in the first 24 to 48 hours when it reaches its final diameter and in this sense comparable to balloon dilation of the biliary tract. Although easily managed by temporary acetaminophen and/or NSAIDS and explained to the patients, it causes some, albeit transient, discomfort. There was no need for early stent removal in any of these patients. Cholecystitis can be a complication of any ERCP but it is well known that the risk is increased when fcSEMS are placed[30]. This might be explained by occlusion of the cystic duct. In our series we had one case of cholecystitis despite the use of periprocedural antibiotics that could be managed conservatively. Another issue with the use of fcSEMS is migration. In our series this occurred with one stent in one patient (3%) leading to cholangitis around the time of scheduled stent exchange. The migration percentage of fcSEMS reported in the literature varies between 0 and 14%[22, 23, 25, 26, 30, 31]. It is conceivable that further improvements in stent design, such as double flares in the stent we used, or anchoring flaps or a completely intraductally located stent might further reduce this potential risk[26, 32]. Two cases of cholangitis were seen in our series that necessitated endoscopic intervention. In both cases clogging of the stent with biliary sludge was observed and easily managed with cleaning of the stent with an extraction balloon without the need for stent exchange.

Despite the routine sphincterotomy before deployment of the fcSEMS we observed worsening of chronic pancreatitis in two patients. Although this has been previously described and probably explained by pressure exerted by the stent on the pancreatic duct in most series this was not a particular concern[30, 33]. Both cases were managed endoscopically by pancreatic sphincterotomy and insertion of a plastic stent in the pancreatic duct for the duration of biliary stenting. In previously published data the

suggestion was made that the risk for developing pancreatitis was increased in those patients without pancreatic duct dilation. Both patients in our series however had an already dilated pancreatic duct. Clearly, based on only two cases one should be cautious to make any recommendations about the prevention of worsening of CP during the treatment of BBS with fcSEMS, but this issue definitely deserves further attention and consideration.

In summary this study shows that a new type of fcSEMS with a proximal lasso can be removed safely and proved efficacious for the treatment of BBS, especially in those patients with strictures not related to chronic pancreatitis, at potentially lower costs and patient burden, compared to progressive stenting with multiple plastic stents.

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Breaking the barrier: using extractable fully covered metal stents to treat benign biliary hilar strictures

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ABSTRACT

Background

Most benign biliary strictures nowadays are managed endoscopically with plastic stents or with the insertion of a fully covered self-expandable metal stent (fcSEMS). The paradigm for the treatment of benign hilar strictures precludes the use of fcSEMS because such obstructs intrahepatic bile ducts, in particular the contralateral hepatic duct. It is unknown whether use of a plastic stent in the opposite hepatic duct after deployment of a fcSEMS across the liver hilum provides an adequate solution for this issue.

Objective

To evaluate the use of fcSEMS in combination with a contralateral plastic stent in the treatment of benign hilar strictures.

Design

Case series.

Setting

Tertiary referral hospital.

Patients

Two consecutive patients with benign hilar strictures.

Interventions

Placement of an intrahepatically deployed fcSEMS in conjunction with a contralateral 10 fr plastic stent during 4 to 5 months followed by stent removal and cholangiogram.

Outcome measurements

Clinical and laboratory follow up of at least 9 months.

Results

In both patients the indwell period of stenting was uneventful as was stent removal. Both strictures resolved and there were no clinical or biochemical signs of a recurrent stricture.

Limitations

Limited number of patients.

Conclusions

Treatment of benign hilar strictures with a fcSEMS deployed across the liver hilum in conjunction with contralateral plastic stent placement is feasible without ensuing cholangitis due to bile duct occlusion.

INTRODUCTION

The aetiology of benign biliary strictures (BBS) is diverse and includes among others chronic pancreatitis, primary sclerosing cholangitis, auto-immune cholangitis and trauma. In the Western world important causes are iatrogenic, in particular postsurgical after cholecystectomy or liver transplantation. The majority of these strictures are, at least initially, managed endoscopically. Both temporary placement of multiple plastic stents according to a so-called progressive stenting protocol and deployment of removable fully covered self expandable metal stents (fcSEMS) have shown promise in this respect with high efficacy rates and an acceptable complication risk, even though prospective randomized controlled clinical trials are lacking[1, 2].

Although the majority of iatrogenic BBS are located below the hepatic bifurcation in up to 14% of cases the stricture extends into or at the level of the hepatic confluence [3, 4]. The prognosis of endoscopic therapy in patients with involvement of the liver hilum is poor with success rates of 25% or lower[3, 4]. This is at least partly due to the fact that placement of multiple plastic stents through these strictures is often difficult while treatment success of BBS in general seems dependent upon the aggressiveness of stricture dilation, i.c. the number of simultaneously inserted plastic stents[5-7]. In this respect the use of fcSEMS is attractive as it has a dilation diameter of 33 fr which is comparable to 7-8 plastic stents of 10 fr positioned side-by-side. However, use of fcSEMS has not been described in this setting given the high likelihood of occlusion of intrahepatic bile ducts., in particular the contralateral hepatic duct and liver lobe. Therefore in all published series describing the use of fcSEMS these strictures had to be located at least 2 cm below the level of the liver hilum[2, 8, 9].

We speculated that the combination of an intrahepatically deployed fcSEMS in conjunction with contralateral plastic stent placement would provide adequate stricture dilation whilst preventing occlusion of the opposite ducts in patients with benign biliary hilar strictures.

METHODS

A novel type of fcSEMS with both a proximal and distal retrieval lasso, a long wire thread integrated in the proximal ends of the wire mesh that hangs freely in the stent lumen, was used (M.I.Tech, Seoul, Korea; figure 1a). Pulling the proximal lasso enables gradual removal of the fcSEMS inside-out and since detachment of the stent from the wall of the common bile duct is gradual this feature should facilitate removal of the stent. The diameter is 33 french (10 mm) with both proximal and distal flares as an antimigration feature. The length, 12 cm, was longer than usual for biliary metal stents

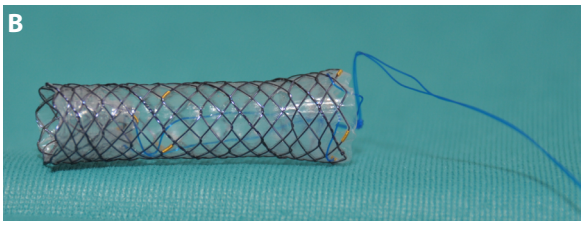

Figure 1A. Proximal retrieval loop inside the lumen at the distal end of the fully covered self-expandable metal stent.

Figure 1B. Partial inside-out after pulling of proximal retrieval lasso

and this batch was manufactured specifically for the purpose of transhilar deployment. We have extensive experience with shorter versions of this stent in the treatment of non-hilar BBS.

ERCPs were performed under conscious sedation. After obtaining a cholangiogram, defining hilar anatomy and assessing the extent of the stricture, two guidewires were introduced into both the left and right biliary system. A 10 fr plastic stent (Cook Endoscopy, Limerick, Ireland) was positioned across the liver hilum into the contralateral liver lobe. Finally the fcSEMS was deployed alongside the plastic stent with the proximal end of the SEMS extending above the stricture. Both stents were removed after 4 to 5 months and a repeat cholangiogram was obtained.

Patients gave informed consent before the procedure and were informed about the new aspects of this treatment.

Case 1

A 36-year-old woman underwent a laparoscopic cholecystectomy for cholecystolithiasis that was converted to an open procedure due to an injury of the common hepatic duct. The lesion was closed peroperatively, nevertheless postoperatively bile leakage was demonstrated at the level of a stricture in the hepatic hilum (Figure 2).

The patient underwent multiple ERCPs with repeated balloon dilation upto 6 mm of both left and right system combined with bilateral 10 french single plastic stent placement during 3 months but the stricture did not resolve and she remained stent dependent.. After the patient was referred to our institution, a MRI/MRCP yielded no additional information. The hepatic artery was open. After discussing all options, including surgical repair, it was decided to re-treat this stenosis endoscopically with a combination of a removable covered metal stent and a contralateral plastic stent. ERCP performed in our institution revealed that the most severe stenosis was located towards the left system. After guidewire placement to both left and right system and balloon dilation up to 6 mm

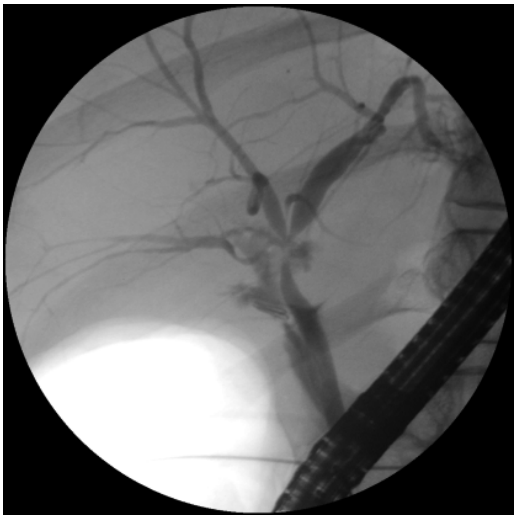

Figure 2. Postoperative hilar stricture with leakage.

a 12 cm 10 french plastic stent was placed in the right system and a 12 cm 10 mm fcSEMS was placed in the left system (Figure 3).

The postprocedural course was uneventful and no signs of cholestasis or cholangitis developed. Antibiotic prophylaxis was given for 72 hours periprocedural. After 5 months

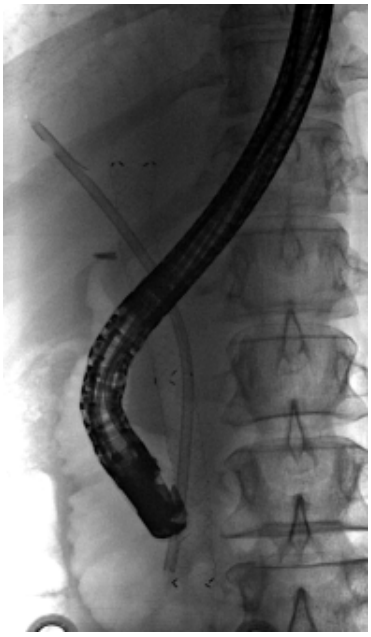

Figure 3. After insertion of both the plastic and fully covered self-expandable metal stents through the hilar stricture.

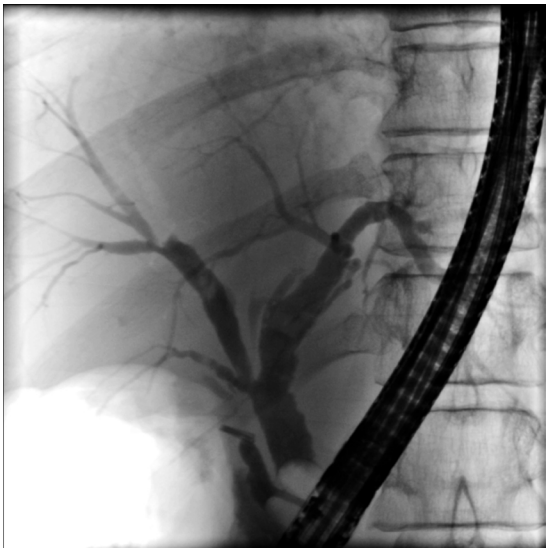

Figure 4. Occlusion cholangiogram showing complete resolution of the hilar stricture.

elective re-ERCP was performed during which the fcSEMS was extracted easily using the proximal lasso. After removal of the fcSEMS the plastic stent was removed as well. Occlusion cholangiography revealed complete resolution of the stricture towards both the left and the right system (Figure 4). At 11 months follow up, 16 months after insertion of the fcSEMS, there are no signs of a recurrent stricture.

Case 2

A 29 year old woman underwent orthotopic livertransplantion from a post-mortem donor 2 years previously because of acute liver failure. Despite an uneventful postoperative course she developed a stricture at the level of the anastomosis that was treated with a progressive stenting protocol over the course of 9 months with initially good results. A maximum of four 10 french stents were inserted during this period. Three months after finishing the protocol she developed recurrent cholestasis and repeat ERCP revealed a recurrent stricture that extended partially into the liver hilum, mainly towards the right system (figures 5 and 6).

At repeat ERCP both left and right system were selectively cannulated and guidewires left in situ. After balloon dilation to 6 mm a 12 cm 10 fr plastic stent was placed into the left system and a 12 cm 10 mm fcSEMS into the right system. The procedure went uncomplicated and cholestasis disappeared. Antibiotic prophylaxis was given periprocedurally (72 hours). At 4 months ERCP was repeated and the fcSEMS was removed uneventfully with the aid of the proximal lasso. Afterwards the plastic stent was removed. Cholangiography revealed complete stricture resolution. Unfortunately no fluoroscopy images of these procedures are available since both ERCP's were performed

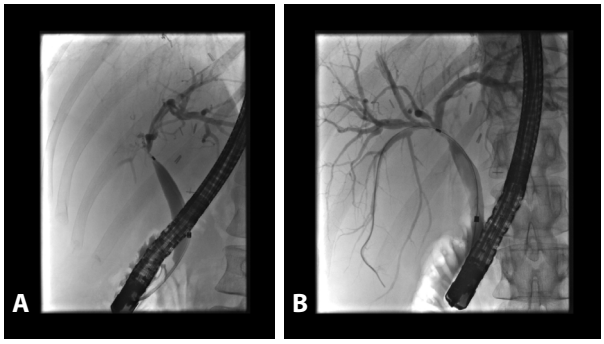

Figure 5A. Left system with hilar stenosis (case 2). **5B.** Hilar anatomy (case 2)

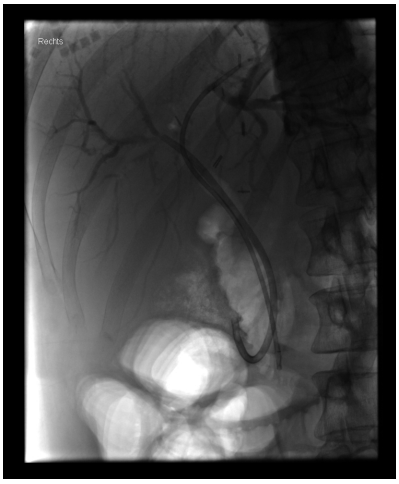

Figure 6. Case 2 with plastic stents in situ.

under general anaesthesia at the OR and at that time, no fluoroscopy images could be stored. Until now, at 9 months follow up, 13 months after placement of the fcSEMS, there are no signs of recurrent strictures.

DISCUSSION

These two cases demonstrate that the use of fcSEMS in the treatment of benign biliary strictures affecting the liver hilum is feasible and potentially effective. Both deployment and removal of the fcSEMS were easy and without complications. The use of a contralaterally postioned plastic stent precluded the feared complication of cholangitis of the contralateral system. This was not encountered during a total of 9 months of treatment in our two patients. Theoretically the chance of occlusion of a secondary bile duct might be larger with deployment of a fcSEMS to the right side since the most commonly oc-

curring biliary anatomic variant has a bifurcation between right posterior and anterior segments above the liver hilum.

Although our 2 patients had BBS that extended into the liver hilum, the same technique can also be used in patients that have strictures located very proximal in the common hepatic duct in whom normally there would be insufficient space for the deployment of a fcSEMS.

Although both our patients had failed stricture resolution after a conventional plastic stenting and showed a satisfactory outcome after fcSEMS treatment, it remains to be proven whether this new treatment is more effective than conventional treatment with plastic stents. This should preferably be studied in a randomized prospective trial even though the relative rarity of this condition will impair such a study. It is not known for how long a fcSEMS should be left in situ in this setting. Based on previous experience we choose a 4 to 5 month period in an attempt to balance the dilation effect and the difficulty of stent removal, both presumably increasing with prolonged in situ duration of fcSEMS.

Apart from cholangitis another potential complication would be secondary strictures in the intrahepatic bile ducts due to the relatively large diameter of the present fcSEMS design in comparison with the diameter of the ducts. A potentially very serious complication and although we have not observed this and potentially the use of a smaller diameter stent might decrease the chance of this complication occurring, caution is warranted.

In conclusion, we believe that this new approach combining an intrahepatically deployed fcSEMS with a protective intrahepatically placed plastic stent into the contralateral liver lobe shows promise in the treatment of benign biliary hilar strictures with regard to efficacy and patient burden, since potentially it can reduce the number of ERCPs a patient has to undergo substantially. Nevertheless, more experience needs to be gained with this approach since especially the safety of this procedure remains a concern and might be dependent on local biliary anatomy.

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SUMMARY AND CONCLUSIONS

In the first section of this thesis, Endoscopic ultrasonography in screening and diagnosis of pancreatic disease, the role of EUS with regards to its diagnostic value is investigated. In chapter 2 we could demonstrate that in a cohort of patients with an increased risk to develop pancreatic cancer (PC) EUS is able to accurately confirm or exclude the presence of benign, premalignant en malignant lesions. Since the prognosis of PC is almost uniformely abysmal when diagnosed after the development of symptoms, one of the potential ways to improve outcome of this disease is to detect these lesions at an earlier, asymptomatic stage. Since the overall incidence of PC is too low to justify population based screening, identifying risk groups and offer them a tailored approach with regards to screening is at present the only option available. These risk groups are mainly those kindreds in whom a hereditary component is present. Some form of inheritance is thought to be present in approximately 10-15% of all PC cases.

To identify this hereditary component both awareness of treating physicians and surgeons and extensive genetic analysis of affected individuals and families are important. In our series we could identify a pathogenic mutation in approximately half of the screened individuals (52%). Once a mutation in a family has been identified it is relatively easy to identify individuals at risk. Furthermore, efficacy and yield of a screening program will increase when the proportion of individuals with proven pathogenic mutations is higher.

We chose to use EUS for screening since with EUS it is possible to visualize the pancreas with unsurpassed detail and resolution. A potential drawback is the fact that it is a relatively invasive procedure that requires conscious sedation and the results are strongly operator dependent.

In our study, describing the results of baseline screening, 44 individuals were screened. Twenty-one of them were from families without a known mutation, known as familial pancreatic cancer (FPC) whereas the remainder of screened individuals were carrier of pathogenic mutations in genes causing Peutz-Jeghers syndrome, hereditary breast- and ovarian cancer and familial atypical multiple mole melanoma syndrome. In three individuals (out of 44; 6.8%) asymptomatic lesions in body and tail were found with diameters of 10, 27 and 50 mm. Despite surgical resection these three patients subsequently developed liver metastases and eventually died from there disease. In seven individuals (15.9%) cystic lesions with sizes between 4 and 15 mm were found. All cystic lesions were unilocular without intramural nodules or solid components. On EUS communication with the pancreatic duct was either demonstrated or very likely and therefore these lesions were highly likely to be side branch intraductal papillary mucinous neoplasias (IPMN). IPMNs are precursor lesions of pancreatic malignancy and the much higher incidence than expected in our series but also in some other published

cohorts is very likely to be related to the increased risk for the development of pancreatic cancer in these families.

Although are study clearly demonstrates that EUS is able to identify asymptomatic benign and malignant in a considerable proportion of individuals thought to be at an increased risk to develop pancreatic cancer, this does not necessarily mean that outcome for these patients will be better.

Our study is the first study on this subject in Europe and differs in one important aspect from previously published studies in that the proportion of individuals with a clearly defined genetic syndrome was much higher. Whether this explains solely the higher incidence of both solid lesions and cystic precursor lesions remains to be investigated although all mass lesions in our series were found in mutation carriers. The aim of the present study was not to establish differences between these groups and lacks statistical power to reliably ascertain whether this is explained by genetic background. Furthermore, other risk factor, e.g. smoking, needs to be taken into account. The incidence of cystic lesions in FPC individuals in our series is 15% (3 out of 20) which is still higher than in the US series mentioned above.

Clearly a surveillance and screening protocol for pancreatic cancer needs to focus on detection and management of premalignant lesions. This is demonstrated by the fate of those patients in whom an invasive malignancy was detected. Despite the asymptomatic stage and curative surgery these patients underwent, the outcome of their disease was not influenced by the early detection. One could argue that screening simply started to late in these patients and that earlier screening procedures would have been able to detect these lesions at an earlier and potentially curable stage.

Another important and still unanswered question is how to manage the IPMN-like cystic lesions that we and others found to be present at an relatively high frequency in individuals at high risk of developing pancreatic cancer, especially in light of the assumption that these may represent precursor lesions of pancreatic cancer. It is known now from several retrospective cohort studies that the likelyhood of malignancy in small branch type IPMN's without involvement of the main pancreatic duct, intramural nodules or solid components is quite small. In sporadic cases a follow-up policy with regular interval screening for these lesions is safe and acceptable. However, the biological behavior of such lesions in patients with a hereditary increased risk for the development of cancer is not known. Whether these high-risk patients should be offered surgery at an earlier stage than what is considered acceptable in sporadic cases or if the same wait-and-see policy can be adopted is unknown. It is also unclear whether the possible development of these precursor lesions into more advanced neoplastic or even malignant lesions is gradual over time with ample opportunity for early detection during surveillance, or sudden and abrupt. These very important questions need to be addressed in further follow-up studies.

For this reason we have initiated a multicenter prospective study in the Netherlands in which the yield of annual MRI and EUS is compared and this study may give us answers on the questions raised by our initial study.

An increasing problem in gastroenterology is how to deal with incidentally found pancreatic cysts. The prevalence in the overall population is estimated to be approximately 2.5% and with the increased use of cross-sectional imaging this generally asymptomatic lesions are found more often and pose clinicians for diagnostic and therapeutic dilemmas. It is well known that a subset of pancreatic cysts have malignant potential, mainly mucinous cysts like mucinous cystadenomas (MCA) and intraductal papillary mucinous neoplasms (IPMN) whereas simple, congenital or serous cystadenomas generally do not require follow-up given the absent or extremely low risk of malignant development. Endoscopic ultrasound has emerged as a valuable technique for the diagnosis of pancreatic cysts given the unrivalled imaging, compared to conventional imaging techniques as CT and MRI, and the ability to safely and easily perform EUS guided fine needle aspiration (EUS - FNA) of cyst contents and cyst wall. In practice however this procedure is often nondiagnostic due to the low cellularity of cyst fluid. The use of biochemical markers in the cyst fluid is potentially useful, however no prospective study exists where EUS-FNA of cyst fluid is evaluated with regards to being technically possible, safety and diagnostic yield. In chapter 3 the results of EUS-FNA in a prospective, observational cohort study of consecutive patients with a cystic pancreatic lesion of unknown etiology are described. In this study the technical success and safety of EUS-FNA are investigated. Of course morphological characteristics such as location, diameter, wall thickness, multilocularity, septations, nodules, calcifications and communication with the pancreatic duct were also noted, described and registered by experienced endosonographers in two tertiary centers. The cyst fluid obtained via EUS-FNA was primarily used for cytopathological analysis. Furthermore biochemical markers, mainly carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (Ca 19.9) and amylase levels were determined.

In 128 out of 143 consecutive patients EUS-FNA was performed. Reasons for not performing EUS-FNA were diverse but in the majority of cases the endoscopist refrained from EUS-FNA due to the necessity to traverse normal pancreatic tissue with the associated risk of pancreatitis. Overall complications arose in 3 patients (2.4%): 2 had symptoms that could be attributed to infection of the cyst and 1 case of pancreatitis occurred. Fluid was available for cytological analysis in 124 patients (87%) but a classifying diagnosis based on cytology was only possible in 44 (31% of all patients). In 80 out of 143 patients fluid was available for biochemical analysis although analysis was successful in only 70 patients (49%).

This study shows that the diagnostic yield even in expert centers of EUS-FNA of pancreatic cysts is disappointingly low although technically possible in the vast majority

of cases. It was possible to obtain a classifying cytopathological diagnosis in approximately one-third of cases and sufficient material for biochemical analysis was available in only half of the cases. Potentially the diagnostic yield may increase if priority would be given to biochemical analysis of the fluid. Furthermore, changing the processing of the cytology specimen to a liquid based medium such as ThinPrep or Cytolyte might also increase cellularity and diagnostic yield.

Another aspect of the diagnostic value of EUS is discussed in chapter 4. In most cases when patients with obstructive jaundice are suspected to have pancreatic cancer, the initial imaging modality is a high quality helical multidetector computer tomography (MDCT). Sensitivity and accuracy of MDCT with regards to detection of the primary tumor and the presence of metastases and determining resectability of pancreatic cancer is generally high and improving with further technological developments. Despite these characteristics, not infrequently patients suspected to have pancreatic cancer do not have a visible tumor on MDCT. We investigated the value of EUS in these patients in a multicenter retrospective cohort study. Over a 2 year period all patients who with painless jaundice or a combination of cholestasis, weight loss and abdominal pain underwent a MDCT according to a local pancreatic protocol and were reported by dedicated GI radiologists. EUS was performed by experienced endosonographers. During this period 290 patients were analyzed with MDCT for suspected pancreatic cancer. A pancreatic mass was found in 258 patients with sizes between 6 and 110 mm (median 30 mm). Therefore in 32 patients (11%) MDCT failed to demonstrate the cause of obstruction. In 23 of those patients (74%) EUS was able to correctly diagnose the cause of obstruction. Fifteen of them were found to have a malignant appearing mass in the head of the pancreas (size between 13 and 45 mm), 3 other patients were found to have an ampullary adenoma. A benign (or premalignant) cause for the obstruction was found in another 8 patients. However, EUS is not perfect: 5 patients with a negative EUS and negative MDCT were found to have a malignancy after all. Three of these 5 patients had a stent in situ during EUS. This may have had a deleterious effect on the diagnostic accuracy in these patients.

To further increase the diagnostic capabilities of EUS - FNA we investigated the feasibility and yield of a newly developed needle in chapter 5. Since its development more than 20 years ago, EUS - FNA has proven to be a reliable, safe, sensitive and accurate method to provide clinicians with cytological samples of intestinal and extra-intestinal mass lesions. However no reliable way to obtain a histological specimen existed. For lesions reachable from the esophagus or from the proximal stomach some studies have shown promising results with either the use of a large caliber regular 19G needle or with the use of a needle with a thrucut mechanism (Quickcore, Cook Endoscopy). In clinical practice

however most endosonographers felt that both methods were not reliable especially in more difficult circumstances, mainly when used from the duodenum. Since especially pancreatic cytology is notoriously difficult to interpret for cytopathologists, the availability of an EUS needle through which histological specimens could be obtained in a reliable and safe way is potentially a breakthrough in EUS. For this reason the later named ProCore needle was developed in collaboration with an international group of experienced endosonographers and Cook Endoscopy. Our first experiences with this needle aimed at acquiring fine needle biopsy (FNB) are described in chapter 4.

This needle is a 19G stainless steel needle with a Nitinol stylet with a reverse cutting bevel of 4 mm located just proximal of the tip of the needle. Tissue acquisition was performed in various ways where according to local preference passes were done with or without the stylet. Other differences were the number of passes (1 to 3), number of to-and-fro passes (1 to 4) and the use of the stylet or flushing with saline to retrieve the sample. Further tissue preparation was done as customary with general biopsies obtained via endoscopy.

In this multicenter, pooled, cohort study of 109 consecutive patients with 114 intra- or extraintestinal mass lesions FNB was attempted. Our main outcome measurement was the percentage of cases in which pathologists classified the sample quality as optimal for histopathological evaluation combined with the overall diagnostic accuracy.

In all 114 lesions were evaluated (84 malignant, 30 benign). EUS - FNB was technically feasible and possible in 112 lesions (98.2%). The sample quality was adequate for full histological assessment in 102 lesions (89.5%). This assessment was found to be correct in 98 cases (86.0%) based on either definite surgical pathology or clinical follow-up leading to an overall accuracy of 92.9% with regards to diagnosing malignancy.

The indications for EUS were highly variable although the largest number of patients had pancreatic tumors (47). Technically all passes through either esophagus, stomach or rectum were successful (n = 79; 100%) whereas two failures (33 / 35; 94.3%) occurred when the puncture was performed through the duodenum. In both cases it proved impossible to remove the stylet from the needle after targeting the lesion. No complications related through the EUS procedure were seen.

Despite the slight variations in technique at univariate analysis only the use of a dedicated GI pathologist compared to generally oriented pathologists was found to be of significance (OR 5.55 (1.54 - 19.94; p = 0.004). We therefore conclude that with this new needle it is feasible and safe to obtain a histological biopsy in the vast majority of cases even when a transduodenal biopsy has to be performed.

Compared to cytology of the pancreas, pancreatic histology may be easier to interpret for pathologists. Furthermore adequate histological specimens enable ample immunohistochemical tests and because the architecture of the specimen is preserved potentially

differentiation can be assessed based on the relationship of the tumor with basement membrane, blood vessels, nerve tissue en connective tissue. Also a reliable call can be made on whether a tumor is invasive or still in the in situ stage. The role of the pathologist is therefore instrumental and in a way endoscopiststst and endosonographers are mere instruments of the pathologists. However, little is known about the reproducibility of the results of the judgments made by the pathology and the interobserver variation. We therefore performed a study in chapter 6 to evaluate the interobserver agreement between dedicated GI pathologists with regards to grading the quality of specimens obtained via the FNB method with a 19G Procore needle on consecutive specimens of both lymphadenopathy and mass lesions. The pathologists were blinded to the final diagnosis and independently reviewed and scored for the presence of a tissue core, adequacy and interpretability of the specimen and the possibility to perform additional analyses on the acquired material such as immunohistochemistry and fluorescence in situ hybridization. Overall 50 cases were judged, 23 samples were pancreatic of nature, 15 of lymph nodes, 7 from submucosal lesions, two from abdominal masses and one each from the left adrenal gland, a mediastinal mass and a peritoneal nodule.

Specimens were judged to be adequate in 91.2% of cases with a kappa value of 0.73 (excellent agreement). The presence of a clear tissue core was reported in 88% of cases with a kappa value of 0.61 (good agreement). Interpretation of the specimen was judged to be easy in approximately 87% of cases with a kappa value of 0.44 (moderate agreement). Additional analyses were possible in in approximately 91% of cases with a kappa value of 0.66 (good agreement). We could demonstrate therefore that for dedicated and experienced GI pathologists overall there was moderate to excellent interobserver agreement on the assessment of material obtained through EUS - FNB.

In recent years EUS is evolving more and more from a purely diagnostic technique, and this includes the use of EUS - FNA or FNB, to a therapeutic modality. With this development EUS parallels most other endoscopic techniques including gastroscopy, colonoscopy and ERCP. In chapter 7 an extensive review is given on therapeutic endosonography including celiac plexus neurolysis, EUS guided fine needle injection, placement of markers for radiotherapy, EUS guided drainage of fluid collections and abscesses, drainage and access of both biliary and pancreatic ducts and vascular interventions. Although various techniques are described in detail along with practical tips and trics we also focus on indications, contra-indications, complications and outcome.

The third section of this thesis, novel developments in the endoscopic treatment of benign biliary and pancreatic disease deals with various complications of benign biliary and pancreatic disease but focuses on the treatment of benign biliary strictures (BBS) that can occur as a consequence of both chronic pancreatitis and iatrogenic damage

to the bile due to for example a complicated cholecystectomy or after orthotopic liver transplantation (OLT) with a duct-to-duct anastomosis.

The first chapter in this section, chapter 8, is an extensive review of the endoscopic treatment of chronic pancreatitis and focuses on treating various complications of this often debilitating disease. Therapeutic endoscopy can be considered in three settings: transpapillary drainage of the pancreatic duct and treatment of ductal strictures and stones, pseudocyst drainage and treatment of biliary obstruction. In this review these techniques are discussed extensively with a focus on patient selection, techniques and duration of drainage and including a summary of the available evidence with regards to morbidity, mortality and long term outcome.

Biliary complications after OLT occur frequently. Up to 30% of transplanted patients suffer from leakage, strictures and stone or cast formation and biliary complications are therefore an important cause of OLT-related morbidity. It is generally accepted that endoscopic treatment via ERCP is the cornerstone of management in these patients since the alternatives, percutaneous or surgical treatment, are considered to be less efficacious or more invasive. The majority of strictures after OLT are located at the anastomosis in case of a duct-to-duct biliary reconstruction and are the most amenable for endoscopic treatment. Non-anastomotic strictures respond less favorably to endoscopic treatment and often require a re-transplant.

The most commonly used approach nowadays for anastomotic strictures is to follow a so called progressive stenting protocol whereby an increasing number of plastic endoprotheses, tailored to the diameter of the duct, are inserted at 3 months intervals over a 1 year period. Even though this method is nowadays considered to be standard of care the quality of data to support this approach is relatively low. Reported success rates are highly variable between 65% and 94% and interpretation is also made difficult since it is not always well known whether patients with early strictures, caused by edema and usually very well responding to therapy, were included as well. Since new therapies are on the horizon, mainly temporary treatment with fully covered self-expandable metal stents, it is of paramount importance that results, complications and efficacy of previous treatment are well known. We therefore aimed to explore the outcome of a progressive plastic stenting protocol in our cohort of patients with an anastomotic stricture after OLT in chapter 9.

Between 2000 and 2009 a total of 375 OLTs were performed. Of the 304 patients in whom a duct-to-duct anastomosis was created, 63 developed an anastomotic stricture (21%). Twenty eight patients were not treated by progressive stenting for various reasons but mainly because of good response to single stenting in patients with early strictures (n=16). Four patients did not complete the protocol; two because of a re-transplant and two patients died of unrelated causes. In those patients who completed the protocol a median of 5 (range 4 - 11) ERCP's were performed and a median maximum number of

10 french stents of 4 (range 2 - 8) were placed. Complications occurred frequently: 21 patients (67.7%) suffered from them although the complication risk as calculated per procedure was lower: 22 serious complications on a total of 155 procedures (14.2%).

Overall treatment success, defined as absence of recurrence of cholestasis, jaundice or cholangitis due to a recurrent anastomotic stricture was achieved in 25 out of the 31 patients who completed the protocol (80.6%) with a median follow-up after stent removal of 28 months.

The endoscopic treatment of biliary anastomotic strictures by means of a progressive plastic stenting protocol is therefore highly efficacious and saves 80% of those patients from undergoing complicated surgery or even a re-transplantation. However this type of protocol is demanding for patients, not without complications and labor intensive for health care providers.

In chapter 10 we looked at cost effectiveness of progressive plastic stenting versus covered metal stenting in patients with anastomotic strictures after OLT in a comparative analysis. Although, as we have shown in chapter 9, progressive stenting is effective, it is also quite burdensome for patients and potentially quite costly given the multiple ERCPs that are necessary for completing the protocol. Recently several case series have been published describing the use of temporary, removable fcSEMS in benign biliary strictures, including anastomotic strictures after OLT. Efficacy and complication rates in these series are roughly similar or better compared to progressive plastic stenting. There are however no data available with regards to the cost-effectiveness of this approach and since no comparative trials have been published we undertook an analysis on our own cohort of patients and calculated several clinical scenarios with variable prices of fcSEMS and number of treatments needed.

The costs of progressive plastic stenting were calculated based on the cohort of 31 patients described in chapter 9. A median of 5 ERCPs were necessary and resulted in a median of 1 complication. Treatment costs were calculated using source data from the financial department of our hospital and for this analysis, based on published series, including from our own unit, it seems reasonable to assume that the efficacy of fcSEMS treatment is equal or greater than progressive plastic stenting and that complication rates would be equal as well. Cost analysis was based on medical direct costs.

Costs of progressive plastic stenting were calculated at €4196. In six scenarios, ranging from very optimistic (patients require only 2 ERCP's and cost of one fcSEMS is €1000) to pessimistic (but probably more realistic) where it was estimated that 30% of patients would need placement of a 2nd fcSEMS and 10% even a 3rd. In all scenarios the use of fcSEMS lead to a reduction in costs ranging from €296 to €1696. We also calculated the mean number of fcSEMS that were allowed per patient to reach a break-even point at 1.97 (price of fcSEMS €1000) and 1.53 (price of fcSEMS €1500).

Treatment of anastomotic strictures after OLT with fcSEMS is therefore potentially cost-effective in calculated clinical scenarios and largely dependent on the price of fcSEMS. Before we can adopt this strategy as routine clinical practice however we need true randomized trials since this analysis is based on several assumptions that are based on either retrospective studies or case series.

As demonstrated and discussed in chapter 9 and 10 the use of fcSEMS in the treatment of anastomotic strictures after OLT but also in other benign biliary strictures is potentially very promising. One major concern however is the removability of these SEMS since not removing them almost invariably leads to patency problems. It is already known for a long time that uncovered SEMS are not removable and therefore not usable for treatment of benign diseases. Although this in general is less of an issue with partially and fully covered SEMS, several removal problems have been described including bleeds, perforations and surgical repair.

Several techniques for removal of fcSEMS are available. The distal end can be grasped with a snare with subsequent removal of the entire stent. Another technique makes use of a distal lasso and although traction on this lasso lengthens the stent, with both techniques the whole surface area of the stent must detach from the wall of the bile duct at more or less the same time and considerable force is sometimes needed, leading to an increased chance of distortion and disintegration of the stent.

We therefore investigated the feasibility and safety of stent removal of a novel type of fcSEMS in chapter 11. This stent has a proximal lasso that enables removal of the stent inside-out in a more controlled way with less force since this would enable gradual inversion and detachment of the stent with the direction of force in a straight line with the orientation of the stent. Another potential advantage could be that in the case of proximal migration this lasso could be manipulated towards the duodenum with the aid of balloon or grasping forceps and thereby providing an easy and safe way to complete stent retrieval.

We conducted a non-randomized prospective follow-up study with a sequential group design. Twentyfour patients were treated in three groups. Group A underwent stent placement for 2 months, if necessary after removal followed by another stent placement for 3 months. For group B this was 3 + 4 months and for group C 4 + 4 months. Unfortunately one patient did not have a benign stricture but a malignant due to a neuroendocrine tumor and fell out of the protocol and the analysis. The remaining 23 patients had strictures due to chronic pancreatitis (n=13), OLT (6), laparoscopic cholecystectomie (n=3) and papillary fibrosis (n=1). In total 39 fcSEMS were deployed and removed without complications. In one patient with chronic pancreatitis and a very tight stricture the wire mesh appeared to be broken at the time of removal. Despite this, the stent could be removed easily and replaced according to protocol. In all other

cases removal was easy. The proximal lasso was seen in the duodenal lumen in 37 of 39 removals and could be used for removal. In the remainder of cases the proximal lasso could be retrieved after sweeping of the stent with an extraction balloon.

Several complications were observed: one case of cholecystitis, two cases of worsening of chronic pancreatitis and three cases of cholangitis; one of them because of migration and two because of stent clogging. Frequently patients had transient, but sometimes severe, pain subsiding within the first week and manageable by temporary analgesics.

The overall success rate after a median follow-up of 15 months (range 11 - 25) was 65% (15 out of 23). The chance of success was considerably lower in those with a BBS due to chronic pancreatitis (46%; 6 / 13) than in those with other causes (80%; 8 / 10) although this did not reach statistical significance ($p = 0.11$). Those patients that had stricture resolution after removal of their first stent (86%; 6 / 7) seemed to have a better outcome than those patients that required placement of a 2nd stent (50%; 8 / 16) although this difference yet again did not reach statistical significance ($p=0.12$)

Of course our study was not powered to detect differences in outcome with regards to stricture resolution, nevertheless our results in both chronic pancreatitis patients and those with other causes of BBS are more or less in line with those from previously published series. It is conceivable that with longer indwelling stent time results could even improve further. The primary endpoint of our study with this newly developed type of fcSEMS was safety and feasibility of removal via a proximal lasso. In the vast majority of cases the lasso could easily be grasped with a snare or forceps and traction on this snare led to easy and controlled removal without excessive force. What is clear from this study is that, despite the attractive starting point of potentially reduction of number of ERCPs needed for treatment, the risk of complications of fcSEMS treatment is not negligible and potentially serious.

At present, based on our study and also other published series, it is still too early to recommend treatment of BBS with fcSEMS as standard of care. A randomized controlled trial, sufficiently powered to detect difference in treatment outcome, is needed before any definite recommendations can be made.

We, in chapter 11, and others have shown that the use of fcSEMS for the treatment of benign biliary strictures is effective and reasonably safe. However the only experience with fcSEMS was limited to those strictures that were located at least 2 cm below the hilum and although this is the case for the majority of BBS up to 14% of these strictures extend into or at the level of the hepatic hilum. Traditionally these patients are managed endoscopically although this is particularly difficult for these type of strictures since in general the outcome is dependent on the aggressiveness of dilation, i.e. the number of stents inserted, and this is technically much more difficult to achieve bilaterally through

a hilar stricture. The use of fcSEMS in this setting, potentially very attractive since a large dilation diameter can be achieved with placement of a single stent, has never been described however due to the high likelihood of occlusion of intrahepatic bile ducts caused by the covering of these stents. We speculated that the combination of an intrahepatically deployed fcSEMS in conjunction with contralateral plastic stent placement and published our results of the first two patiented treated this way in chapter 12. For these patients we used a specially developed fcSEMS of the same design as described in chapter 11, only now with a length of 120 mm.

The first patient was a 36 year old woman with a history of a complicated cholecystectomy who developed a hilar stricture at the site of previously noted leakage. Multiple ERCPs elsewhere with repeated balloon dilation and bilateral single 10 fr stent placement did not lead to resolution of the stricture. We placed a 10 fr plastic stent into the, less severely affected, right system and a 12 cm 10 mm fcSEMS in the left. The procedure went uncomplicated and after 5 months both stents were removed and cholangiography demonstrated complete resolution of the stricture towards both left and right sided biliary system. Follow up of now over 2 years did not reveal signs of recurrent stricture.

Our second patient was a 29 year old woman who developed an anastomotic stricture of the duct-to-duct anastomosis two years after OLT for acute liver failure. She underwent progressive stenting for this stricture with initially good response. Three months later however she developed recurrent cholestasis and at ERCP a recurrent stricture, partially extending into the liver hilum, was seen. She was treated with a 12 cm 10 fr plastic stent into the left system and a 12 cm 10 mm fcSEMS into the right system. At removal after 4 months cholangiography revealed complete stricture resolution and after now more than 1 year follow up no signs of recurrent stricture are seen.

These cases nicely demonstrate that this new approach to benign hilar strictures is technically feasible and potentially efficacious. Some concerns remain however. Especially placement of a relatively large, compared to the diameter of the duct, fcSEMS intrahepatically could potentially lead to secondary strictures. Of course to answer the question whether this approach is more efficacious and at least as safe as progressive plastic stenting, ideally a randomized controlled trial should be performed. Due to the relative rareness of these strictures such a trial will very likely never be performed. Careful registry of treated patients is therefore very important. We have started a prospective multicenter cohort study where we will treat patients with hilar benign biliary strictures with bilateral fcSEMS placement with a diameter of 7 mm.

NEDERLANDSE SAMENVATTING

In het eerste deel van dit proefschrift, **Endoechografie in screening en diagnose van alvleesklierziekten**, worden enkele aspecten van de diagnostische waarde van endoechografie (EUS) onderzocht. EUS is een techniek waarbij door middel van een echoapparaatje op de tip van een flexibele endoscoop heel nauwkeurig vanuit de slokdarm, maag, 12-vingerige darm en endeldarm omliggende organen bekeken kunnen worden. Ook kan op deze manier relatief eenvoudig, weinig belastend en veilig weefsel of vocht worden afgenomen voor verder onderzoek. Vooral de alvleesklier kan op deze manier heel nauwkeurig onderzocht worden.

In **hoofdstuk 2** beschrijven we een onderzoek waarbij EUS gebruikt wordt om mensen met een sterk verhoogd risico op het krijgen van alvleesklierkanker te onderzoeken op afwijkingen voordat klachten aanwezig zijn. De prognose van alvleesklierkanker is dermate slecht als de aandoening ontdekt wordt op het moment dat er symptomen zijn, dat vroege opsporing van alvleesklierkanker, of één van de voorstadia hiervan ,één van de weinige manieren is waarmee potentieel de prognose van deze vreselijke ziekte verbeterd zou kunnen worden. Op dit moment komen alleen mensen en families voor een dergelijke screening in aanmerking als er sprake is van een erfelijke aanleg. Geschat wordt dat in ongeveer 10% tot 15% van alle gevallen van alvleesklierkanker er sprake is van een vorm van erfelijkheid.

Met EUS kan vanuit maag en 12-vingerige darm de alvleesklier zeer nauwkeurig geïnspecteerd worden; vandaar dat wij deze methode gekozen hebben als basis van ons screeningsprogramma. In deze studie beschrijven wij de resultaten van het eerste onderzoek met EUS in 44 individuen met een verhoogd risico op het krijgen van alvleesklierkanker als gevolg van een erfelijke aanleg. In drie individuen (6.8%) werden op dat moment nog asymptomatische gevallen van alvleesklierkanker gevonden met een grootte van 10, 27 en 50 mm. Ondanks een operatie waarbij de tumor in alle gevallen succesvol verwijderd kon worden, zijn al deze patiënten uiteindelijk toch aan de ziekte overleden als gevolg van uitzaaiingen in de lever die later ontdekt werden. Bij 7 patiënten (15.9%) werden cysteuze afwijkingen gevonden met afmetingen tussen de 4 en 15 mm. Al deze cysten waren enkelvoudig zonder intramurale nodules of solide componenten. Omdat bij EUS communicatie met de ductus pancreaticus, de afvoergang van de alvleesklier, ofwel aangetoond kon worden danwel zeer waarschijnlijk gemaakt, zijn deze cysteuze afwijkingen zeer waarschijnlijk intraductale papillaire mucineuze neoplasieën (IPMN). IPMNs zijn bekende voorstadia van alvleesklierkanker en het lijkt waarschijnlijk dat de veel hogere frequentie van voorkomen dan verwacht in onze serie, maar ook in andere, gerelateerd is aan de ontwikkeling van alvleesklierkanker in deze families.

Hoewel wij duidelijk aantonen dat EUS inderdaad in staat is om zowel vroege, nog asymptomatische, gevallen van alvleesklierkanker maar ook voorloperstadia daarvan,

op te sporen bij individuen met een verhoogd risico hierop, is hiermee natuurlijk niet aangetoond dat de uitkomst voor deze patiënten ook verbeterd. Het lijkt in elk geval wel duidelijk dat een screeningsprogramma voor alvleesklierkanker zich zal moeten concentreren op het detecteren en vervolgen van premaligne aandoeningen. Dit wordt mede onderstreept doordat alle drie de patiënten bij wie er reeds sprake was van kanker uiteindelijk aan de ziekte overleden zijn en in feite alleen maar eerder patiënt geworden zijn.

Vanwege het toenemend aantal CT-scans en MRI's die gemaakt worden, soms zelfs voor een zogenaamde, commerciële check-up, worden steeds vaker cysten in de alvleesklier gevonden. De prevalentie in de algemene bevolking wordt geschat op circa 2.5%. Deze cysten kunnen volkomen onschuldig zijn, zonder dat verdere analyse of follow-up noodzakelijk is, kunnen kwaadaardig worden of kunnen zelfs al kwaadaardig zijn. Met EUS kan niet alleen heel goed gekeken worden, het is ook mogelijk om vloeistof uit de cyste te halen voor verdere analyse, EUS – FNA. In **hoofdstuk 3** hebben wij in een prospectieve studie de technische uitvoerbaarheid, veiligheid en opbrengst van EUS – FNA onderzocht naast de bekende morfologische criteria. Het verkregen cystevocht werd primair voor pathologisch onderzocht gebruikt en bij voldoende opbrengst werden ook biochemische tests gedaan naar tumormarkers en amylase.

Bij 128 van de 143 patiënten werd EUS – FNA verricht. In de andere gevallen werd van EUS – FNA afgezien, meestal doordat de afstand die de naald door normaal alvleesklierweefsel moest gaan als te groot werd ingeschat aangezien daarmee de kans op acute alvleesklierontsteking toeneemt. Complicaties werden gezien in 3 patiënten (2.4%). Uiteindelijk werd bij 124 patiënten daadwerkelijk vocht verkregen voor analyse door de patholoog. Helaas kon slechts in 44 patiënten (31%) een classificerende diagnose op de cytopathologie gesteld worden. In 80 van de 143 patiënten was vocht beschikbaar voor biochemische analyse al kon deze in slechts 70 patiënten (49%) verricht worden. In deze studie laten we zien dat zelfs in ervaren handen de diagnostische opbrengst van EUS – FNA bij cysteuze alvleesklierafwijkingen laag is hoewel technisch vrijwel altijd mogelijk. Deze opbrengst zou mogelijk verhoogd kunnen worden als gekozen zou worden om voorrang te geven aan de biochemische analyse in plaats van die door de patholoog en als het verkregen vocht voor de patholoog op een andere manier verwerkt zou worden.

Een ander aspect van de diagnostische waarde van EUS wordt besproken in **hoofdstuk 4**. Patiënten die zich presenteren met obstructie icterus en waarbij de klinische verdenking op een pancreaskopcarcinoom groot is, ondergaan over het algemeen in eerste instantie een CT scan. Hoewel de sensitiviteit en accuratesse van CT wat betreft de detectie van de primaire tumor en het bepalen van afstandsmetastasen en resectabiliteit goed is en met de verdergaande technologische ontwikkeling ook steeds beter wordt, komt

het desondanks regelmatig voor dat op de CT scan de oorzaak van de obstructie icterus niet vastgesteld kan worden. Wij hebben de waarde van EUS onderzocht in deze setting in een multicenter retrospectieve cohort studie waarbij gedurende een periode van 2 jaar alle patiënten die vanwege obstructie icterus en/of cholestase, gewichtsverlies en buikpijn een CT scan ondergingen volgens pancreasprotocol geanalyseerd werden.

Hierbij werden uiteindelijk 290 patiënten geïncludeerd. In 258 werd een tumor in de pancreas gevonden; derhalve kon bij 32 patiënten geen oorzaak worden aangetoond middels CT-scan. Bij deze patiënten werd EUS verricht waarbij deze in 31 compleet was. In 23 patiënten (74%) kon de oorzaak correct worden vastgesteld middels EUS: in 15 leek er sprake te zijn van een maligne tumor; dit bleek correct in 13 van de 15. In 3 gevallen werd vastgesteld dat er sprake was van een papiladenoom hetgeen correct was in 2 patiënten en in 8 gevallen werd terecht geconcludeerd bij EUS dat er sprake was van een benigne oorzaak van de obstructie. EUS is echter niet perfect: in 5 patiënten (16%) kon geen oorzaak worden gevonden en bleek er uiteindelijk toch sprake van een maligne oorzaak van de obstructie icterus. In 3 van deze 5 patiënten werd de EUS verricht met een galwegstent in situ, een bekende oorzaak van verminderde accuratesse van EUS.

In **hoofdstuk 5** werd de waarde en bruikbaarheid van een nieuw type EUS naald onderzocht. Hoewel EUS – FNA een techniek is die al meer dan 20 jaar bestaat en bewezen heeft veilig, accuraat, specifiek en sensitief te zijn, worden hierbij cytologische samples verkregen. Met cytologie kunnen losse cellen of celgroepjes bekeken worden. Voor de patholoog is met name cytologisch materiaal van de alvleesklier soms lastig te beoordelen. Bij histologisch materiaal kan de differentiatiegraad van een kwaadaardige tumor beoordeeld worden evenals de relatie met basaalmembraan, bloedvaten, zenuwen en bindweefsel. Hierdoor is er op zijn minst een potentiële meerwaarde voor het verkrijgen van histologisch materiaal. Er bestond echter geen betrouwbare manier om histologisch materiaal te verkrijgen, vooral niet onder moeilijker omstandigheden vanuit bijvoorbeeld de 12-vingerige darm. Wij onderzochten de bruikbaarheid en opbrengst van een nieuw type naald, ontwikkeld in samenwerking met een internationale groep gebruikers en Cook Endoscopy, die later tot ProCore omgedoopt zou worden en gericht is op het verrichten van een fine needle biopsy (FNB). Deze roestvrijstalen naald heeft een diameter van 19G en een snijrand 4 mm van de tip waarmee, door de naald heen en weer te bewegen in de laesie, histologisch materiaal verkregen zou moeten worden.

In totaal werd in 114 laesies bij 109 patiënten FNB gepoogd. De belangrijkste uitkomstmaat van deze studie was het percentage waarin het ook lukte om een histologisch biopt te verkrijgen, beoordeeld door de patholoog. Het bleek technisch mogelijk om in 112 van 114 laesies (98.2%) de FNB te verrichten waarbij in 102 gevallen (89.5%) er daadwerkelijk een volledige histologische analyse verricht kon worden. Deze analyse bleek correct in 98 gevallen (86.0%) uitgaande van ofwel definitieve chirurgisch verkre-

gen pathologie of klinische follow-up. De uiteindelijke accuratesse met betrekking tot het diagnosticeren van een maligniteit was 92.9%.

De indicaties voor EUS waren verschillend al betrof het in het grootste deel patiënten met een pancreastumor (n = 47). De twee gevallen waarin EUS – FNB niet mogelijk bleek, betrof het puncties door het duodenum (33 / 35 succes). In beide gevallen bleek het onmogelijk om de stylet te verwijderen na puncteren van de laesie. In alle overige gevallen was EUS – FNB technisch mogelijk door slokdarm, maag of rectum. Complicaties werden niet gezien. Bij univariate analyse bleek alleen beoordeling door patholoog met specifieke gastrointestinale interesse van invloed op de uitkomst wanneer vergeleken met algemene pathologen (Odds ratio 5.55; p = 0.004). Samenvattend bleek het met deze nieuwe naald goed mogelijk en veilig om onder vrijwel alle omstandigheden histologisch materiaal te verkrijgen, ook onder moeilijke omstandigheden als door het duodenum heen gebiopteerd moet worden.

In zekere zin zijn endoscopisten en endosonografisten slechts instrumenten van de patholoog als het gaat om het stellen van een definitieve diagnose van tumoren van de tractus digestivus. Er is echter weinig bekend over de interobserver variabiliteit en de reproduceerbaarheid van oordelen door de patholoog. Wij hebben daarom in **hoofdstuk 6** hiernaar gekeken door ervaren gastrointestinale pathologen 50 histologische preparaten verkregen middels EUS – FNB te laten beoordelen op de aanwezigheid van een weefselbiopt, representabiliteit en beoordeelbaarheid van het preparaat en de mogelijkheid om aanvullende kleuringen te doen op het preparaat. Zowel biopten van de alvleesklier alsook andere tumoren en lymfklieren werden met elkaar vergeleken.

De preparaten werden als adequaat beschouwd in 91.2% met een kappa waarde van 0.73 (uitstekende overeenstemming). De interpretatie van het preparaat werd als makkelijk ingeschat in 87% van de gevallen; kappa van 0.44, gemiddelde overeenstemming. Additionele analyses waren mogelijk in 91% van de preparaten met wederom goede overeenstemming; kappa waarde van 0.66.

Wij konden derhalve aantonen dat voor ervaren gastrointestinale pathologen het materiaal dat verkregen wordt middels EUS – FNB goed te beoordelen is en dat er tussen hen een uitstekende overeenstemming bestaat voor wat betreft de beoordeling op een aantal essentiële punten.

Net als bij de meeste andere endoscopische technieken ontwikkelt ook EUS zich van een puur diagnostische techniek, inclusief EUS – FNA en EUS – FNB, naar een vorm van endoscopie waarmee ook therapeutische interventies verricht kunnen worden. In **hoofdstuk 7** wordt een uitgebreide review gegeven van therapeutische EUS waarbij onder andere plexus coeliacus blokkade, EUS fine needle injectie, EUS geleid plaatsen van markers voor radiotherapie, drainage van vochtcollecties en abcessen, toegang, drainage en

rendez-vous technieken van de galwegen en alvleesklier en vasculaire interventies. Naast een beschrijving van technieken inclusief praktische tips wordt ook uitgebreid stilgestaan bij indicaties, contra-indicaties, complicaties en lange-termijn resultaten.

In het derde deel van dit proefschrift, **nieuwe ontwikkelingen in de endoscopische behandeling van benigne galweg- en alvleesklieraandoeningen**, ligt de nadruk op de behandeling van benigne galwegstricturen. Deze kunnen onder andere ontstaan als gevolg van chronische pancreatitis maar ook door iatrogene schade, bijvoorbeeld als complicatie na cholecystectomie of levertransplantatie.

In **hoofdstuk 8** wordt een uitgebreide review gegeven van de endoscopische behandelmogelijkheden bij chronische alvleesklierontsteking met de nadruk op de complicaties van deze aandoening: transpapillaire drainage van de ductus pancreaticus en de behandeling van stenen en stricturen, drainage van pseudocysten en behandeling van galwegobstructie. Er wordt tevens uitgebreid stilgestaan bij patiëntenselectie, technieken en duur van drainage in het licht van het beschikbare bewijs met betrekking tot morbiditeit, mortaliteit en lange termijn uitkomsten.

Galwegcomplicaties komen frequent voor na orthotope levertransplantatie (OLT). Tot 30% van de getransplanteerde patiënten heeft last van lekkage, stricturen of stenen van de galwegen na de transplantatie. Het grootste deel van de stricturen bevindt zich op de anastomose tussen donor- en acceptorgalweg indien er een duct-to-duct anastomose wordt aangelegd. Deze zijn over het algemeen goed toegankelijk voor endoscopische therapie; de alternatieven zoals percutane of chirurgische behandeling zijn ofwel minder effectief ofwel veel meer invasief.

Tegenwoordig wordt meestal gekozen voor een progressief stenten protocol waarbij met tussenpozen van 3 maanden een toenemend aantal stents door de anastomose wordt geplaatst gedurende 1 jaar. In de studies die hierover tot nu toe gepubliceerd zijn, worden wisselende succespercentages gemeld waarbij de interpretatie van de gepubliceerde data ook moeilijk is doordat niet altijd duidelijk is in hoeverre ook zogenaamde vroege stricturen geïncludeerd zijn; deze zijn tijdelijk en behoeven slechts kortdurend endoscopische therapie. Mede omdat nieuwe therapieën, met name het tijdelijk plaatsen van volledig gecoverde metalen stents (fcSEMS), in opkomst zijn, is het extra belangrijk om de resultaten van de standaardbehandeling goed te kennen. Wij hebben daarom de uitkomst van progressief stenten onderzocht in ons eigen cohort van OLT patiënten in **hoofdstuk 9**.

Tussen 2000 en 2009 werden in totaal 375 OLTs uitgevoerd. Hiervan werd bij 304 een duct-to-duct anastomose uitgevoerd. Van hen ontwikkelde 63 (21%) een anastomotische strictuur; 28 van hen werden niet geïncludeerd in het progressief stenten protocol om verschillende redenen maar vooral omdat er sprake was van een goed resultaat op

1 stent bij vroege stricturen. Vier patiënten maakten het protocol niet af: twee van hen vanwege een re-transplantatie en twee overleden. Bij de 31 patiënten die het protocol afmaakten, werden mediaan 5 (range 4 – 11) ERCP's verricht waarbij een mediaan maximaal aantal 10 french stents van 4 (range 2 – 8) werden geplaatst. Complicaties werden regelmatig gezien; 21 patiënten (67.7%) ontwikkelden 1 of meer complicaties gedurende de behandelperiode. Per procedure bedroeg het complicatiepercentage 14.2% (22 / 155). De behandeling was uiteindelijk succesvol in 25 van de 31 patiënten (80.6%) met een mediane follow-up van 28 maanden.

De endoscopische behandeling van anastomotische stricturen na OLT middels progressief stenten met plastic stents is derhalve effectief; ruim 80% van de patiënten kan succesvol behandeld worden zonder dat uitgebreide chirurgie of zelfs re-transplantatie noodzakelijk is. Echter deze behandeling is belastend voor de patiënten maar ook voor ziekenhuizen en de endoscopie afdeling aangezien een groot aantal ERCP's noodzakelijk is en het complicatierisico niet te verwaarlozen is.

In **hoofdstuk 10** hebben wij een analyse gedaan van de kosteneffectiviteit van progressief stenten vergeleken met een behandeling met een tijdelijke, verwijderbare, gecoverde metalen stent (fcSEMS). Zoals we in hoofdstuk 9 hebben laten zien is de eerste behandeling weliswaar effectief maar ook potentieel kostbaar gezien het grote aantal benodigde ERCP's. In de laatste jaren zijn meerdere studies verschenen die het gebruik van tijdelijke fcSEMS voor benigne galwegstricturen, waaronder die na OLT, onderzoeken waarbij complicatierisico en succespercentages ongeveer hetzelfde lijken te zijn. Er zijn echter geen directe vergelijkende studies gepubliceerd. Wij hebben daarom een analyse verricht op ons cohort dat met progressief stenten werd behandeld en deze vergeleken in verschillende scenario's waarbij met fcSEMS werd behandeld. Voor de progressief stenten methode zijn mediaan 5 ERCP's benodigd. Behandelkosten werden berekend op basis van bedragen afkomstig uit de financiële administratie van het ziekenhuis en voor deze analyse zijn we er vanuit gegaan dat succespercentage en complicatierisico gelijk was voor beide behandelingen.

Een behandeling met progressief stenten kost gemiddeld €4196. Het meest optimistische scenario bij het gebruik van fcSEMS ging uit van 2 ERCP's en een prijs van de fcSEMS van €1000. Meer realistisch berekenden wij ook dat 30% van de patiënten een tweede fcSEMS nodig zou hebben en 10% een derde. In alle scenarios leidde het gebruik van fcSEMS tot een reductie van kosten variërend van €296 tot €1696. Het gemiddelde aantal fcSEMS dat geplaatst zou kunnen worden per patiënt waarbij de kosten gelijk zouden blijven was 1.97, bij een fcSEMS prijs van €1000, en 1.53 bij een prijs van €1500.

De behandeling van anastomotische stricturen na OLT met fcSEMS is derhalve potentieel kosteneffectief in alle onderzochte scenario's en vooral afhankelijk van de

prijs van fcSEMS. Voordat deze strategie als voorkeursbehandeling gekozen kan worden, zijn prospectieve gerandomiseerde trials echter noodzakelijk aangezien wij in onze analyse uitgegaan zijn van verschillende veronderstellingen die alle gebaseerd zijn op retrospectieve studies of case series.

Zoals we in hoofdstukken 9 en 10 hebben laten zien, is het gebruik van fcSEMS voor benigne galwegstricturen (BBS) veelbelovend. Een groot potentieel probleem is echter de verwijderbaarheid van deze stents. Bij het gebruik van niet gecoverde, en niet verwijderbare, stents voor BBS is gebleken dat deze uiteindelijk vrijwel zonder uitzondering weer dicht gaan zitten en derhalve moeten voor benigne indicaties gecoverde, partieel danwel volledig, metalen stents gebruikt worden.

Bij het verwijderen van deze stents wordt gebruik gemaakt van een distale lasso of verwijderlus of de gehele stent wordt in één keer omvat met een snaar waarna deze verwijderd wordt. Al deze methoden hebben als nadeel dat veel kracht moet worden uitgeoefend omdat het gehele intraductale oppervlak van de stent in één keer los moet laten van de wand van de ductus choledochus. Hierbij zijn bloedingen en perforaties van de galweg beschreven.

Wij hebben in **hoofdstuk 11** onze ervaringen beschreven met een nieuw type fcSEMS. Deze heeft niet alleen een distale lasso maar ook een proximale lasso. Tractie aan deze lasso zorgt ervoor dat de stent gradueel binnenstebuiten gekeerd wordt waardoor de kracht geleidelijk aan leidt tot verwijdering. Onze studie was dan ook primair gericht op verwijderbaarheid. Hiertoe werden 24 patiënten met BBS geïncludeerd in een niet gerandomiseerde prospectieve studie met een sequentieel groep design. Groep A onderging stentplaatsing gedurende 2 maanden, indien nodig gevolgd door nog eens 3 maanden. Voor groep B en C waren deze periodes 3 +4 en 4 + 4 respectievelijk.

Bij 1 patiënt bleek er helaas tijdens de behandeling toch sprake te zijn van een onderliggende maligniteit waardoor hij uit het protocol viel. Bij de overblijvende 23 patiënten waren de BBS als gevolg van chronische pancreatitis (n=13), OLT (n=6), laparoscopische cholecystectomie (n=3) en papilfibrose (n=1). In totaal 39 fcSEMS werden geplaatst en verwijderd zonder complicaties. In één patiënt met chronische pancreatitis en een zeer nauwe strictuur bleek er sprake te zijn van een stentbreuk, desondanks kon de stent zonder veel problemen verwijderd worden. In alle andere gevallen was de verwijdering eenvoudig volgens de endoscopist. De proximale lasso hing in het duodenum in 37 van de 39 gevallen; in de overige twee gevallen kon deze met ballon makkelijk tot in het duodenum gemobiliseerd worden.

Wij zagen meerdere complicaties: één patiënt ontwikkelde in aansluiting op de stentplaatsing cholecystitis, bij twee zagen we een verergering van de onderliggende chronische pancreatitis en er waren drie gevallen van cholangitis. Eén hiervan door migratie en bij de andere twee door verstopping van de stent. Tevens zagen we frequent

de eerste dagen na de stentplaatsing passagère pijn optreden als gevolg van uitzetting van de stent. Dit was in het algemeen goed te behandelen met pijnstillers.

Voor de gehele groep was het succespercentage na een mediane follow-up van 15 maanden (11 – 25) 65% (15 van de 23). Het percentage was met 46% (6 / 13) duidelijk lager in de chronische pancreatitisgroep dan in de groep met andere oorzaken: 80% (8 / 10) hoewel dit verschil niet statistisch significant was ($p = 0.11$). Tevens leek het zo te zijn dat bij de patiënten bij wie een tweede stent noodzakelijk was de kans op uiteindelijk succes (50%; 8 / 16) ook lager was vergeleken met hen bij wie slechts 1 stent geplaatst werd (86%; 6 / 7) hoewel ook dit verschil niet statistisch significant was ($p = 0.12$).

Vanzelfsprekend was onze studie niet gepowerd op het aantonen van verschillen in uitkomst. Desalniettemin zijn onze resultaten min of meer in overeenkomst met de resultaten zoals bekend uit de literatuur. Het is denkbaar dat bij langer in situ blijven van de stents de uitkomst nog verder verbetert. Het primaire eindpunt van deze studie was veilige verwijderbaarheid en het blijkt duidelijk het geval te zijn dat deze stent met behulp van de proximale lasso makkelijk en veilig verwijderd kan worden. Tevens blijkt dat, hoewel het gebruik van fcSEMS bij BBS conceptueel heel aantrekkelijk is, dit een behandeling is die niet zonder complicaties verloopt. Daarom is het ons inziens nog te vroeg om deze behandeling als de standaard behandeling te zien; idealiter dient hiervoor een adequaat gepowerde gerandomiseerde studie verricht te worden.

Wij en anderen hebben laten zien dat de behandeling van BBS met fcSEMS een effectieve en redelijk veilige behandeling is met mogelijk voordelen boven de behandeling met meerdere plastic stents. Tot nu toe was de ervaring beperkt tot stricturen waarbij de afstand ten opzichte van de bifurcatie van de galwegen, de leverhilus, tenminste 2 cm was. Deze grens werd gehanteerd vanwege het risico op afsluiten van contralaterale galwegen. Hoewel de meeste BBS inderdaad tenminste enkele centimeters onder de hilus zijn, strekt de strictuur zich in tot 14% van de gevallen uit tot in de hilus. De endoscopische behandeling van deze stricturen is traditioneel lastig omdat de prognose vooral bepaald wordt door de agressiviteit van de behandeling; in dit geval het maximaal aantal stents dat door de strictuur ingebracht kan worden aan beide zijden en dit is technisch veel lastiger dan bij stricturen die zich niet in het hilusgebied bevinden.

Wij onderzochten in **hoofdstuk 12** bij twee patiënten met benigne hilaire galwegstricturen of de combinatie van een fcSEMS en een beschermende contralaterale plastic stent technisch haalbaar was, veilig en mogelijk effectie. Hiertoe gebruikten wij een stent als beschreven in hoofdstuk 11, echter nu van 12 cm lengte.

De eerste patiënte betrof een 36-jarige vrouw die gezien werd met een hilaire strictuur na een gecompliceerd verlopende cholecystectomie (lekkage en stricturen). Meerdere ERCP's met stentplaatsing en ballondilatatie leidde niet tot adequate behandeling en patiënte bleef stent-afhankelijk. Wij plaatsten een 10 fr plastic stent in het minder aangedane rechter systeem en een 10 mm 12 cm fcSEMS in het linkergalwegsysteem.

Plaatsing en verwijdering na 5 maanden verliepen ongecompliceerd en op het cholangiogram was de hilaire strictuur verdwenen. Na meer dan 2 jaar follow-up zijn er geen aanwijzingen voor recidief strictuur.

De tweede patiënte was een 29-jarige vrouw die een anastomotische strictuur ontwikkelde van haar duct-to-duct anastomose 2 jaar na OLT. Zij werd hiervoor behandeld middels progressief plastic stenten met aanvankelijk goed resultaat. Drie maanden later was er echter sprake van een recidief strictuur, zich nu uitbreidend tot in de leverhilus. Zij werd vervolgens behandeld met een 10 fr 12 cm plastic stent in het linkersysteem en 12 cm 10 mm fcSEMS naar rechts. Na 4 maanden werden de stents verwijderd en bij cholangiografie was er geen strictuur meer zichtbaar. Ook na meer dan 12 maanden follow-up waren er geen aanwijzingen voor een recidief.

Hoewel deze 2 casus laten zien dat deze nieuwe behandeling van benigne hilaire galwegstricturen technisch haalbaar is, veilig lijkt en mogelijk effectief is, zijn er nog een aantal potentiële nadelen. Met name het plaatsen van een 10 mm stent in een intrahepatische galgang kan soms een te forse diameter zijn en mogelijk leiden tot secundaire stricturen. Wij zijn daarom een prospectieve multicenter registratie gestart waarbij patiënten met benigne hilaire galwegstricturen behandeld zullen worden met bilaterale 7 mm fcSEMS met proximale lasso.

LIST OF ABBREVIATIONS (LOA)

AS	Anastomotic Strictures
BBS	Benigne Biliary Strictures
BRCA1/2	Breast Cancer gene 1/2
CA	Carbohydrate Antigen
CDKN2A	Cyclin Dependent Kinase inhibitor 2A
CEA	Carcinoembryonic Antigen
CI	Confidence Intervals
CP	Chronic Pancreatitis
CPN	Celiac Plexus Neurolysis
CRP	C-Reactive Proteine
CT	Computed Tomography
ERCP	Endoscopic Retrograde Cholangio Pancreaticography
EUS	Endoscopic Ultrasonography
EUS-FNA	Endoscopic Ultrasonography Fine Needle Aspiration
ESWL	Extracorporeal Shock Wave Lithotripsy
FAMMM	Familial Atypical Multiple-Mole Melanoma
fcSEMS	fully covered Self Expandable Metal Stents
FNA	Fine Needle Aspiration
FNB	Fine Needle Biopsy
FNI	Fine Needle Injection
FPC	Familial Pancreatic Cancer
GI	Gastro Intestinal
HBOC	Hereditary Breast and Ovarian Cancer
IPMN	Intraductal Papillary Mucinous Neoplasia
IPMT	Intraductal Papillary Mucinous Tumour
LCx	Laparoscopic Cholecystectomy
LOA	List of abbreviations
MCNs	Mucinous Cystic Neoplasms
MDCT	Helical Multidetector Computer Tomography
MRCP	Magnetic Retrograde Cholangio Pancreaticography
MRI	Magnetic Resonance Imaging
NOTES	Natural Orifice Transluminal Endoscopic Surgery
NPV	Negative Predictive Value
OLT	Orthotopic Liver Transplantation
OR	Odds Ratio
Pan-IN	Pancreatic Intraepithelial Neoplasia
PBC	Primary Biliary Cirrhosis

PCs	Pancreatic Cancer
pcSEMS	partially covered Self Expandable Metal Stents
PET	Positron Emission Tomography
PF	Papillary Stenosis
PPPD	Pylorus Preserving Pancreaticoduodenectomies
PPS	Progressive Plastic Stenting
PPV	Positive Predictive Value
PRSS1	Protease Serine 1 (trypsin 1)
PTT	Partical Thromboplastin Time
Pt-INR	Prothrombin time International Normalized Ratio
SEMS	Self Expandable Metal Stents
SOC	Standard of Care
SPSS	Statistical Package for the Social Sciences
WOPN	Walled Off Pancreatic Necrosis

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Lieve Willeke en lieve Jack, ook al kan mama dit niet meer meemaken, ik ben wel heel blij dat wij dit samen kunnen delen. Ik ben ontzettend trots op jullie. Trots op de manier hoe jullie samen in het leven staan en er in makkelijke, maar vooral ook in moeilijke tijden, samen zijn voor elkaar.

Dear Sanne and Nick, even though we get together infrequently for obvious reasons, I am very happy to have become part of your family as well. We are really looking forward to coming over to Perth next year and teach the boys the first principles of surfing.

Lieve John en Hanna, lieve opa en oma, lieve extra opa en oma. Natuurlijk ben ik heel blij met jullie dochter maar het is vooral ook zo mooi om te zien hoe jullie genieten van het leven, van elkaar en van Joost en Oscar. Zij hadden zich geen betere opa en oma kunnen wensen en ik geen betere schoonouders.

Lieve Emma, Wick, Raf en Joost, jullie weten bijna niet beter dan dat papa weg is, weg gaat (voor een spreekbeurt) of net terug is en zelfs op vakantie nog gebeld wordt door "het ziekenhuis". En dan ook nog eens iets doet wat toch echt wel ontzettend vies is. Daarom is dit een mooie gelegenheid om niet alleen te zeggen maar ook eens te schrijven dat ik jullie alle vier even liefheb en ontzettend trots ben op jullie. Het is geweldig om jullie groot te zien worden, om te zien hoe jullie op elkaar lijken maar ook van elkaar verschillen. Samen koken, samen klap 's in je handjes zingen of samen naar een film kijken. Soms slaande ruzie maar toch altijd in de eerste en laatste plaats broers en zus en er voor elkaar zijn. Ik hou van jullie.

Lieve Lotte, wie had dat gedacht alweer ruim 4 jaar geleden? Ik ben zo ontzettend blij dat je toch min of meer bij toeval mijn leven en mijn armen in bent gestruikeld. Eigenlijk is alles daarna heel natuurlijk en vanzelf gegaan en zijn we nu ontzettend gelukkig met z'n drieën (of met z'n zessen). Ik vind het zo knap om te zien hoe je om weet te gaan met een overvol en soms veel te druk leven dat geregeerd lijkt te worden door agenda's en schema's maar tegelijkertijd ook je eigen carrière hebt en ontzettend goed en bevlogen bent in wat je doet.

Je bent er voor mij maar ook voor Emma, Wick en Raf (ook al eten ze niet meer zo vaak bij de McD) en natuurlijk ook voor Joost. Het is altijd fijn om bij jou te zijn en samen thuis te komen of samen op reis te gaan. Ik hoop dat we dat de komende jaren en de rest van ons leven steeds meer kunnen gaan doen en blijven genieten van ons leven samen.

CURRICULUM VITAE

Na zijn geboorte op 31 januari 1968 in Hamburg en omzwervingen via Rotterdam en Hoogezand groeide Jan-Werner Poley op in Delfzijl. In 1987 deed hij eindexamen atheneum op het Fivelcollege aldaar. Na een jaartje rechten te hebben gestudeerd, begon hij in 1988 met de studie geneeskunde aan de Rijksuniversiteit Groningen. Na het afronden van zijn doctoraal in 1994 verhuisde hij naar Amsterdam om daar, na een wetenschappelijke stage op de afdeling kinderendocrinologie van het AMC, zijn co-schappen te lopen aan de Vrije Universiteit. In 1997 behaalde hij het artsexamen (cum laude) en begon als arts – assistent niet in opleiding in het toenmalige Sint Lucas ziekenhuis (nu Sint Lucas Andreas ziekenhuis) te Amsterdam. In 1999 begon hij, ook in het Sint Lucas Andreasziekenhuis, aan de opleiding Interne Geneeskunde (opleider dr. J.J.M. van Meyel) in de vaste overtuiging uiteindelijk internist – intensivist te worden. Tijdens zijn gastroenterologie stage en na de eerste schreden op het endoscopiepad gezet te hebben, besloot hij een carrière in de Maag-, Darm- en Leverziekten na te streven. Als zij – instromer begon hij in 2002 met de vervolgopleiding tot maag-, darm- en leverarts in het Erasmus MC (opleiders prof. dr. E.J. Kuipers en dr. R.A. de Man) die hij op 1 januari 2005 afrondde. Sindsdien is hij werkzaam als MDL-arts in het Erasmus MC met als aandachtsgebied pancreaticobiliaire aandoeningen en interventie – endoscopie. Sinds 1 december 2012 is hij hoofd en medisch coördinator van de MDL – endoscopie in het Erasmus MC.

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PhD PORTFOLIO

Oral Presentations

2002

Dutch Society of Gastroenterology, Veldhoven, NL: technique and efficacy of push-enteroscopy

2003

Themadag MDL Rotterdam: Virtual colonoscopy

Dutch Society of Gastroenterology, Veldhoven, NL: Digestive and systemic complications following oral ingestion of concentrated acetic acid or alkaline agents

Erasmus Endoscopy Day, Rotterdam, NL; 4 september 2003; Management of caustic esophageal strictures

2004

Dutch Society of Gastroenterology, Veldhoven, NL: Endosonographic staging of obstructive esophageal cancer: how far should we go?

Erasmus Endoscopy Day, Rotterdam, NL: Endoscopic ultrasonograpy: the next generation

Dartmouth Medical Center, Hanover, NH; USA: Ingestion of acid and alkaline agents: outcome and prognostic value of early upper endoscopy

2005

Single topic cholelithiasis, University Medical Center, Groningen; 12 april: Endoscopy and gallstones

Annual Meeting Dutch Society Clinical Phsyics, Doorwerth 22-23 april: Clinical Applications of Endosonography

International Society for Gastrointestinal Hereditary tumours (Insight), 14-17 juni, Newcastle, UK: Biallellic mismatch repair gene defects – A cause for multiple pediatric malignancies

2006

Dutch Society of Gastroenterology, Veldhoven, NL: Endoscopic pancreatic duct decompression in treating pancreatic leakage: a successful and safe method in selected patients

Esophageal Cancer Workshop, Timisoara, Romania, 1 april: Staging of esophageal cancer

NVMBR annual meeting, Utrecht, NL 12 mei: review ERCP

UEGW, Berlin; 22 oktober; ESGE hands on course

Annual meeting Gastroenterologists: Making the invisible visible with endoscopic ultrasound

2007

Dutch Society of Gastroenterology, Veldhoven, NL: Endoscopic ultrasonography: a valuable tool in screening high-risk patients for pancreatic cancer

Dutch Society of Gastroenterology, Veldhoven, NL: New wireguides and new systems in ERCP

Follow-up after polypectomy of early invasive cancer; november 6; Daniel Den Hoed Cancer Clinic, Rotterdam

Bucharest, Romania; December 7: pancreatic cancer and bile duct drainage

Bucharest, Romania; December 7: Endoscopic ultrasonography and pancreatic cancer

Bucharest, Romania; December 7: Debate on the value of ERCP in differentiating pancreatic cancer from chronic pancreatitis

2008

Dutch Society of Gastroenterology, Veldhoven, NL: Management of upper GI bleeding in patients on anticoagulants

Dutch Society of Gastroenterology, Veldhoven, NL: Endoscopic Ultrasonography is a valuable tool with high yield in screening of patients at high risk for pancreatic cancer

Dutch Society of Gastroenterology, Veldhoven, NL: Endoscopic elastosonography is highly predictive of definite pathology

Dutch Society of Gastroenterology, Veldhoven, NL: Endoscopic interobserver agreement for the Spigelman classification in patients with familial adenomatous polyposis (FAP)

Rikshospitalet Oslo (live course): Tips and indiciations for EUS

Rikshospitalet Oslo: Therapeutic EUS

Reijkjavik, Iceland: Endoscopic Ultrasonography – a little bit of everything

Digestive Disease Week, San Diego USA: Endoscopic Ultrasonography is a valuable tool with high yield in screening of patients at high risk for pancreatic cancer

Digestive Disease Week, San Diego USA: Endoscopic elastosonography is highly predictive of definite pathology

2009

American Society of Clinical Oncology – Gastrointestinal Cancers, San Francisco, USA: Use of endoscopic ultrasonography in screening patients at high risk for pancreatic cancer

EUS live meeting (Leuven, Belgium): interventional endosonography

2010

3rd Advanced Education Course of Endoscopy, Taipei, Taiwan: metallic stenting for biliary hilar and distal obstruction

3rd Advanced Education Course of Endoscopy, Taipei, Taiwan: Tips for esophageal malignant obstruction including upper esophageal stenosis

3rd Advanced Education Course of Endoscopy, Taipei, Taiwan: metallic stenting for enteral obstruction

Dutch Society of Gastroenterology, Veldhoven: a prospective study evaluating a new SEMS for the treatment of benign biliary strictures

Tel Aviv: screening for pancreatic cancer

Rikshospitalet Oslo: presentations on enteral stenting and interventional EUS

7th Summer School of Gastroenterology Prague – Endoscopic interventions in chronic pancreatitis

Barcelona UEGW: advances in EUS technology

2011

Hamburg: Can pancreatic cancer be prevented?

Rotterdam: Het Gastroenterologisch Jaar; nieuwe ontwikkelingen in de endoscopie

Kaunas, Lithuania: new developments in stenting of hilar cholangiocarcinoma

Dutch Society of Gastroenterology, Veldhoven, NL: endoscopic diagnosis and treatment of chronic pancreatitis

Dutch Society of Gastroenterology, Veldhoven, NL: fully covered metal stents for the treatment of benign biliary strictures

Dutch Society of Gastroenterology, Veldhoven, NL: a newly developed EUS needle to reliably obtain histologic material

Digestive Disease Week, Chicago, USA: Pancreatic screening: where are we now, where are we going?

Workshop Reykjavik, Iceland: EUS and the pancreas

Corso Avanco Teoretico-Pratico di Ecoendoscopia, Roma, Italia: role of EUS in pancreatic cysts

SGI Seoul, Korea: Breakfast with the masters on biliary stenting in benign disease

Erasmus Liver Day: biliary stenting in liver disease

2012

Erasmus Gastroenterology Day: endoscopic treatment of complications of cholecystectomy

Endo club Nord Helsinki – the use of fully covered SEMS in benign biliary disease

Endoscopic treatment of chronic pancreatitis – Groningen

How to obtain EUS guided histology? – Copenhagen, Kolding; Danmark

Santiago de Compostela, Spain: EUS live course & screening for pancreatic cancer

EUS and ERCP – Oslo, Norway

Amsterdam Live Endoscopy – EUS histology: which needle, which patient

2013

Review of the GI year in endoscopy – Rotterdam

Endoscopic treatment of benign biliary strictures in chronic pancreatitis – Zeist

A large International Multicenter Experience with an Over-The-Scope Clipping Device for Endoscopic Management of Gastrointestinal Defects in 188 Patients – Dutch Society of Gastroenterology, Veldhoven

Endoscopic treatment of chronic pancreatitis – Japanese Gastrointestinal Endoscopy Society, Kyoto, Japan

Acute pancreatitis – UEG Summer School Prague, Czech Republic

European view of quality in colonoscopy – IMAGE live endoscopy course, Milan, Italy

Tips and tricks in EUS & Evolution in metal stenting – Workshop on EUS and ERCP, Oslo, Norway

Memberships

Dutch Society of Gastroenterologists

Dutch Society of Gastroenterology

European Society of Gastrointestinal Endoscopy

American Society of Gastrointestinal Endoscopy (including special interest group on EUS)

Dutch Pancreatitis Study Group

European Pancreatic Club

International Association of Pancreatology

Positions

Staff member Department of Gastroenterology & Hepatology, Erasmus MC (2005 -)

Head of Endoscopy, Department of Gastroenterology & Hepatology, Erasmus MC (2012 -)

Expert panel on acute and chronic pancreatitis (Dutch Pancreatitis Study Group)

Board member Endoscopy section of Dutch Society of Gastroenterology

Board member Quality committee Dutch Society of Gastroenterologists

Board member EURO – EUS