—Original Article—

Pancreatic cystic lesions: The value of contrast-enhanced endoscopic ultrasound to influence the clinical pathway

Michael Hocke[1], Xin-Wu Cui[2], Dirk Domagk[3], Andre Ignee[2], Christoph F. Dietrich[2]

[1]Klinikum Meiningen GmbH, Bergstrasse 3, D-98617 Meiningen, Germany, [2]Caritas Krankenhaus Bad Mergentheim, Uhlandstraße 7, D-97980 Bad Mergentheim, Germany, [3]University of Muenster, D-48143 Muenster, Germany

ABSTRACT

Background and Objectives: Cystic pancreatic lesions are a growing diagnostic challenge. The aim of this study was to proof a new diagnostic concept based on contrast-enhanced endoscopic ultrasound (CE-EUS) for differential diagnosis. **Patients and Methods:** A total of 125 patients with unclear cystic pancreatic lesions were included. The initial diagnostic was made by CE-EUS dividing the lesions in a group without contrast enhancing effect in the cystic wall, septae or nodule indicating pseudocysts or dysontogenetic cysts and a group with contrast enhancing effect in the described structures indicating cystic neoplasias. The investigations were performed using a Pentax echoendoscope and Hitachi Preirus ultrasound machine. The contrast enhancer used was 4.8 mL SonoVue® (Bracco, Italy). The group with suspected cystic neoplasia was referred for endoscopic fine-needle puncture for further diagnostic or treatment decisions. **Results:** The dividing of the groups by contrast-enhanced ultrasound was feasible because all ($n = 56$) suspected cystic neoplasias showed a contrast enhancing effect, whereas in only 4 from 69 pseudocystic or dysontogenetic cystic lesions a contrast enhancing effect in the wall could be observed. Endoscopic fine-needle puncture could diagnose all malignant neoplasias and relevant premalignant conditions. The long-term follow-up did not show any development of malignant cystic lesions. **Conclusion:** Using CE-EUS and endoscopic fine-needle puncture as diagnostic criteria seemed to be a feasible method to deal with different cystic lesions in daily practice.

Key words: Cystic lesion, diagnosis, endoscopic ultrasound, microbubble, pancreas, puncture

INTRODUCTION

Due to the increasing resolution of cross-sectional diagnostic methods and percutaneous ultrasound, the detection of pancreatic cystic lesions became clinical relevant.[1,2] The knowledge of the malignant potential of some cystic pancreatic tumors has a major impact on the decision about referring the patient to major surgery and leaves the gastroenterologist with the question if follow-up can be safely advised to the patient or not. The decision seems to be even harder to make because so far there are no clear criteria to discriminate bland cystic lesions like dysontogenetic cysts and pseudocysts from benign and malignant cystic lesions. Therefore, overtreatment is a common approach and seems to be rectified.[3]

The introduction of contrast-enhanced low mechanical index endoscopic ultrasound (CELMI-EUS) in the year 2010 as a commercially available tool did change the diagnostic possibilities of EUS.[4] Unfortunately, the hope that the new method will have a major impact in the discrimination possibilities of EUS for solid pancreatic lesions could not be proved so far,[5] contrast-enhanced diagnosis of cystic pancreatic lesions seems to be feasible to use.[6] Basically, all cystic lesions of the pancreas can be investigated

Access this article online	
Quick Response Code:	Website: www.eusjournal.com
	DOI: 10.4103/2303-9027.131040

Address for correspondence
Dr. Michael Hocke, E-mail: michael.hocke@klinikum-meiningen.de
Received: 2014-01-18; **Accepted:** 2014-03-05

adequately by EUS and due to the high resolution even the smallest details like small septae can be visualized. Using CELMI-EUS with SonoVue® as the contrast enhancing substance – the movement of the microbubbles right down to the capillary bed can be investigated. This is pointing out the major advantage of the method in comparison to all other diagnostic methods because of the detection of a wall or nodule vascularization of the cystic lesion in a very high resolution.[7,8] The observation that wall and nodule vascularization indicates a cystic tumor and cannot be seen in dysontogentic cysts and pseudocysts has a major impact for the following diagnostic workflow pancreatic cystic lesions.[9-11] The aim of this study is to investigate the impact of CE-EUS as a part of a diagnostic workflow and should give an answer if the workflow chosen in this study is safe to follow.

PATIENTS AND METHODS

A total of 125 patients (age 64 ± 11 years, male = 68, female = 57) were included in the study with unclear cystic lesions of the pancreas which have been transferred for further diagnosis to perform EUS. Unclear cystic lesions were defined as lesions with no definite diagnosis made by cross sectional imaging methods. The study workflow was introduced at the beginning of the collection period; the data however, were collected retrospectively. Percutaneous sonography, computed tomography (CT)-scan or magnetic resonance imaging (MRI)-scan have been performed for initial diagnosis, but not for the purpose of the study. The initial diagnosis did not influence the EUS diagnosis and the following workflow. The hospital acts as a tertiary referral centre for EUS and almost all patients included in the study have been referred with the diagnosis: Unclear cystic lesion of the pancreas without the CT or MRI results present for initial diagnosis.

Endoscopic ultrasound for the pancreas was performed as recently described[5] by using a radial or longitudinal EUS probe type Pentax FG 38 UX and EG 3270 UK. An ultrasound machine Hitachi Preirus with special software for CELMI-EUS was used.

After displaying the cystic lesion, the setup for low MI endosonography was used, and the MI and gain adapted to the cystic lesion. MI was chosen in between 0.02 and 0.18 and gain was adapted as low as possible to avoid tissue signal. To display cystic wall and nodule vascularization 4.8 mL of SonoVue® (Bracco, Italy) was used. The dosage of 4.8 mL was chosen (recommended in the EFSUMB nonliver guideline 2011). Due to the high frequency EUS probe smaller bubbles of ultrasound contrast enhancer are necessary for adequate displaying. A higher dosage is necessary because of the bubble distribution (smaller amount of necessary bubbles) in the contrast enhancer SonoVue. Cystic wall and nodule vascularization was defined as visible contrast enhancer bubble movement within the cystic wall, septae and nodules. After the diagnosis of vascularization, high MI contrast-enhanced Doppler endosonography was used to display crossing vessels, and since January 2012 a three-dimensional reconstruction of the low MI and high MI result was made, but not for the purpose of the study.[12,13]

Patients with no visible wall, septae or nodule vascularization were assumed not to be cystic pancreatic tumors and only for the purpose of the study followed-up.

Patients with a visible wall, septae or nodule vascularization were assumed to be cystic pancreatic tumors and for further diagnosis referred to endoscopic fine-needle puncture if consent was given and if the result would influence the following workflow.

Endoscopic ultrasound fine-needle aspiration was performed outside of the workflow in seven patients with suspected pancreatic pseudocysts due to other reasons like infection of the cyst or pseudocyst drainage. The result of the fine-needle aspiration was included in the study.

Endoscopic ultrasound fine-needle puncture of the cystic lesion was performed in a second investigation after antibiotic premedication (ceftriaxone 2 g intravenously 30 min. before the puncture). Immediate endoscopic fine-needle puncture of cystic lesions was avoided to provide the patient the necessary consent time and for starting the antibiotic treatment before the fine-needle aspiration. In addition but not in all cases, a longitudinal scanner was used for initial diagnosis. For fine-needle puncture, a 22 G needle (Cook, Ireland) was used. The cystic content was aspirated in a 20 mL vacuum syringe and after finishing the aspiration of fluid and removing the syringe the needle was moved along the cystic wall or nodule to collect cells for cytologic investigation.

Patients with mucous liquid or carcinoembryonic antigen (CEA) level >400 or cytological tumor criteria were advised for surgical removal of the lesion. Patients

with serous liquid, CEA level <400 and cytological normal cells were advised for follow-up. Lipase level was estimated if enough fluid remained for further laboratory investigations. Lipase was selected instead of amylase because it is the diagnostic enzyme of choice in Germany for diagnosing acute pancreatitis.

If liquid of the lesion was too little, cytological analysis was preferred over CEA analysis. For cytological analysis, air-dried specimens on slides were stained by May/Gruenwald staining and if necessary slides were saved for further immunocytological staining.

In case of refusal of endoscopic fine-needle puncture, the decision about follow-up or operation was made according to the morphological appearance of the lesion.

The workflow is summarized in Figure 1. Patients consent to EUS, CE-EUS and endoscopic fine-needle puncture was taken.

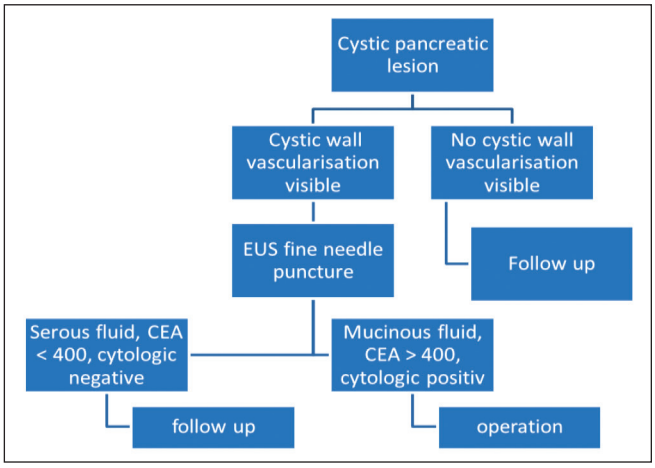

Figure 1. Workflow for study analysis of contrast-enhanced endoscopic ultrasound

Statistical analysis was made with the help of inbuilt statistical analysis in the software solution Excel Microsoft. For statistical analysis, Chi-square test was used.

Due to the conservative approach of the study final diagnosis of cystic lesions was made by:

1. Histology in case of operation;
2. Morphological appearance in connection with the result of fine-needle aspiration result or
3. Morphological appearance without result of fine-needle aspiration (in case fine-needle aspiration was not indicated or refused by the patient).

Morphological criteria are given in Table 1 adapted to the criteria of Degen *et al.*[34] Due to the limitation of not always being able to compare the result with the histological examination of the cystic lesion a level of certainty was introduced and given in Table 2. Level a is according to an histological and cytological proven lesion, level b is according to cytological and morphological very likely lesion and level c an assumption of the lesion by morphological criteria with the follow-up result fitting the diagnosis.

RESULTS

The CELMI-EUS was successful in all included patients. The visualization of the cystic wall and the inner parts like nodules and septae of the cysts were always possible.

The results of the endosonographic diagnostic including the results of fine-needle aspiration and the follow-up are summarized in Table 2. To estimate the impact of the contrast-enhanced EUS in relation to the normal B-mode EUS regarding the discrimination of dysontogenetic and pseudocysts in relation to cystic

Table 1. Morphological criteria in EUS for diagnosis of cystic pancreatic lesions

Cystic lesion	Morphological criteria
Dysontogentic cyst	Simple cyst without visible nodules, septae and wall thickening, no visible connection to the pancreatic duct
Pseudocyst	Signs of chronic pancreatitis with visible cystic lesion, no visible duct connection or duct alteration caused by the cyst, dilatation of the pancreatic duct was accepted due to the destroyed pancreas
Serous cystadenoma	Microcystic: Multiple cystic lesions with a very small size - cystic complex with sharp delineation to the surrounding tissue, no duct involvement; Macrocystic: Cystic lesion with visible septaes but no duct involvement
Mucinous cystadenoma	Macrocystic lesion with wall thickening, visible nodules and septae, no duct involvement
Branch duct IPMN	Cystic lesion with visible septae and nodules with connection to the main duct but no main duct involvement
Main duct IPMN	Cystic lesion with septae and nodules and wall thickening with involvement and dilatation of the pancreatic duct
Cystic NET and cystic pancreatic carcinoma	Various appearance-final diagnosis was made by fine-needle aspiration or histology

IPMN: Intraductal papillary mucinous neoplasia, NET: Neuroendocrine tumor, EUS: Endoscopic ultrasound

Table 2. Differential diagnosis of cystic lesions based on endosonographic morphological appearance, result of operation and fine-needle puncture

N = 125	*N*	Cystic wall vascularisation	EUS fine-needle aspiration	Quality of cystic fluid (a = serous; b = mucinous)	Follow-up (months)	Result	Level of certainty (a = definite; b = probable; c = uncertain)
Dysontogenetic cyst	23	1	1 (Pap II)	a=1 b=0	13.6±8.4	22 no change 1 decreased size	a=0 b=22 c=1
Pseudocyst	46	3	10 (Pap II, CEA <400)+10 operation	a=10 b=0	17.6±13.9	16 no change 20 decreased size 10 operation	a=11 b=34 c=1
Serous cystic adenoma	26	26	20 (19 Pap II, 1 Pap 0) CEA <400	a=10 b=0	17.8±11.2	23 no change 1 decreased size 2 increased size (operation refused)	a=0 b=26 c=0
Mucinous cystic adenoma	1	1	Not performed		0	Operation confirmed	a=1 b=0 c=0
Branch duct IPMN	16	16	8 Pap II, CEA <400 (1 operation)	a=7 b=1	16.1±12.5	14 no change 1 increased size + operation confirmed	a=1 b=15 c=0
Main duct IPMN	6	6	2 Pap IV >1 operation	a=2 b=0	15.6±12.7	2 no change 2 increased size 2 operation	a=4 b=2 c=0
Cystic NET	4	4	4 Pap V (3 operation)	a=4 b=0	0	Confirmed	a=4 b=0 c=0
Cystic pancreatic carcinoma	3	3	3 Pap V (1 operation)	a=3 b=0	0	Confirmed	a=3 b=0 c=0

N: Number, IPMN: Intraductal papillary mucinous neoplasia, NET: Neuroendocrine tumor, Pap: Papanicolaou staging, CEA: Carcinoembryonic antigen, EUS: Endoscopic ultrasound

tumors we performed a Chi-square test using a 2 × 2 table [Table 3]. The result was highly significant with a $P < 0.001$. Nine of 125 patients included in the study (7.20%) were proved to have a malignant cystic lesion. All malignant cystic lesions showed a contrast enhancing effect in the cystic wall or in the structures within the cyst and could be therefore diagnosed by fine-needle aspiration cytology or operation by following the workflow. An example of the different vascularization behavior of a pancreatic pseudocyst and a cystic neoplasia is given in Figures 2 and 3.

Table 3. 2 by 2 table with Chi-square test of discrimination of pancreatic pseudocysts and dysontogenetic cysts versus cystic neoplasia using gold standard criteria and contrast-enhanced EUS criteria

Kind of lesion	Gold standard criteria (EUS)	Contrast criteria	Sum
Cystic tumor	51	5	56
Pseudocyst and dysontogenetic cyst	45	24	69
Sum	96	29	125

Two sided significance: < 0.001, Chi-square value: 11.597, Degree of freedom: 1 highly significant, EUS: Endoscopic ultrasound

In this study, all patients ($n = 56$) diagnosed with cystic tumors regardless of benign or malignant origin, showed a contrast enhancing effect within the cystic structures. In one of the 23 cystic lesions diagnosed as dysontogenetic cyst was a contrast-enhanced wall effect visible and an endoscopic fine-needle puncture was performed. A cystic wall vascularization was visible in three of 46 pseudocystic lesions. All of those three patients received a Whipple resection because of other reasons, which confirmed chronic pancreatitis with pseudocysts. Furthermore in the group of chronic pancreatitis another seven patients were operated on because of complication of the pancreatitis such as inadequate pain relief and stenosis of the duodenum. Included in the group of pseudocysts were seven patients with interventional endoscopic cyst drainage because of superinfection or necrosis, those patients all showed a regredient cyst after the endoscopic intervention. Spontaneous regredient cyst could be observed in a further 13 patients.

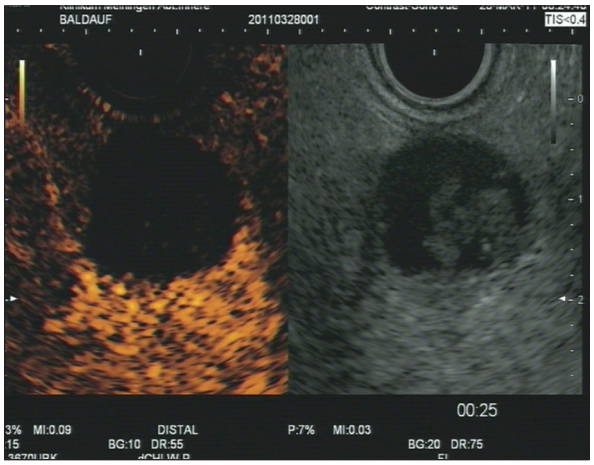

Figure 2. Contrast-enhanced endoscopic ultrasound in low mechanical index mode in a patient with a pancreatic pseudocyst. Because of the echogenic material within the cyst a nodule cannot be excluded in B-mode ultrasound. Contrast-enhanced technique shows no contrast-enhanced effect within the cyst and the cystic wall indicating pancreatic pseudocyst

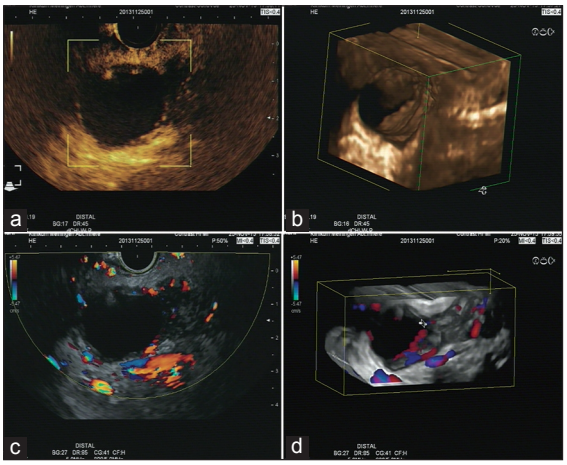

Figure 3. Series of different imaging methods of a macrocystic serous cystadenoma – diagnosis is based on the endoscopic fine-needle puncture with serous cystic fluid, low carcinoembryonic antigen level and benign cytology. Contrast-enhanced low mechanical index (MI)-endoscopic ultrasound revealed contrast-enhanced effect within the cystic wall as well as in a nodule indicating cystic neoplasia. (a) Three-dimensional (3D) reconstruction of the same lesion shows especially on the left lower area of the cyst the contrast-enhanced effect. (b) High MI contrast-enhanced ultrasound displays Doppler signals from the cystic wall. (c) 3D reconstruction of the same cyst reveals cystic wall vessels (d)

All patients (n = 26) with serous cystadenoma showed cystic wall and septae vascularization. In this group, six patients refused endosonographic fine-needle aspiration because of lack of consequence in an age over 70 years and comorbidity. Only one patient aged 56 years refused the diagnostic puncture, but however took part in the follow-up program. The mean follow-up of the group was 17.8 ± 11.2 months (range: 3-40 months). No patient in the follow-up developed signs of malignancy and only in two patients a slight increase of size <1 cm could be observed (33 and 28 months follow-up so far). Both patients refused operation and will still be included in the followed-up program.

Only one patient so far could be included in the study with a macrocystic mucinous cystadenoma of the pancreatic tail. The patient showed a clear contrast enhancing effect in the thick cystic wall and included nodules and was operated on without endoscopic fine-needle aspiration beforehand, confirming the diagnosis without signs of malignancy.

A total of 16 patients with visible main duct connection to the cystic lesion were assumed to be branch duct intraductal papillary mucinous neoplasia (IPMN). The sof the cystic lesions were in the range of 1-2.5 cm. Only eight patients agreed to the endoscopic fine-needle aspiration mostly due to age and comorbidity reasons. Again, cystic wall and septae vascularization could be observed in all patients. Only in one patient an increase of size of the cystic lesion was observed in a period of 20 months, and the patient was referred for surgery. The histological examination revealed branch duct IPMN with low grade dysplasia. The mean follow-up in this group was 16.1 ± 12.5 months (range of 1-40 months) without any signs of malignancy.

Six patients with main duct IPMN were included in the study. Because of the characteristic endoscopic appearance (typical duct appearances and fish-mouth papilla) the diagnosis did not require CE-EUS however for the purpose of the study CE-EUS was performed in all patients. The visible nodules and the visible septae took up the contrast enhancer very heavily as anticipated in all patients. Because of suspicion of malignant transformation and refusal of operation in one patient endoscopic fine-needle aspiration was performed and confirmed tumorous cells in cytology. After the result, the patient was referred to surgery confirming the main duct IPMN with high grade dysplasia. Another patient was operated on immediately after diagnosis confirming main duct IPMN with cancerous transformation. A third patient could not be operated on because of comorbidity and received chemotherapy. Comorbidity and age was the reason for only following-up the remaining three patients over 22, 20, and 4 months so far. Only in the patient with 20 months follow-up an increase of the tumorous lesion could be observed, but still without any signs of malignancy.

Seven patients with heterogeneous cystic lesions, but thick cystic walls and nodules within the lesions could be observed with different degree of contrast enhancer uptake in the cystic wall. According to the study design, all of the patients underwent endoscopic fine-needle aspiration cytology and were diagnosed 3 times as cystic pancreatic adenocarcinoma and 4 times as cystic neuroendocrine tumor (NET). Three of the patients in the group of NETs and one of the patients in the group of pancreatic carcinoma could be operated on and the diagnosis was confirmed.

DISCUSSION

There is a great variety of histological cystic pancreatic lesions. However, many of these lesions are rare and cannot be seen very often in clinical practice.[14] In addition, there is no way for the diagnostician to get the correct diagnosis with the help of morphology, contrast enhancer behavior and even endoscopic fine-needle aspiration in all those different lesions before final histological examination. Despite that fact, the most important problem for the gastroenterologist is the correct further treatment of the patient, which means avoiding overtreatment and still having a safe approach to select patients who will benefit from surgery.

It can be safely stated that patients with pseudocysts and congenital or dysontogenetic cyst do not have a risk of carcinomatous transformation.[1] Patients with benign cystic tumors on the other hand, have the risk of malignant transformation and should be therefore considered for surgery.[15] Recent studies suggest that the malignant risk of serous cystadenomas is very low, which means that patients suffering from those benign tumors can be safely followed-up and do not need immediate surgery.[1,16,17] A risk of malignant transformation is evident in mucinous cystic pancreatic lesions and is as high as 30-60%.[18,19] The aim of the diagnostic efforts should be to select those patients and not to overlook patients with existing malignant cystic lesions.

For the sake of grouping cystic pancreatic lesions into the most common lesions with typical morphological signs, which can be figured out before surgical removal, the following entities were used in the study despite the knowledge that misdiagnosis can happen.

In this study, a two-step diagnostic approach was used to figure out the likely diagnosis of the cystic lesion and later on their malignant potential. Signs of cystic neoplasia in the pancreas are according to Habashi and Draganov:[20] Cystic wall >3 mm, septae, nodules within the cyst, pancreatic duct dilatation and cystic wall vascularization. Until the introduction of CELMI-EUS, the last sign described above was figured out by Doppler examination with all its problems.[21] Using CELMI-EUS, the bubble movement can be observed right down to the capillary bed, which considerably increases the sensitivity of displaying cystic wall vascularization.[7] Cystic wall vascularization cannot be observed in dysontogentic or pseudocysts and is therefore, a good discrimination method for cystic lesions in the pancreas. According to the results of this study, the criteria of cystic wall vascularization were safe to discriminate between dysontogenetic and pseudocysts to cystic pancreatic tumors. Cystic wall vascularization could rarely be observed in patients with dysontogenetic cysts and pseudocysts in this study. A reason for the visible vascularization in four of the 69 patients might be inflammatory involvement of the wall of the pseudocysts or a misdiagnosis in the patient with the dysontogenetic cyst.

Having discriminatory criteria for dysontogenetic and pseudocysts, there is then a need for another set of criteria to distinguish between serous or mucinous lesions because of their different malignant potential. In this study, a semi invasive approach was selected. Using endoscopic fine-needle puncture at least three established parameters could be determined to discriminate the cystic lesion further for malignancy or malignant potential.[22-24] Fine-needle aspiration for diagnosis of cystic pancreatic lesions is regarded as safe in the literature if antibiotic premedication is applied.[25,26] In this study, no side-effects could be observed in all 48 patients receiving the procedure. However, unnecessary fine-needle punctures should be avoided.

The analysis criteria of the cystic fluid were based on morphological characteristics of the lesions and according to the actual literature and limitations in a communal hospital. The discrimination of the fluid into serous and mucinous was made by the endoscopist according to the fluid behavior.[27,28] If the fluid was water-like it was called serous, and if the fluid was gel-like, it was called mucinous. Modern cytological methods can actually quantify the fluid content however, it was not used in this study.[29] Cytological specimens are known to be hard to get

from cystic lesions, although we got adequate material in 47 of 48 punctured patients in our study.[30] As a laboratory test, the CEA level of the cystic fluid is so far the easiest and most reliable factor for establishing malignant potential. We used the cut-off of 400 to avoid too many false positive tests.[31] It has to be mentioned that CEA levels are different from the laboratory to the laboratory and can therefore not be recommended widely.

The usefulness of estimating lipase level in the cystic fluid for discrimination of pancreatic pseudocysts and mucinous neoplasia is low; however, we used the enzyme as an additional parameter for differential diagnosis because of the easy and cheap estimation.[32]

The majority of cystic lesions included in the study did not show any symptoms and were of a size of 1-5 cm (excluding the main duct IPMN's). According to the literature, it is supposed to be safe to follow-up lesions up to 3 cm especially if there are no signs of septae or nodules.[1,19] Therefore, the study design includes a great deal of long-term following-up instead of aggressive surgical treatment. The weakness of this study is the lack of adequate histological confirmation of the patient groups and therefore, the reliance on the long-term follow-up. Keep in mind that a malignant transformation can occur in a time frame of 5-20 years; however, it proved safe enough to deal with those patients in daily practice in unselected patients so far.[33] The benefits of the present approach are that it is minimally invasive, and the possibility to react if the cystic lesion shows signs of changing. Because the study is done in a communal hospital and not in a tertiary referral center, the result is projectable into daily practice and includes the polymorbiditiy taking into account the advanced age of the patients.

The limitation of this study is the lack of histological proven pancreatic cysts according to the end diagnosis. EUS fine-needle aspiration only provided results for cytological examination and not for further histological assessment. Accordingly, we believe that operation of cystic lesions like dysontogenetic and pseudocysts as well as serous cystadenoma would be an overtreatment. Nevertheless, our patients reflect the broad spectrum of pancreatic cystic lesions in daily practice and therefore the limitation can be rectified.

CONCLUSION

Contrast-enhanced-endoscopic ultrasound seems to be reliable enough to discriminate pancreatic cystic neoplasias from cystic pseudocysts and dysontogenetic cysts. Therefore CE-EUS can influence the clinical pathway in defining pancreatic cystic lesions if fine-needle puncture should be performed for further evaluation.

REFERENCES

1. Zaheer A, Pokharel SS, Wolfgang C, *et al*. Incidentally detected cystic lesions of the pancreas on CT: Review of literature and management suggestions. *Abdom Imaging* 2013;38:331-41.
2. Scoazec JY, Vullierme MP, Barthet M, *et al*. Cystic and ductal tumors of the pancreas: Diagnosis and management. *J Visc Surg* 2013;150:69-84.
3. Kim SC, Song KB, Jung YS, *et al*. Short-term clinical outcomes for 100 consecutive cases of laparoscopic pylorus-preserving pancreatoduodenectomy: Improvement with surgical experience. *Surg Endosc* 2013;27:95-103.
4. Hocke M, Dietrich C. Contrast-enhanced sonography and endoscopic ultrasound for the diagnosis of pancreatic diseases. *Zentralbl Chir* 2013;Oct 16 [Epub ahead of print].
5. Hocke M, Ignee A, Dietrich CF. Advanced endosonographic diagnostic tools for discrimination of focal chronic pancreatitis and pancreatic carcinoma – Elastography, contrast enhanced high mechanical index (CEHMI) and low mechanical index (CELMI) endosonography in direct comparison. *Z Gastroenterol* 2012;50:199-203.
6. Hocke MD, Dietrich CF. Perkutane sonografie des gastrointestinaltrakts. *Verdauungskrankheiten* 2013;31:8.
7. Seicean A, Badea R, Stan-Iuga R, *et al*. The added value of real-time harmonics contrast-enhanced endoscopic ultrasonography for the characterisation of pancreatic diseases in routine practice. *J Gastrointestin Liver Dis* 2010;19:99-104.
8. Sakamoto H, Kitano M, Kamata K, *et al*. Diagnosis of pancreatic tumors by endoscopic ultrasonography. *World J Radiol* 2010;2:122-34.
9. Ohno E, Itoh A, Kawashima H, *et al*. Malignant transformation of branch duct-type intraductal papillary mucinous neoplasms of the pancreas based on contrast-enhanced endoscopic ultrasonography morphological changes: Focus on malignant transformation of intraductal papillary mucinous neoplasm itself. *Pancreas* 2012;41:855-62.
10. Piscaglia F, Nolsøe C, Dietrich CF, *et al*. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): Update 2011 on non-hepatic applications. *Ultraschall Med* 2012;33:33-59.
11. Beyer-Enke SA, Hocke M, Ignee A, *et al*. Contrast enhanced transabdominal ultrasound in the characterisation of pancreatic lesions with cystic appearance. *JOP* 2010;11:427-33.
12. Hocke M, Ignee A, Dietrich CF. Three-dimensional contrast-enhanced endoscopic ultrasound for the diagnosis of autoimmune pancreatitis. *Endoscopy* 2011;43 Suppl 2 UCTN:E381-2.
13. Hocke M, Dietrich CF. New technology – Combined use of 3D contrast enhanced endoscopic ultrasound techniques. *Ultraschall Med* 2011;32:317-8.
14. Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, *et al*. Primary pancreatic cystic neoplasms of the pancreas revisited. Part IV: Rare cystic neoplasms. *Surg Oncol* 2012;21:153-63.
15. Schmid RM, Siveke JT. Approach to cystic lesions of the pancreas. *Wien Med Wochenschr* 2014;164:44-50.
16. de Jong K, Bruno MJ, Fockens P. Epidemiology, diagnosis, and management of cystic lesions of the pancreas. *Gastroenterol Res Pract* 2012;2012:147465.

17. Del Chiaro M, Verbeke C, Salvia R, *et al*. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 2013;45:703-11.
18. Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, *et al*. Primary pancreatic cystic neoplasms revisited: Part II. Mucinous cystic neoplasms. *Surg Oncol* 2011;20:e93-101.
19. Pausawasdi N, Heidt D, Kwon R, *et al*. Long-term follow-up of patients with incidentally discovered pancreatic cystic neoplasms evaluated by endoscopic ultrasound. *Surgery* 2010;147:13-20.
20. Habashi S, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol* 2009;15:38-47.
21. Dietrich CF, Jenssen C, Allescher HD, *et al*. Differential diagnosis of pancreatic lesions using endoscopic ultrasound. *Z Gastroenterol* 2008;46:601-17.
22. Hawes RH, Clancy J, Hasan MK. Endoscopic ultrasound-guided fine needle aspiration in cystic pancreatic lesions. *Clin Endosc* 2012;45:128-31.
23. Barresi L, Tarantino I, Granata A, *et al*. Pancreatic cystic lesions: How endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle. *World J Gastrointest Endosc* 2012;4:247-59.
24. Cizginer S, Turner BG, Bilge AR, *et al*. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. *Pancreas* 2011;40:1024-8.
25. Carrara S, Arcidiacono PG, Mezzi G, *et al*. Pancreatic endoscopic ultrasound-guided fine needle aspiration: Complication rate and clinical course in a single centre. *Dig Liver Dis* 2010;42:520-3.
26. Jenssen C, Alvarez-Sánchez MV, Napoléon B, *et al*. Diagnostic endoscopic ultrasonography: Assessment of safety and prevention of complications. *World J Gastroenterol* 2012;18:4659-76.
27. Bhutani MS, Gupta V, Guha S, *et al*. Pancreatic cyst fluid analysis – A review. *J Gastrointestin Liver Dis* 2011;20:175-80.
28. Leung KK, Ross WA, Evans D, *et al*. Pancreatic cystic neoplasm: The role of cyst morphology, cyst fluid analysis, and expectant management. *Ann Surg Oncol* 2009;16:2818-24.
29. Morris-Stiff G, Lentz G, Chalikonda S, *et al*. Pancreatic cyst aspiration analysis for cystic neoplasms: Mucin or carcinoembryonic antigen – Which is better? *Surgery* 2010;148:638-44.
30. de Jong K, Poley JW, van Hooft JE, *et al*. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: Initial results from a prospective study. *Endoscopy* 2011;43:585-90.
31. Oguz D, Öztaş E, Kalkan IH, *et al*. Accuracy of endoscopic ultrasound-guided fine needle aspiration cytology on the differentiation of malignant and benign pancreatic cystic lesions: A single-center experience. *J Dig Dis* 2013;14:132-9.
32. Petrone MC, Arcidiacono PG. Role of endosocopic ultrasound in the diagnosis of cystic tumours of the pancreas. *Dig Liver Dis* 2008;40:847-53.
33. Chung JW, Chung MJ, Park JY, *et al*. Clinicopathologic features and outcomes of pancreatic cysts during a 12-year period. *Pancreas* 2013;42:230-8.
34. Degen L, Wiesner W, Beglinger C. Cystic and solid lesions of the pancreas. *Best Pract Res Clin Gastroenterol* 2008;22:91-103.

How to cite this article: Hocke M, Cui X, Domagk D, Ignee A, Dietrich CF. Pancreatic cystic lesions: The value of contrast-enhanced endoscopic ultrasound to influence the clinical pathway. *Endosc Ultrasound* 2014;3:123-30.

Source of Support: Nil. **Conflict of Interest:** None declared.