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# Cystic pancreatic neoplasms in a tertiary gastroenterologic referral center: Evaluation of the diagnostic accuracy of endoscopic ultrasound, progression rate and malignancy rate in a large unicentric cohort

## Zystische pankreatische Neoplasien in einem tertiären gastroenterologischen Referenzzentrum: Evaluation des endoskopischen Ultraschalls bezüglich diagnostischer Genauigkeit, Progressionsrate und Malignitätsrate in einer grossen unizentrischen Kohorte

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ABSTRACT

**Introduction** Cystic pancreatic neoplasms (CPN) are frequently diagnosed due to better diagnostic techniques and patients becoming older. However, diagnostic accuracy of endoscopic ultrasound (EUS) and value of follow-up are still unclear.

**Material and Methods** The aim of our retrospective study was to investigate the frequency of different cystic pancreatic neoplasms (intraductal papillary mucinous neoplasm [IPMN], serous and mucinous cystadenoma, solid pseudopapillary neoplasia), diagnostic accuracy, size progression, and rate of malignancy using EUS in a tertiary reference center in Germany. Between January 1, 2012 and December 31, 2018, 455 patients were diagnosed with cystic pancreatic lesions (798 EUS examinations).

**Results** Endoscopic ultrasound diagnosed 223 patients with cystic pancreatic neoplasms, including 138 (61.9 %) patients with branch duct IPMN, 16 (7.2 %) with main duct IPMN, and five (2.2 %) with mixed-type IPMN. In the largest subgroup of branch duct IPMN, cysts were size progressive in 20 patients (38.5 %). Fine needle aspiration (FNA) was performed in 21 patients, and confirmed the suspected diagnosis in 12/21 patients. 28 surgical resections were performed, in 7/28 patients (25 %), high-grade dysplasia or cancer was diagnosed. Endoscopic ultrasound diagnosis of serous and mucinous cystic pancreatic neoplasms was correct in 68.4 %.

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**Conclusions** Endoscopic ultrasound differential diagnosis of CPNs is challenging. Even in a tertiary expert center, differentiation of serous and mucinous cystic neoplasia is not guaranteed. Relevant size progression of CPN, however, is rare, as is the rate of malignancy. The data of this study suggest that morphologic criteria to assess pancreatic cysts alone are not sufficient to allow a clear diagnosis. Hence, for the improved assessment of pancreatic cysts, EUS should be combined with additional tests and techniques such as MRT/MRCP, contrast-enhanced EUS, and/or FNA/fine needle biopsy including fluid analysis. The combination and correlation of imaging studies with EUS findings is mandatory.

## ZUSAMMENFASSUNG

**Einleitung** Zystische pankreatische Neoplasien (ZPN) werden angesichts besserer diagnostischer Techniken und älter werdender Patienten häufiger diagnostiziert. Nichtsdestotrotz sind diagnostische Präzision und Bedeutung von Verlaufskontrollen des EUS unklar.

**Material und Methodik** Das Ziel der retrospektiven Studie war die Erhebung der Häufigkeit distinkter ZPNs (intraduktale papilläre muzinöse Neoplasie [IPMN], seröse und muzinöse Zystadenome, solide pseudopapilläre Neoplasie), der diagnostischen Präzision (Feinnadelpunktion, operative Resektion), der Grössenprogression sowie der Rate an maligner Entartung mittels EUS in einem tertiären Referenzzentrum in Deutschland. Hierfür wurden 455 Patienten mit zystischen pankreatischen Läsionen vom 1. Januar 2012 bis zum 31. Dezember 2018 untersucht (798 EUS Untersuchungen).

**Ergebnisse** 223 Patienten mit ZPN wurden diagnostiziert, davon 138 (61.9 %) Patienten mit Seitengang-IPMN, 16 (7.2 %) mit Hauptgang-IPMN und 5 (2.2 %) mit mixed-type IPMN. In der größten Sub-Gruppe der Seitengang-IPMN waren die Zysten bei 20 Patienten (38.5 %) größenprogredient. Feinnadelpunktionen wurden bei 21 Patienten durchgeführt, und bestätigten die vermutete EUS-Diagnose bei 12/21 Patienten. 28 Operationen wurden durchgeführt, dabei wurden bei 7/28 Patienten (25 %) high-grade Dysplasien oder Malignome diagnostiziert. Die mittels EUS vorgenommene Einteilung in seröse und muzinöse ZPNs war in 68.4 % der Patienten korrekt.

**Schlußfolgerungen** Die EUS-basierte Differenzialdiagnose zystischer pankreatischer Neoplasien ist ebenso wie die Differenzierung zwischen serösen und muzinösen Zysten auch in einem Referenzzentrum schwierig. Eine relevante Größenprogression der ZPN im Zeitverlauf ist insgesamt jedoch selten zu verzeichnen, die Rate an malignen Entartungen ist niedrig. Die Daten dieser Studie suggerieren, daß morphologische Kritierien allein nicht ausreichen, um eine klare Diagnose zystischer pankreatischer Neoplasien zu stellen. Deshalb sollte der EUS für eine genauere Einteilung von ZPNs mit zusätzlichen Verfahren wie zum Beispiel der MRT/MRCP, dem Kontrastmittel-Ultraschall und/oder der Feinnadelpunktion/-biopsie inklusive einer Flüssigkeitsanalyse kombiniert werden. Eine Kombination und Korrelation bildgebender Studien mit EUS-Ergebnissen ist unbedingt zu fordern.

## Introduction

Cystic pancreatic lesions (CPL) are frequently found in transabdominal ultrasound, CT, or MRI scans of the abdomen [1]. Prevalence data on CPL range from 2.4 % [2] to 49.1 % in MRI, increase with age [3] and better resolution capacity due to recent developments in imaging techniques [4]. Our study focused on the five most frequent lesions, comprising 95 % of all CPL that include: pseudocysts, intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystic neoplasms (SCN), and solid pseudopapillary neoplasms (SPN). Due to their premalignant potential the latter four are designated as cystic pancreatic neoplasms (CPN).

Pancreatitis-associated pseudocysts are the most often detected CPL (30 %) [5] and develop when peripancreatic lipid necroses are resorbed. There is no danger of malignant progression [6].

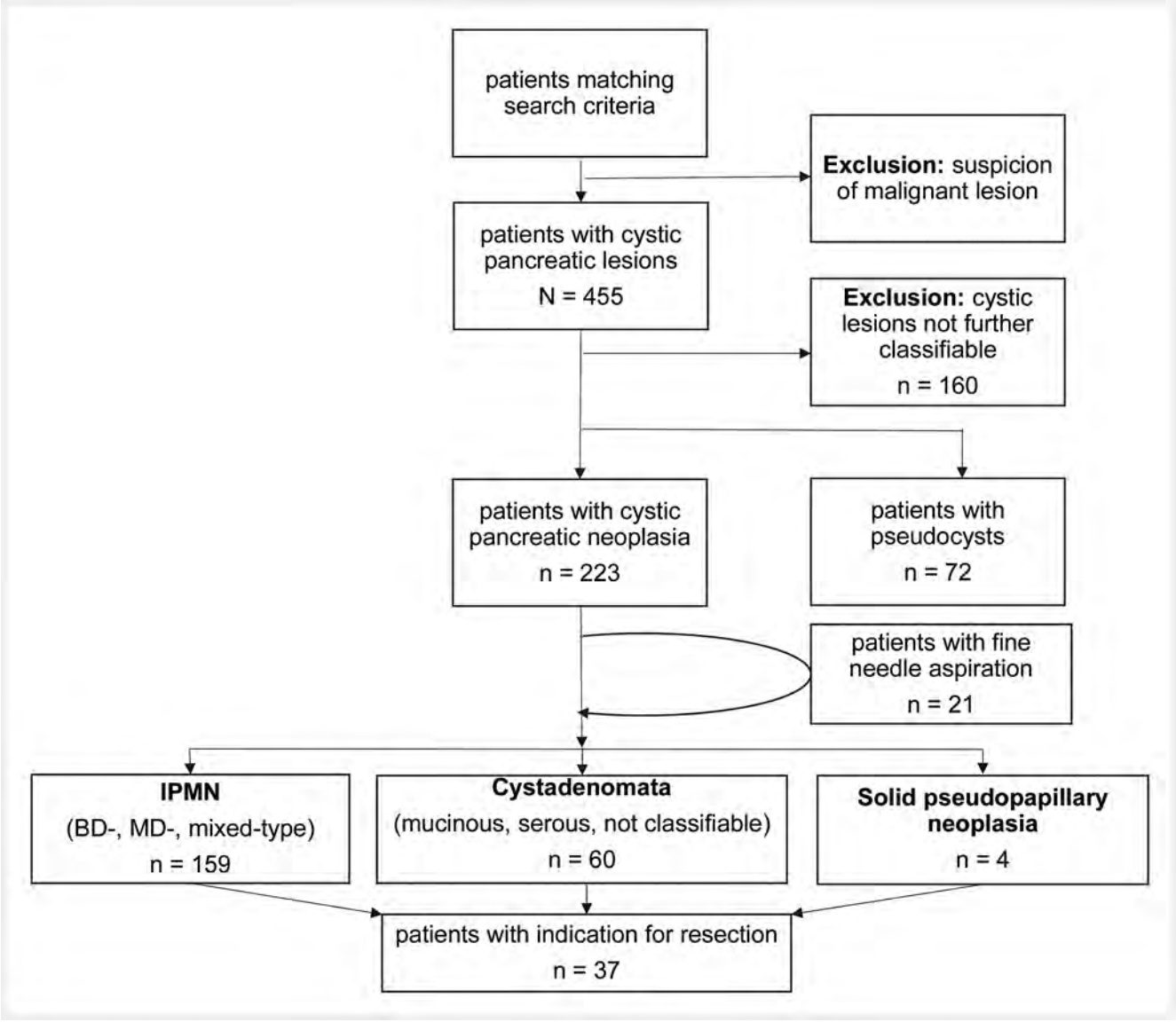
IPMN as mucine-producing neoplasia account for about 20 % of CPL [5], and can be divided into main duct (MD-IPMN), branch duct (BD-IPMN) and mixed type IPMN implicating different prognoses [7]. In 2017, a meta-analysis on BD-IPMN reported a probability of 0.98 % per patient year for malignant transformation [8]. In contrast, in resected MD-IPMN, 38 % to 68 % of cases exhibited high grade dysplasia or even carcinoma [9].

Cystadenomata can be differentiated into SCN and MCN. MCN are found in 10 % of CPL, show a female preponderance, do not communicate with the pancreatic duct, and in most cases are found in the pancreatic tail. High-grade dysplasia or carcinoma are seen in 9.9 % of patients, often showing sizes > 60 mm and mural nodules [10]. About 20 % of CPL are SCN, 75 % affecting the female sex, and are characterized by a cluster of small cysts often resembling honeycomb. SCNs are most often asymptomatic and grow slowly with a minimal risk of malignant transformation [11].

SPN (5 % of CPL), 90 % affecting women, show a mean size of 8.6 cm (SD +/–4.3), and can often be well demarcated from normal pancreatic tissue by pseudopapillary and pseudo-cystic parts [12]. Despite their malignant potential with metastases in 7.7 % to 19 % of patients, SPN generally show a good prognosis [13].

Due to the low specificity of morphological signs, endoscopic ultrasound (EUS) assignment of CPNs to one of the described entities can be challenging, and often is only feasible when clinical data and/or other imaging techniques are integrated. Of central importance is the differentiation in serous and mucinous cysts as the latter exhibit a risk for malignant transformation [14]. Analysis of carcinoembryonic antigen (CEA) in cyst content can help classify cyst entity; however, CEA is not capable of differentiating IPMN from MCN or high-grade dysplasia from carcinoma [15].

Bearing in mind the increasing rate of random diagnoses of CPL, the questions arise of how to adequately supervise particular patients and how to balance the risk of malignant development




▶ **Fig. 1** Stratification of patients with cystic pancreatic lesions using endoscopic ultrasound.

versus the implication of surgery with consecutive post-surgical restrictions patients often have to face.

## Material and Methods

For our retrospective study, data on EUS examinations with first diagnosis of a CPL were analyzed from January 1st 2012 to December 31st 2018. Patients and EUS data were extracted from our electronical reporting system (ClinicWinData, version 8.08.03.) in the Hospital Barmherzige Brüder Regensburg, Germany. EUS had been performed by 4 experienced endoscopic physicians with at least 5 years of experience using radial and linear endoscopes [Pentax], and a EUS processor Preirus (Hitachi). Diagnostic criteria are defined as outlined in the European guidelines on pancreatic cystic neoplasms [16]. Diagnoses of CPN were made by referring to the last EUS diagnosis in the patients' charts; thus, also information on differences in size over time, changes in cystic structure, results of fine needle aspiration (FNA) or complementary imaging could have been taken into account. FNA was used to further delineate the character and dignity of cystic processes, and was performed using a 22G needle. Extracted material was analyzed biochemically (CEA, lipase), cytologically (serous or mucinous fluid) and/or histologically. Histopathological results after surgery enabled a comparison of EUS diagnoses and served as gold standard for correctness of EUS.

Institutional Review Board approval for the study was obtained from the University of Regensburg (ethical committee No. 20-1948-104).

Statistical analysis was performed using "IBM SPSS statistics version 25". For analysis of change in size, first and last examination were used. Statistical analysis comprised Chi-square test in larger groups, Fisher's-exact test in smaller groups, and Mann-Whitney U-test. A difference was considered significant at $p < 0.05$.

## Results

### EUS diagnoses in CPN

After exclusion of all directly malignoma-suspect findings, 455 patients with 798 examinations were diagnosed with a CPL. In 160 patients (35.2 %) the CPLs could not be categorized as CPN (no wall irregularities, no relation to pancreatic duct, "harmless cyst") and were excluded from further analysis. 72 patients exhibited pseudocysts. The remaining group of CPN included 223 patients involving 390 examinations (▶ **Fig. 1**). BD-IPMN was diagnosed in 138 patients, and was the most frequent diagnosis in our study collective. MD-IPMN diagnosis was made in 16 patients, mixed-type IPMN in 5 patients. 60 patients were diagnosed with cystadenoma, classified as SCN in 46 patients and MCN in 6. In 8 patients, the cystadenoma could not be sub-specified ( = unclassifiable). SPN were seen in 4 patients. Epidemiological data are summarized in ▶ **Table 1**.

▶ **Table 1** Patients' characteristics in the CPN study population.

| Patients | Number | Sex [f/m] | Median age (range) [years] |
|---|---|---|---|
| All CPN patients | 223 | 146/77 | 69 (15–95) |
| BD-IPMN | 138 | 91/47 | 71 (34–95) |
| MD-IPMN | 16 | 11/5 | 76 (54–88) |
| Mt-IPMN | 5 | 2/3 | 79 (73–88) |
| SCN | 46 | 19/27 | 67 (21–81) |
| MCN | 6 | 5/1 | 67 (46–74) |
| Unclassifiable cystadenoma | 8 | 8/– | 76 (62–82) |
| SPN | 4 | 2/2 | 30 (15–42) |

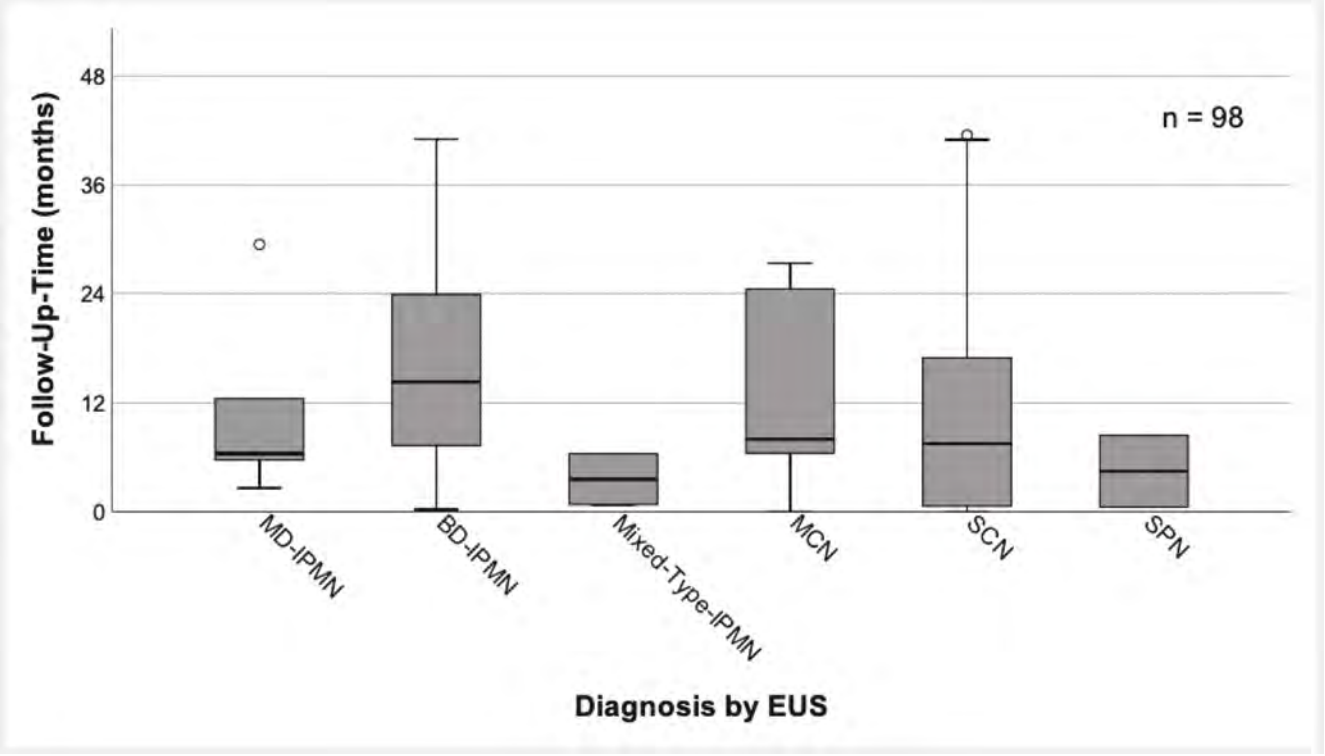
Abbreviations: CPN = cystic pancreatic neoplasm; IPMN = intraductal papillary mucinous neoplasms; MD-IPMN = main duct IPMN; BD-IPMN = branch duct IPMN; Mt-IPMN = mixed type IPMN; SCN = serous cystic neoplasms; MCN = mucinous cystic neoplasms; SPN = solid pseudopapillary neoplasms.

### Size progression

Follow-up time was defined as the period of time between first and last documented EUS. 98 patients with more than one examination had a median follow-up time of 11.7 months (range 1 to 41), and a mean of 2.7 ± 1.05 examinations per patient (▶ **Fig. 2**). Progression in cystic size was seen in 20/52 patients with BD-IPMN, but in only 6/20 patients size increase measured > 2 mm. 2/5 patients with MCN and 6/21 SCN patients showed increases in size, while in the latter only 4/6 size increases > 2 mm were detected. In all other patients, no progression in cystic size could be observed during the follow-up period.

### Fine needle aspiration and cytological analysis

FNA was performed in 21 patients. In 14/21 patients, FNA supported the diagnosis of SCN (serous fluid or inconsistent findings arguing against a mucinous process, CEA < 192 ng/ml). In 1 out of 3




▶ **Fig. 2** Time of follow-up in patients with different CPNs.

▶ **Table 2** Characterization of cystic pancreatic neoplasms in comparison before and after FNA using lipase concentration, CEA concentration and cytological analysis. Numbers in bold represent the decisive parameter(s) for diagnosis after having performed FNA.

| Number of patients | Diagnosis *before* FNA | Lipase | CEA | | | Cytology | | | | Diagnosis *after* FNA |
|---|---|---|---|---|---|---|---|---|---|---|
| | | [µ/l] | <cut-off | >cut-off | not available | serous | mucinous | not indicative | not available | |
| 8 | SCN | 8.8; *SD* 5,5 (n = 2) | **5** | 0 | 3 | **2** | 0 | 5 | 1 | 8 SCN |
| 1 | BD-IPMN | 695.3 (n = 1) | **1** | 0 | 0 | 0 | 0 | **1** | 0 | 1 SCN |
| 4 | Unspecified | 60726.8; *SD* 60633,2 (n = 2) | **2** | 1 | 1 | **2** | 0 | 2 | 0 | 4 SCN |
| 1 | Cystadenoma | 20.9 (n = 1) | 0 | 1 | 0 | 0 | 0 | **1** | 0 | 1 SCN |
| 1 | Unspecified | 36865.0 (n = 1) | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 MCN |
| 2 | MCN | – | 2 | 0 | 0 | 0 | **1** | 0 | 1 | 2 MCN |
| 2 | MD-IPMN | – | 1 | 0 | 1 | 0 | **2** | 0 | 0 | 2 MD-IPMN |
| 2 | SCN | 736259.7 (n = 1) | 1 | **1** | 0 | 1 | **1** | 0 | 0 | 2 BD-IPMN |
| **21** | | – | **13** | **3** | **5** | **5** | **4** | **10** | **2** | |

Abbreviations: IPMN = intraductal papillary mucinous neoplasms; MD-IPMN = main duct IPMN; BD-IPMN = branch duct IPMN; MCN = mucinous cystic neoplasms; SCN = serous cystic neoplasms; SPN = solid pseudopapillary neoplasms; CEA = carcinoembryonic antigen; FNA = fine needle aspiration.

▶ **Table 3** Reasons for resection in 8 patients without fulfilling European evidence-based guidelines on pancreatic cystic neoplasms, post-surgery diagnoses.

| Patient | Age [years], sex | Reason for resection | Resection performed? | Post-surgery diagnosis |
|---|---|---|---|---|
| 1 | 43, female | size progressive cyst within one year – no pre-EUS documented | yes | SCN |
| 2 | 54, male | MD-IPMN | yes | SCN |
| 3 | 68, male | MCN and size progression of 4 mm in two years | no resection, only indication | – |
| 4 | 58, male | no differentiation between MCN and IPMN possible | yes | ductal adenocarcinoma |
| 5 | 21, female | polycystic SCN of 10 cm size without single cyst >40 mm | yes | pancreatic pseudocyst |
| 6 | 64, male | non-classifiable CPN after having used different imaging techniques | no resection due to intra-surgery ultrasound finding | – |
| 7 | 84, male | polycystic CPN of 6 cm size without single cyst >40 mm | no resection, only indication | – |
| 8 | 25, male | suspicion of non-classifiable cystadenoma, indication because of young age | no resection, only indication | – |

Abbreviations: EUS = endoscopic ultrasound; IPMN = intraductal papillary mucinous neoplasms; MD-IPMN = main duct IPMN; MCN = mucinous cystic neoplasms; SCN = serous cystic neoplasms.

▶ **Table 4** EUS diagnosis of serous and mucinous cystic pancreatic neoplasms when compared to histopathological diagnosis after surgery.

| EUS diagnosis | n | Correct | Not correct | Diagnosis after surgery |
|---|---|---|---|---|
| pseudocyst | 4 | 3 | 1 | intrapancreatic mucinous neoplasia |
| MD-IPMN | 7 | 6 | 1 | SCN |
| MCN | 2 | | 2 | 1 “no findings”, 1 pseudocyst |
| SCN | 2 | 1 | 1 | retroperitoneal neurinoma |
| SPN | 4 | 3 | 1 | MCN |
| **Total** | **19** | **13** | **6** | |

Abbreviations: EUS = endoscopic ultrasound; IPMN = intraductal papillary mucinous neoplasms; MD-IPMN = main duct IPMN; MCN = mucinous cystic neoplasms; SCN = serous cystic neoplasms; SPN = solid pseudopapillary neoplasms.

suspected MCN, 2 MD-IPMN and 1 BD-IPMN patients, mucinous fluid was detected. Overall, cytological analysis was obtained in 19 patients but was able to differentiate between serous and mucinous only in 9 patients. In 13/16 patients, CEA levels were below the cut-off value of 192 ng/mL, underscoring the rather benign character of the lesion. Taken together, FNA ± cytological/CEA analysis confirmed the suspected diagnosis in 12/21 patients, and enabled an alternative diagnosis in 9/21 patients. For further detail see ▶ **Table 2**.

## Indication for surgery

37 patients were listed for surgery. According to the European Consensus Guidelines, 8/37 patients fulfilled absolute criteria for surgery: jaundice in 5 patients, main duct (MD) dilatation in 4 patients. Other absolute indications for surgery like positive cytology for malignancy, high grade dysplasia, a solid mass, or mural nodules ≥ 5 mm were not detected. 22/37 patients (9.4 % of all 223 patients with CPN) listed for surgery were diagnosed with ≥ 1 relative criteria for surgery (one patient exhibited criteria of both absolute and relative indications): 8 with cyst diameter ≥ 40 mm, 6 with MD dilatation 5–9.9 mm, 7 with acute, and 13 with chronic pancreatitis.

8 of these 37 patients were listed for surgery without fulfilling the European Consensus Guidelines’ criteria for surgery. For further detail see ▶ **Table 3**.

Whereas surgical resection was indicated already in 23/28 patients after the first EUS examination, surgery was indicated in only 5 patients during follow-up (data not shown).

### Comparison EUS and post-surgery diagnoses

(Partial) pancreatectomy was performed in 28 patients. In 10 of 28 patients (35.7 %) EUS diagnosis was correct: 3 pseudocysts, one SPN, 6 MD-IPMN. The highest rate of correct classification was found in the group of MD-IPMN patients (6/7 patients, 85.7 %), 5 of whom had exhibited absolute risk criteria, one patient a relative risk criterion. The remaining assumed MD-IPMN lesion was diagnosed as SCN without risk of malignant transformation. EUS differentiation into serous and mucinous CPNs when compared to histopathological diagnosis after surgery was correct in 13/19 patients (68.4 %; ▶ **Table 4**). In 8/28 patients, EUS had not been able to categorize the CPN, 4 of which constituted malignant tumors. In the remaining 10 patients EUS diagnosis turned out to be not correct (for details see ▶ **Table 5**). 9 patients did not undergo surgery due to individual reasons (▶ **Table 6**).

Overall, 7 of 28 resected CPNs (25 %) showed malignant transformation (3 patients with MD-IPMN, 4 patients with unspecified findings in EUS: 2 ductal adenocarcinomata, 1 neuroendocrine carcinoma, and 1 neuroendocrine tumor with suspected malignancy). Fisher's-Exact-Test showed no correlation between positive absolute criteria for surgery and malignancy ($\chi^2(1.\ N = 28) = 2.455$, $p = 0.117$). Relative criteria for surgery did not correlate with malignancy either ($\chi^2(1,\ N = 28) = 0{,}474$ $p = 0{,}491$).

## Discussion

Our study was a retrospective analysis of CPLs (798 patients) with focus on CPNs (223 patients) in a tertiary referral center in Germany. The high percentage of IPMN and the low portion of MCN is of note: IPMN were diagnosed in 159 patients of which 16 were MD-IPMN (7.2 %), five mixed-type IPMN (2.2 %) and 138 BD-IPMN (61.9 %). These frequencies are similar to a recent survey reporting numbers of 4.6, 6.2, and 70.1 %, respectively [16], but contrast with a study by Sahora et al. [17]. Differing frequencies of diagnoses between observational studies and studies investigating resected CPNs could be caused by selection bias on the one hand; since in 90/138 patients with BD-IPMN (65.2 %) no clear communication with the main pancreatic duct could be demonstrated, on the other hand this fact could open the possibility that some of these patients potentially might have had another pathology like MCN. After all, according to recent guidelines, this differentiation appears to be difficult [18]. Following this possibility, of 60 cystadenomata only 6 were defined as MCN. This small number of patients with differing epidemiological data when compared to the literature (median age 68 years; thus, far higher than 45 to 48 years; lower female percentage of 83.3 % when compared to 95 % [19] to 99.7 % [11, 14]; median cystic size with 3.5 cm smaller than 5 to 8.7 cm [14, 20]; localization less often in pancreas corpus or tail (50 % versus up to 97 % [14, 21], respectively) might underline the explanation given above.

Whereas patients with suspected MD-IPMN, MCN, and SPN diagnoses most often underwent surgery, BD-IPMN and SCN patients were most likely to have EUS follow-up. In 38.5 % of patients with BD-IPMN cystic size increased over time which is comparable to the literature ranging from 29 % [21] to 54.2 % [22]. Of note is

▶ **Table 5** Incorrect EUS diagnoses in 10 patients after comparison with post-surgery diagnosis.

| | EUS diagnosis | Post-surgery diagnosis |
|---|---|---|
| 1 | pseudocyst | intrapancreatic mucinous neoplasia |
| 2 | MD-IPMN | SCN |
| 3 | unclassifiable cystadenoma | pseudocyst |
| 4 | MCN | no pathological finding |
| 5 | MCN | MD-IPMN |
| 6 | SCN | pseudocyst |
| 7 | SCN | retroperitoneal neurinoma |
| 8 | SPN | chronic calcifying pancreatitis |
| 9 | SPN | chronic calcifying pancreatitis |
| 10 | SPN | MCN |

Abbreviations: EUS = endoscopic ultrasound; IPMN = intraductal papillary mucinous neoplasms; MD-IPMN = main duct IPMN; MCN = mucinous cystic neoplasms; SCN = serous cystic neoplasms; SPN = solid pseudopapillary neoplasms.

▶ **Table 6** 9 patients with indication for surgery but actually not undergone, reasons as found in patients' charts.

| Age | Description of CPN | No surgery – reasons |
|---|---|---|
| 47 | CPN non-classifiable | during follow-up diagnosis of pseudocyst |
| 78 | BD-IPMN | icterus presumably caused by cholelithiasis |
| 68 | MCN | using FNA diagnosis of only low-grade dysplasia |
| 69 | SCN | during follow-up diagnosis of pancreatic carcinoma (different localization) |
| 53 | CPN non-classifiable | explorative laparotomy with biopsy, no malignoma |
| 78 | CPN non-classifiable | surgery denied by patient |
| 64 | CPN non-classifiable | due to intraoperative ultrasound no curative surgery possible any more |
| 84 | CPN non-classifiable | due to age and multimorbidity |
| 25 | Cystadenoma non-classifiable | lost to follow-up |

Abbreviations: CPN = cystic pancreatic neoplasia; IPMN = intraductal papillary mucinous neoplasms; BD-IPMN = branch duct IPMN; MCN = mucinous cystic neoplasms; SCN = serous cystic neoplasms; SPN = solid pseudopapillary neoplasms.

that depending on the study, the definition of when a cyst is classified as size progressive is different, as is the method of measurement [23, 24]. In our study, any change of size was defined as either size increasing or decreasing and might therefore explain differences compared to other studies. When applying a cut-off of 2 mm, in only 11.5 % of BD-IPMN patients was size progression detected. In patients with SCN, when applying the cut-off value of 2 mm of size change [25], only seven patients would have qualified for a relevant size progression. Due to these low frequencies of relevant size progression, no BD-IPMN and only two SCN patients underwent surgery.

Size progression is variably linked to an enhanced risk of malignancy; whereas some studies could not detect a difference in the rate of malignancy between size progressors and non-progressors [24, 25], Akahoshi et al. found a higher risk of malignancy for a cut-off value of 3.5 mm/year with a sensitivity of 88 %, a specificity of 91 %, and a precision of 93 % [26]. Whereas European guidelines define a size progression of 5 mm/year as relative surgery indication [19], this criterion could not be found in our study collective – cut-offs of 2 mm or 3.5 mm would have applied for only three patients each, respectively. Within the time of supervision over 3.5 years, no malignant transformation in our BD-IPMN patients was documented. Bearing in mind the risk of malignant transformation of 0.65–0.8 % per year as described in a systematic review in 2017 and a cumulative incidence of pancreatic carcinoma of 7.77 % in ten years, our results are well in line with the literature.

Only 21 patients (17 presumed cystadenomata, among which 14 SCN; two BD-IPMN and two MD-IPMN patients) underwent FNA due to suggestive (pre)malignant signs or size progression. Since there were no evident differences between the 4 investigators with respect to the indication for FNA, this relatively small proportion also reflects the low proportion of size progressors and/or missing suspect signs of the cystic lesion. In 12 cases, cytological results underscored the presumed diagnosis, in 16 cases CEA levels could be determined, the latter reflecting with 76.2 % a slightly higher proportion of patients with available CEA when compared to studies by Winner (72,5 %; [21]) and Khalid (67 %; [25]). For classification into mucinous and serous cysts the cut-off of 192 ng/mL was used as recommended by European guidelines. In 8 patients, CEA levels and cytological analysis were not coherent; this contrasting finding is not unknown and has led to an algorithm published in 2004 classifying cysts as mucinous if one of the parameters morphology, cytology, or CEA levels are positive resulting in a higher sensitivity of 91 % but lower specificity [26]. Unfortunately, adoption of this proposed algorithm would not have led to more coherent results either.

It is common sense that CEA levels are not capable of distinguishing pre-malignant and malignant mucinous lesions [27, 28]. In line with this difficulty, 4 patients underwent surgical resection after FNA: in neither the patients with very low nor the patient with extremely high CEA levels did the lesions histologically turn out to be malignant. The largest prospective study with 198 patients so far investigating the quality of FNA proposed the combination of CEA and cytological analysis to better estimate malignancy, and actually identified lesions correctly in only 45.8 % of cases as malignant [29]. Compared with this study, recall ratio between mucinous and non-mucinous lesions in our study was 68.4 %.

In 7 MD-IPMN patients, surgery was executed, in 85.7 % the EUS diagnosis turned out to be correct. The percentage of malignancy was 42.8 %, and, thus, smaller than in a study by Hinz et al., who found malignancy in 55.8 % of patients [29]. In this study, malignancy of 33 % was true in patients exhibiting a pancreatic duct of 5–9.9 mm, whereas malignancy could be demonstrated in 67 % with a main duct of ≥ 9.9 mm [30]. Due to the small number of patients with this diagnosis in our study, stratification according to the main duct diameter could not be performed. In only 1/4 patients with suspected SPN this diagnosis was actually histologically proven. Even though the presumed diagnosis of SPN was rather discussed as differential diagnosis in these 4 cases the fact that only one turned out to be correct implies a difficult EUS diagnosis. In line with this presumption, Yu et al. reported in a systematic review in 2010 on only 23.7 % correct SPN diagnoses in 325 histologically proven SPN lesions [31]. In contrast, Tjaden et al. showed in 70 % a correct SPN pre-surgery diagnosis in 2019 [32]. In turn, Liu et al. reported in 2019 on relatively unspecific EUS findings in SPN lesions [30].

The proportion of patients in our study in which EUS diagnosis could be correlated with the gold standard histopathology was in fact low (surgical resection indicated in 37 patients (8.1 %) and – due to individual reasons – actually performed in only 28 patients). Of note, in only 7 patients, malignoma was diagnosed.

With respect to 20 defined diagnoses presumed by EUS, 10 were correct (50 %). If 8 further patients in which our investigators had not been able to specify a diagnosis via EUS pre-surgery were included in the analysis, 35.7 % of the diagnoses were correct. In comparison, a study performed to differentiate SCN, MCN, and cystadenocarcinoma reported on correct assignment in 34 %, 28 %, and 22 %, respectively [33].When trying to classify into mucinous or non-mucinous, accuracy to diagnose mucinous CPL was 68.4 %, and, thus, in the same range as in a prospective study by de Jong et al. (75 %; [32]). Again, better values in our study could potentially be explained by additional information accessible to our investigators.

## Limitations of the study

Our patient collective was not representative of the general population. A loss to follow-up bias could not be excluded. Furthermore, investigators in our study could use results from other imaging studies leading potentially to a higher hit rate of EUS with respect to the correct diagnosis. Since results were analyzed according to prevailing European guidelines, parameters such as CA 19-9 in serum or newly diagnosed diabetes mellitus were not part of the analysis. Moreover, contrast enhanced ultrasound (CEUS) was not performed on a regular basis. Analysis of size variability was restricted to the largest cyst, and, therefore, other pancreatic cysts were neglected. In total, only few patients underwent FNA (21/223).

Exclusion of 160 patients with non-defined entities, assignment of cysts to seven entities, and a low frequency of these distinct CPNs rendered statistical analysis difficult, despite the initial relatively high number of 455 patients. In contrast, inclusion of any defined CPNs to the analysis enabled a robust overview on the frequency of CPNs in a third level reference center in Germany.

While studies so far have focused solely on distinct patient groups such as specific CPNs, defined risk criteria, FNA, or resections, our study involved all of the mentioned parameters; furthermore, our analysis also comprised the course of distinct CPNs over time. Our study, thus, enabled a comprehensive overview of frequency, diagnostic correctness, and course over time of distinct CPNs in clinical routine.

## Conclusions

Size progression in CPN during follow-up is rather rare, and most frequently, not clinically relevant. Detection of malignancy is seldom. Even in a tertiary reference center and following European guidelines, EUS accuracy in delineating diagnosis and dignity of CPNs is rather low. The data of this study suggest that morphologic criteria to assess pancreatic cysts alone are not sufficient to allow a clear diagnosis. Hence, for the improved assessment of pancreatic cysts, EUS should be combined with additional tests and techniques such as MRT/MRCP, contrast-enhanced EUS, and/or FNA/fine needle biopsy including fluid analysis. The combination and correlation of imaging studies with EUS findings is mandatory.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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