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Cytopathological Analysis of Cyst Fluid Enhances Diagnostic Accuracy of Mucinous Pancreatic Cystic Neoplasms

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Abstract: Widespread use of cross-sectional imaging and increasing age of the general population has increased the number of detected pancreatic cystic lesions. However, several pathological entities with a variety in malignant potential have to be discriminated to allow clinical decision making. Discrimination between mucinous pancreatic cystic neoplasms (PCNs) and nonmucinous pancreatic lesions is the primary step in the clinical work-up, as malignant transformation is mostly associated with mucinous PCN. We performed a retrospective analysis of all resected PCN in our tertiary center from 2000 to 2014, to evaluate preoperative diagnostic performance and the results of implementation of the consensus guidelines over time. This was followed by a prospective cohort study of patients with an undefined pancreatic cyst, where the added value of cytopathological mucin evaluation to carcinoembryonic antigen (CEA) in cyst fluid for the discrimination of mucinous PCN and nonmucinous cysts was investigated. Retrospective analysis showed 115 patients operated for a PCN, with a correct preoperative classification in 96.2% of the patients. High-grade dysplasia or invasive carcinoma was observed in only 32.3% of mucinous PCN. In our prospective cohort (n = 71), 57.7% of patients were classified as having a mucinous PCN. CEA ≥192 ng/mL had an accuracy of 63.4%, and cytopathological mucin evaluation an accuracy of 73.0%. Combining these 2 tests further improved diagnostic accuracy of a mucinous PCN to 76.8%. CEA level and mucin evaluation were not predictive of the degree of dysplasia. These findings show that adding cytopathology to cyst fluid biochemistry improves discrimination between mucinous PCN and nonmucinous cysts.

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Abbreviations: CEA = carcinoembryonic antigen, EUS = endoscopic ultrasound, EUS-FNA = endoscopic ultrasound-fine needle aspiration, IPMN = intraductal papillary mucinous neoplasm, MCN = mucinous cystic neoplasm, MD-IPMN = main duct-intraductal papillary mucinous neoplasm, MT-IPMN = mixed type-intraductal papillary mucinous neoplasm, PCN = pancreatic cystic neoplasm, SB-IPMN = side branch-intraductal papillary mucinous neoplasm, SCA = serous cystic adenoma, SPN = solid pseudopapillary neoplasm.

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INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are potential premalignant lesions which can lead to pancreatic ductal adenocarcinoma or colloid carcinoma.[1] The prevalence of pancreatic cysts, including nonneoplastic cysts, was estimated around 2% in patients undergoing preventive cross-sectional imaging, and increases with age.[2] Four distinct PCN entities with varying malignant potential are recognized according to WHO classification: serous cystic adenoma (SCA), solid pseudopapillary neoplasm (SPN), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN), with the latter 2 classified as mucinous PCN.[1] Early differentiation of mucinous PCN and nonmucinous cysts is essential to clinical management, decision to resect, and patient survival. SCA has minimal malignant potential and excellent prognosis even in metastatic disease.[3] SPN is considered as a neoplasm with malignant potential but a rather favorable survival rate exceeding 95% in 5 years.[4] In contrast, MCN has a higher risk of malignant degeneration although the rates of invasive carcinomas are variable in different studies, between 6% and 36%.[5,6] The prognosis of MCN is much improved if the cyst is resected prior to invasion, with a 5-year disease-specific survival of 100%.[7] Because identification of high-risk MCN is not possible preoperatively, current guidelines recommend resection of MCN in all surgically fit patients. The frequency of high-risk dysplasia and invasive carcinoma in IPMN varies between 24% and 62%, depending on the anatomical involvement of the pancreatic duct, and is categorized in main duct-IPMN (MD-IPMN), side branch-IPMN (SB-IPMN), and mixed type-IPMN (MT-IPMN).[8] After adjusting for stage, the prognosis of IPMN-associated adenocarcinoma is similar to that of pancreatic ductal adenocarcinoma.[9]

Currently, the management of MCN and IPMN is based upon international consensus guidelines established in 2006,[10] which were updated in 2012.[8] The algorithm for the management of cystic lesions of the pancreas involves evaluation by imaging such as magnetic resonance cholangiopancreatography or endoscopic ultrasound (EUS). However, the interobserver agreement for both modalities remains moderate at best for characteristics of PCN, and additional markers to discriminate mucinous from nonmucinous PCN may be helpful, particular in hospitals where imaging is less frequently performed.[11,12]

We performed a retrospective analysis of all resected PCN in our tertiary referral center, showing an increased number of

PCN diagnosed over time, with increased sensitivity of identification of high-risk mucinous PCN upon the introduction of the updated Sendai guidelines. Nevertheless, nonmalignant PCN is still frequently resected. In a first step toward identification of PCN with the highest malignant potential, we subsequently show in a prospective cohort, that inclusion of biochemical and cytological analysis of cyst fluid improves accuracy of detection of potentially malignant mucinous lesions.

METHODS

Retrospective Study

From 2000 to 2014, all patients who underwent pancreatic surgery at the Erasmus MC, Rotterdam, The Netherlands, were identified using the ''PALGA,'' (pathologisch anatomisch landelijk geautomatiseerd archief) a nationwide network and registry of histo- and cytopathology in The Netherlands. The identified cases were cross-checked with a list of patients who underwent any form of pancreatic surgery during that period at the Erasmus MC. Only patients who had a histopathologically proven PCN were included. All clinical data were retrospectively collected using the electronic patient files.

Prospective Study

From January 2009 to October 2013 all patients suspected with a pancreatic cyst based on physical complaints or incidental findings, who subsequently underwent endoscopic ultrasound-fine needle aspiration (EUS-FNA), were included. In this cohort, 27 patients underwent surgery, of which 22 patients were part of both the retrospective and prospective cohorts (the remaining 5 were operated in other hospitals). The remainder of the included patients in the prospective cohort did not undergo resection, but only EUS-FNA. Appropriate ethical approval was obtained for all procedures involving patients or patient material, from the Institutional Review Board (MEC-2008–233).

Definitions

Dysplasia

The WHO classification was used to describe dysplasia ranging from no dysplasia, low-grade dysplasia, moderate dysplasia, and high-grade dysplasia, to invasive carcinoma. The highest grade of dysplasia found throughout the resection specimen was used. High-grade dysplasia and invasive carcinoma were then classified as ''high-risk PCN.'' SPN was also considered high-risk PCN as these lesions are generally recommended to be resected. No dysplasia, low-grade dysplasia, and moderate dysplasia were classified as ''low-risk PCN.''

Pancreatic Cyst Fluid

After EUS-FNA of a pancreatic cyst, carcinoembryonic antigen (CEA) levels were measured in pancreatic cyst fluid. Furthermore, cytopathology was evaluated for the presence of neoplastic epithelial cells and mucinous background. Mucinous background refers to the presence of mucin in cytopathological analysis, which is microscopically visible in the May-Grünwald-Giemsa staining.

Outcome

The classification of a pancreatic cysts as a mucinous PCN or nonmucinous cyst was based on the pathology reports after resection, confirmation in EUS-FNA obtained cyst fluid, or the clinical diagnosis when neither were available.

TABLE 1. Patient Characteristics of the Retrospective Cohort

	Total (n = 115*)	Low-Risk PCN (n = 76)†	High-Risk PCN (n = 37)†
Age, years			
Range	14.5–84.4	20.2–79.3	14.5–84.4
Mean (SD)	60.1 (16.0)	60.4 (14.5)	59.1 (19.2)
Gender, n, %			
Male	38 (33.0)	23 (30.3)	15 (40.5)
Female*	77 (67.0)	53 (69.7)	22 (59.5)
Histological diagnosis, n (%)			
Main branch-IPMN	24 (20.9)	13 (17.1)	11 (29.7)
Side branch-IPMN*	24 (20.9)	17 (22.4)	6 (16.2)
Mixed type-IPMN	23 (20.0)	12 (15.8)	11 (29.7)
Mucinous cystic neoplasm*	27 (23.5)	24 (31.6)	2 (5.4)
Serous cystadenoma	10 (8.7)	10 (13.2)	0 (0)
Solid pseudopapillary neoplasia	7 (6.1)	0 (0)	7 (18.9)
Presentation, n, %			
Incidental	36 (31.3)	25 (32.9)	11 (29.7)
Abdominal pain	31 (27.0)	21 (27.6)	10 (27.0)
Jaundice*	13 (11.3)	6 (7.9)	6 (16.2)
Acute pancreatitis	19 (16.5)	14 (18.4)	5 (13.5)
Chronic pancreatitis	1 (0.9)	1 (1.3)	0 (0)
Weight loss	6 (5.2)	4 (5.3)	2 (5.4)
Surveillance	3 (2.6)	1 (1.3)	2 (5.4)
Other	4 (3.5)	3 (3.9)	1 (2.7)
Unknown*	2 (1.7)	1 (1.3)	0 (0)

IPMN = intraductal papillary mucinous neoplasm, PCN = pancreatic cystic neoplasm, SD = standard deviation.
* Numbers do not add up because dysplasia of 2 cases could not be retrieved.
† Lesions with adjacent adenocarcinoma were classified based upon dysplasia as found in the cyst.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 21. Univariable and multivariable logistic regression were used for the performance of CEA and mucinous background in differentiating between mucinous PCN and nonmucinous cysts. A P-value of <0.05 was considered statistically significant.

RESULTS

Retrospective Analysis of PCN Resections

Between 2000 and 2014 a total of 115 patients underwent pancreatic resection for a pancreatic cystic lesion. The clinical characteristics of these patients are presented in Table 1. In total, 37 (32.7%; 2 cases could not be classified) were classified as high-risk PCN. Of the mucinous PCN, only 30 out of 96 (31.3%) were high risk. Over the years, a significant increase in resections of PCN, in particular of IPMN and MCN (Figure 1A), was observed, with the majority occurring in the last 6 years. Of this increasing number of resections, a considerable percentage (34.2%) were asymptomatic lesions found incidentally or during surveillance for familial pancreatic cancer or a genetical predisposition for pancreatic cancer (see Supplemental Figure 1, http://links.lww.com/MD/A304, Supplemental Content, which illustrates the distribution of initial presentation of patients with a PCN over the years). Thus, increased frequency of imaging and improvement of surveillance tools in recent years have lead to increased incidental finding of pancreatic lesions.

Diagnostic Performance of Resected PCN

Proper diagnosis of mucinous PCN is essential to prevent unnecessary resection of nonmucinous lesions such as SCA and pseudocysts. To determine the accuracy of preoperative diagnosis based on imaging techniques and clinical characteristics, we compared the preoperative diagnosis with the gold standard of diagnosis, that is, histopathological assessment of resection specimens. After exclusion of 9 patients with an inconclusive preoperative diagnosis, 106 remained for analysis (see Supplemental Figure 2, http://links.lww.com/MD/A304, Supplemental Content, which illustrates the rate of preoperative diagnostic accuracy of all PCN resections). In total, there were 93 mucinous PCN of which 96.8% were diagnosed correctly in the preoperative assessment. In contrast, nonmucinous lesions were diagnosed correctly in only 53.8% of the cases. Overall, there were 9 misdiagnosed cases (Table 2), of which 3 cases (out of 4, 75%) were before 2006 and 6 cases (out of 102, 5.9%) were from 2006 onwards, demonstrating improved diagnosis upon introduction of the initial Sendai guidelines.[10] Potentially serious were case 1, preoperatively diagnosed as SPN, which turned out to be high-grade IPMN, and case 2 which was an MCN with invasive carcinoma preoperatively misdiagnosed as pseudocyst. Case 3 was an MCN misdiagnosed as a SCA, and cases 8 and 9 were SPN mistaken for an MCN and cystic panNET, respectively. Four SCA were misdiagnosed before resection, 2 of which were mistakenly identified as mucinous lesions. In this misdiagnosed cohort, only 2 cases underwent EUS-FNA. Over time, there was a gradual improvement in the diagnostic performance, with up to 96.2% of the mucinous PCN correctly distinguished from nonmucinous cysts between 2012 and 2014 (Figure 1B). However, although the performance in differentiation of mucinous PCN and nonmucinous cysts improved over time, there was a consistent high rate of resections of low-risk PCN, with up to 67.7% (31 out of 96 cases) resected without having high-grade dysplasia or invasive carcinoma (Figure 1C and see Supplemental Table 1, http://links.lww.com/MD/A304, Supplemental Content, which shows the distribution of subtypes and dysplasia of IPMN and MCN patients in the retrospective cohort).

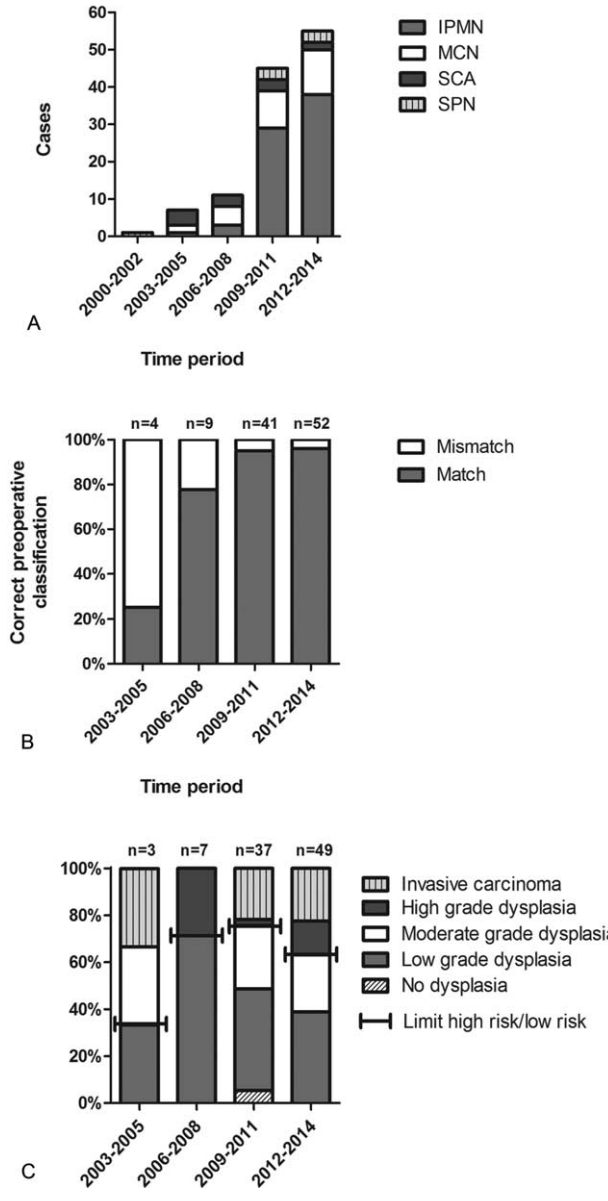

FIGURE 1. Numbers and presentation of PCN over the years. (A) Graph depicting all PCN resections from 2000 to 2014 (n = 115) in the Erasmus MC, Rotterdam, The Netherlands. For all types of PCN, a triennial increase of resections can be noted. (B) The percentage matching preoperative diagnosis compared with the histopathological diagnosis over time in the retrospective cohort. (C) Graph depicting the distribution of dysplasia in resected mucinous PCN over the years. PCN = pancreatic cystic neoplasm.

IPMN Description

In IPMN specimens involving the main pancreatic duct, MD-IPMN and MT-IPMN, the frequency of samples containing

TABLE 2. Characteristics of Misdiagnosed Patients in Retrospective Cohort

Case Number	Gender	Age	Preoperative Diagnosis	Histological Diagnosis, Dysplasia	Year of Resection	EUS-FNA Performed
1	Female	45	SPN	SB-IPMN, high-grade	2008	No
2	Male	66	Pseudocyst	MCN, invasive carcinoma	2003	No
3	Female	67	SCA	MCN, unknown	2007	Yes
4	Female	37	MD-IPMN	SCA	2004	No
5	Female	77	Cystic PanNET	SCA	2005	No
6	Female	40	Cystic PanNET	SCA	2011	No
7	Male	73	MD-IPMN	SCA	2014	Yes
8	Female	36	MCN	SPN	2009	No
9	Female	24	Cystic PanNET	SPN	2012	No

EUS-FNA = endoscopic ultrasound-fine needle aspiration, MCN = mucinous cystic neoplasm, MD-IPMN = main duct-intraductal papillary mucinous neoplasm, PanNET = pancreatic neuroendocrine tumor, SB-IPMN = side branch-intraductal papillary mucinous neoplasm, SCA = serous serous cystadenoma, SPN = solid pseudopapillary neoplasm.

high-grade dysplasia or invasive carcinoma was 46.8% (22 out of 47). In contrast, the incidence of high-risk PCN in SB-IPMN was much lower (26.1%, 6 out of 23). Of note, in 2 cases of MD-IPMN and 7 of SB-IPMN, adenocarcinoma was found adjacent to the IPMN. Although in these cases IPMN was scored based on its own malignant state (eg, IPMN with low-grade dysplasia and adjacent unrelated carcinoma were classified as low risk), resection was of course warranted due to the carcinoma present. Excluding unrelated adjacent carcinoma, the rate of high-risk PCN in SB-IPMN was 35.3% (6 out of 17, 1 unknown). In the period between 2009 and 2011, 27.6% of resected IPMN cases were high risk (8 out of 29) whereas between 2012 and 2014 this proportion was 48.6% (18 out of 37) (see Supplemental Figure 3, http://links.lww.com/MD/A304, Supplemental Content, which illustrates the distribution of dysplasia in resected IPMN over the years), suggesting that the updated Sendai guidelines of 2012 result in fewer false positive cases. Of the 71 patients who underwent a pancreatic resection, 1 histology report could not be retrieved, 20 had low-grade dysplasia (28.2%), 21 had moderate dysplasia (29.6%), 10 had high-grade dysplasia (14.1%), and 19 had invasive carcinoma (26.8%). Forty four out of 71 (62%) patients presented with symptoms before resection, whereas others were incidental findings or found during surveillance for familial pancreatic cancer.

Histology of IPMN

Of the 71 IPMNs, the distribution of the histologic classification was as follows: 23 were of the intestinal type, 12 of the pancreatobiliary type, 19 of the gastric type, and 2 were of the oncocytic type (see Supplementary Figure 4, http://links.lww.com/MD/A304, Supplemental content, which shows examples of different subtypes of IPMN as can be evaluated with regular H&E staining). Twelve patients were found to have 2 subtypes in their respective pancreatic resection specimen. The pancreatobiliary (58.3%) or oncocytic (100%) types were more associated with high-risk PCN. In contrast, the rate of high-risk PCN was lower in intestinal (21.1%) and gastric subtypes (26.1%) (see Supplemental Table 1, http://links.lww.com/MD/A304, Supplemental Content, which shows the distribution of subtypes and dysplasia of IPMN and MCN patients in the retrospective cohort).

Recurrence of IPMN

The median follow-up after surgery was 12.1 months (IQR 5.7–24.9). During follow-up, there was progression of residual IPMN in 9 (12.9%) patients. New onset of IPMN was observed in 3 (4.3%) cases, suggestive of a predisposition for pancreatic lesion development in accordance with the field defect theory in IPMN.[8] In 35 cases (50.0%) no follow-up imaging after surgery was performed, but patients were routinely followed up at the outpatient department and evaluated based on clinical grounds. In the remaining 23 cases (32.9%), imaging demonstrated a stable pancreas.

Mucinous Cystic Neoplasm Description

A total of 27 MCN were resected from 2000 to 2014. The incidence of high-risk PCN was 7.7% (2 out of 26, 1 case could not be retrieved), while 92.3% was considered a low-risk PCN (see Supplemental Table 1, http://links.lww.com/MD/A304, Supplemental Content, which shows the distribution of subtypes and dysplasia of IPMN and MCN patients in the retrospective cohort). The majority of the MCN, including the 2 malignant ones, was located in the tail (92.6%). The average size was 5.8 cm (±2.6). More than half (61.5%) presented with symptoms.

The median follow-up after surgery was 11.9 months (IQR 0.7–34.3). After follow-up, 10 out of 27 patients had a demonstrable stable residual pancreas, while in the other 17 patients no imaging was performed.

Prospective Analysis of Mucinous Background Addition to Diagnosis

Although in our specialist tertiary referral center, preoperative diagnosis of resected PCN is almost 100% accurate, global decision making would benefit from additional easily implementable markers distinguishing mucinous PCN and nonmucinous lesions. Pancreatic surgery is associated with important morbidity and mortality, and even incidental unnecessary surgeries should be prevented. We therefore decided to investigate the added value of distinguishing mucinous background in EUS-FNA samples in the discrimination between mucinous PCN and nonmucinous cysts. To this aim, we determined CEA in cyst fluid and performed cytological evaluation of the collected fluid that included rapportage of the presence or absence of mucin and evaluation of the epithelial component. Seventy one subjects were included in this prospective study and underwent EUS-FNA. The patient characteristics are described in Table 3.

TABLE 3. Characteristics of Patients in Prospective Cohort

	Total (n = 71)	Nonmucinous (n = 30)	Mucinous (n = 41)
Age, years			
Range	19.9–82.0	31.6–78.9	19.9–82.0
Mean (SD)	60.9 (12.7)	58.7 (13.4)	62.4 (12.0)
Mean CEA (SD), ng/mL	3039 (13390)	252 (237)	5078 (2716)
Gender, n, %			
Male	28 (39.4)	11 (36.7)	17 (41.5)
Female	43 (60.6)	19 (63.3)	24 (58.5)
Diagnosis, n, %			
Main branch-IPMN	2 (2.8)	0 (0)	2 (4.9)
Side branch-IPMN	20 (28.2)	0 (0)	20 (48.8)
Mixed type-IPMN	6 (8.5)	0 (0)	6 (14.6)
Mucinous cystic neoplasm	13 (18.3)	0 (0)	13 (31.7)
Pseudocyst	13 (18.3)	13 (43.3)	0 (0)
Serous Cystadenoma	16 (22.5)	16 (53.3)	0 (0)
GIST	1 (1.4)	1 (3.3)	0 (0)
Surgery, n, %			
Yes	27 (38.0)	4 (13.3)	23 (56.1)
No	44 (62.0)	26 (86.7)	18 (43.9)
Dysplasia, of resected (n = 27)			
No dysplasia	2 (7.4)		
Low-grade dysplasia	13 (48.1)		
Moderate-grade dysplasia	4 (14.8)		
High-grade dysplasia	4 (14.8)		
Not applicable	4 (14.8)		

CEA = carcinoembryonic antigen, GIST = gastrointestinal stromal tumor, IPMN = intraductal papillary mucinous neoplasm, SD = standard deviation.

The median follow-up after EUS-FNA was 13.1 months (IQR 5.3–33.4). During that time 38.0% (27 out of 71 patients) were resected of which 4 out of 27 (14.8%) contained high-grade dysplasia, meaning the other 85.2% had moderate dysplasia at highest, or were a pseudocyst or SCA.

Carcinoembryonic Antigen (CEA)

The mean CEA level was higher in mucinous PCN (5078 ng/mL; n = 41) compared with nonmucinous cysts (252 ng/mL; n = 30). The frequently used cutoff value of 192 ng/mL[13,14] resulted in a sensitivity of 39% and specificity of 96.7%, yielding an overall accuracy of 63.4% to differentiate between mucinous PCN and nonmucinous cysts (see Supplemental Table 2, http://links.lww.com/MD/A304, Supplemental Content, which shows the diagnostic performance of CEA and the presence of mucin in cytological analysis). Univariable logistic regression yielded an OR of 18.6 (95%CI 2.3–150.0; $P = 0.006$) of having a mucinous PCN (Table 4). Evaluating CEA as a predictor for dysplasia did not yield a correlation given the wide range in low- and high-risk PCN (low-risk PCN: 1.3–83,690.0 ng/mL, n = 19; high-risk PCN: 0.2–172.1 ng/mL, n = 4; $P = 0.33$).

Cytopathology and Mucin Evaluation

Next, we determined the presence of mucin in the EUS-FNA samples, which were available for 67 patients (examples in Figure 2A–D). Cytopathology results were available in 52 cases, 15 samples were not diagnostic and another 4 were not available for evaluation. Epithelial cells were present in 8 (11.9%) samples, which actually contributed to diagnosis in only 5 (7.5%) cases. Mucin was present in 24 of the 52 cases, and yielded a sensitivity of 66.6%, specificity of 81.8%, PPV of

TABLE 4. Logistic Regression for the Differentiation of Mucinous Pancreatic Cystic Neoplasm Versus Nonmucinous Cysts

	Odds Ratio	95% Confidence Interval	*P*-Value
Univariable analysis			
CEA≥192 ng/mL	18.6	2.3–150.0	0.006
Mucin background	9.0	2.4–33.8	0.001
Multivariable analysis			
CEA≥192 ng/mL	11.2	1.2–105.3	0.034
Mucin background	7.7	1.9–31.3	0.004

CEA = carcinoembryonic antigen.

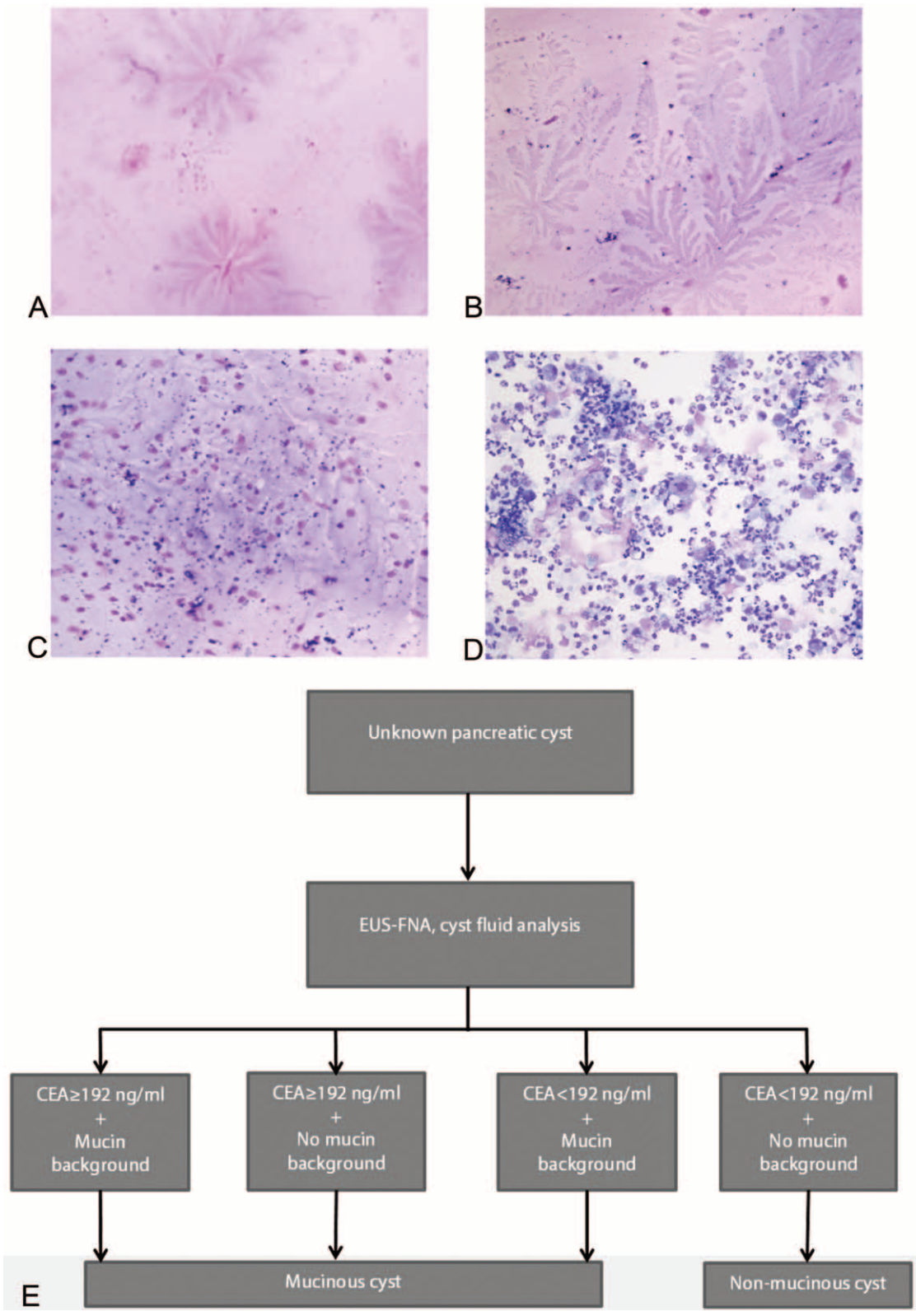

FIGURE 2. The use of mucinous background in the diagnosis of mucinous PCN. Representative microscopical images of mucinous background in cytopathological analysis of pancreatic cyst fluid (A–C) and representative image of a reactive background obtained from a pseudocyst without mucin present (D) (200× magnification). (E) Proposed diagnostic algorithm incorporating the use of pancreatic cyst fluid obtained by EUS-FNA. EUS-FNA = endoscopic ultrasound-fine needle aspiration, PCN = pancreatic cystic neoplasm.

83.3%, NPV of 64.3%, and accuracy of 73.0% of predicting a mucinous PCN (see Supplemental Table 2, http://links.lww.com/MD/A304, Supplemental Content, which shows the diagnostic performance of CEA and the presence of mucin in cytological analysis). Univariable analysis of the presence of mucinous background had an OR of 9.0 (95%CI: 2.4–33.8; $P = 0.001$) (Table 4). Similar to CEA, no association of mucinous background to the degree of dysplasia was observed ($P = 0.135$).

Combining Tests

Using both CEA levels and detection of mucin delivered the highest diagnostic properties. The combined test had a sensitivity of 75% and specificity of 79.1% with a diagnostic accuracy of 76.8%. Multivariable logistic regression still indicates both as an independent predictor of mucinous PCN; CEA OR 11.2 (95%CI 1.2–105.3; $P = 0.034$) and mucinous background OR 7.7 (1.9–31.3; $P = 0.004$) (Table 4). Figure 2E shows our proposed diagnostic algorithm using cyst fluid analysis.

DISCUSSION

In this combined retrospective and prospective analysis of PCNs we observed that PCNs, in particular IPMN and MCN, are resected with increasing incidence. Between 2006 and 2008, there were 11 pancreatic resections performed for a PCN, which increased 5-fold between 2012 and 2014. The growth in resections of PCN observed in this study is in accordance with the increased detection of pancreatic cysts due to the improvement of imaging techniques and the widespread use of cross-sectional imaging.[15]

In our tertiary referral center, the misclassification rate of PCN was lower than 5% in the last 6 years. During the last 3 years 96.2% out of 52 resected PCN were correctly classified preoperatively. Misclassification occurred in 9 cases, 5 of which were nevertheless justified resections as these were a high-grade SB-IPMN, 2 SPNs, and 2 MCNs. Seven out of 9 misclassified cases did not undergo the EUS-FNA which might have avoided false-positive surgery. Although diagnostic pancreatic cyst fluid with low levels of CEA and absence of mucin was available in 1 patient (7), this was not taken into consideration and the patient was misdiagnosed with an IPMN. Using our currently proposed algorithm, this patient would have more likely been diagnosed with an SCA.

Especially in centers with lower pancreatic cyst volume, the clinical diagnosis may be strengthened by tools that are less hampered by interobservational differences. Importantly, discrimination between mucinous PCN and nonmucinous pancreatic lesions is the primary step in the clinical work-up, as malignant transformation is mostly associated with mucinous PCN. Routine diagnostics include the cytological evaluation of the epithelial component in cyst fluid. However, in accordance to earlier studies, cytologic evaluation of the epithelial component (without mucinous background evaluation) performed poorly, most likely due to paucicelullarity;[13,14] presence of epithelial cells was detected in only 11.9% of the cases, with diagnostic usefulness limited to a mere half of these.

CEA has been described as a diagnostic tool for the evaluation of mucinous PCN.[13,14] In our study, diagnostic accuracy of CEA in discriminating between mucinous PCN and nonmucinous cysts was 63.4%, which is comparable to an earlier report.[14] Previous studies using separate mucin staining for diagnosing mucinous PCN found varying results.[16,17] In our study, evaluation of the presence of mucin (without additional staining required) in cytopathological analysis (OR 7.7), additional to CEA, can improve diagnostic accuracy to 76.8%. Thus, we show that a simple evaluation such as mucinous background analysis, which is easy to perform in the routine histopathological practice, can lead to enhanced diagnostic accuracy. We therefore advise pathologists to evaluate and report the background status in cytopathological analysis of pancreatic cyst fluid.

Importantly, our cohorts show that despite improvements in diagnostics and updated guidelines, the rate of resections with no, low, or moderate dysplasia remains high, especially in SB-IPMN and MCN, demonstrating the need for better diagnostic tools for clinical decision making. The occurence of high-grade dysplasia and invasive carcinoma in IPMN involving the main duct was 46.8%, and therefore the current management to resect all MD-IPMN and MT-IPMN in surgically fit patients is warranted.[18,19] In contrast, we found that only 26.1% of the resected SB-IPMN were histologically classified as a high risk, while the majority of resected SB-IPMN showed low-grade or moderate dysplasia only. Excluding cases with adjacent carcinoma, the rate of high-risk SB-IPMN would only be 35.3%, implying a low correlation of the current guidelines with degree of dysplasia. This low correlation is in accordance with earlier reports and has led to a debate regarding Sendai guidelines and the management of SB-IPMN.[20,21] The incidence of carcinoma in MCN was found to be even lower with 7.7%, similar to an earlier report.[6] In fact, most resected MCN (82.3%) had low or moderate dysplasia only. Currently, there are no reliable predictors for the identification of high-risk mucinous PCN, as promising markers in pancreatic cyst fluid such as microRNAs and p53 require clinical validation.[22,23] Furthermore, improved clinical-risk stratification is needed to reduce the burden of pancreatic surgery with high morbidity and mortality in selected patients.

We acknowledge several limitations in our study. The retrospective part of the study is unavoidably exposed to selection bias as mainly PCN with high-risk stigmata were resected. Additionally, the outcome in our prospective cohort was not always based on the golden standard of histopathology but on clinical diagnosis. However, more than 50% was confirmed histologically and the performance of classifying PCN in this institution based on clinical data was shown to be very accurate in our retrospective data.

CONCLUSIONS

In summary, we show that the number of patients who are diagnosed with PCN is increasing over time. Combination of cytopathology and cyst fluid biochemistry is highly specific and sensitive for discrimination between mucinous PCN and nonmucinous cysts. However, preoperative discrimination of high-grade from low-grade PCN is still problematic and requires novel biomarkers and long-term surveillance data to better predict the course of the PCN, especially those with low rate of progression, including MCN and SB-IPMN.

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