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Diagnosis of Pancreatic Cystic Neoplasms: A Report of the Cooperative Pancreatic Cyst Study

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Background & Aims: **Cysts of the pancreas display a wide spectrum of histology, including inflammatory (pseudocysts), benign (serous), premalignant (mucinous), and malignant (mucinous) lesions. Endoscopic ultrasonography (EUS) may offer a diagnostic tool through the combination of imaging and guided, fine-needle aspiration (FNA). The purpose of this investigation was to determine the most accurate test for differentiating mucinous from nonmucinous cystic lesions.** ***Methods:*** **The results of EUS imaging, cyst fluid cytology, and cyst fluid tumor markers (CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3) were prospectively collected and compared in a multicenter study using histology as the final diagnostic standard.** ***Results:*** **Three hundred forty-one (341) patients underwent EUS and FNA of a pancreatic cystic lesion; 112 of these patients underwent surgical resection, providing a histologic diagnosis of the cystic lesion (68 mucinous, 7 serous, 27 inflammatory, 5 endocrine, and 5 other). Receiver operator curve analysis of the tumor markers demonstrated that cyst fluid CEA (optimal cutoff of 192 ng/mL) demonstrated the greatest area under the curve (0.79) for differentiating mucinous vs. nonmucinous cystic lesions. The accuracy of CEA (88 of 111, 79%) was significantly greater than the accuracy of EUS morphology (57 of 112, 51%) or cytology (64 of 109, 59%) ($P < 0.05$). There was no combination of tests that provided greater accuracy than CEA alone ($P < 0.0001$).** ***Conclusions:*** **Of tested markers, cyst fluid CEA is the most accurate test available for the diagnosis of mucinous cystic lesions of the pancreas.**

Pancreatic cystic neoplasms are composed of a variety of neoplasms with a wide range of malignant potential.[1,2] Serous cystadenomas are composed of multiple small compartments that are lined with a glycogen-containing cuboidal epithelium and are nearly always benign in their clinical course.[3] In contrast, mucinous cystic neoplasms are composed of large compartments that are lined with a mucin-secreting columnar epithelium and exhibit variable malignant potential (Figure 1).[4] The cysts that arise from side branches of the intraductal papillary mucinous neoplasms (IPMN) demonstrate similar characteristics. The degree of epithelial dysplasia is used to classify mucinous cystic neoplasms into benign, borderline, and malignant tumors.[4,5] Resected malignant cystic neoplasms have a better prognosis than solid adenocarcinomas, with a 6-year survival of 36%.[6] Resection of early mucinous cystic neoplasms can provide an excellent prognosis. Pancreatic pseudocysts are focal fluid collections that arise as a result of inflammatory diseases of the pancreas and should be managed conservatively or with a drainage procedure. Their radiologic appearance can mimic cystic neoplasms of the pancreas.[7]

Imaging tests, fine-needle aspiration (FNA), and/or cyst fluid analysis have been utilized to provide a diagnosis in patients with a cystic lesion of the pancreas. However, none of these diagnostic modalities are uniformly effective in making a diagnosis. Cross-sectional imaging is often nondiagnostic because of the small size of the lesion and the difficulty in directing FNA.[8] Cytologic examination of the cyst fluid is often nondiagnostic because of the low cellularity of the aspirated fluid.[9] Warshaw et al.[10] and Hammel et al.[11] first demonstrated that tumor markers CEA and CA 72-4 were present in high concentrations in the cyst fluid from mucinous cystic neoplasms. Subsequent studies from other centers have confirmed this finding.[12,13] Endoscopic ultrasound (EUS) may be a useful new diagnostic tool for cystic neoplasms because it can provide high resolution images of pancreatic cyst lesions and direct

Abbreviations used in this paper: EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasms.

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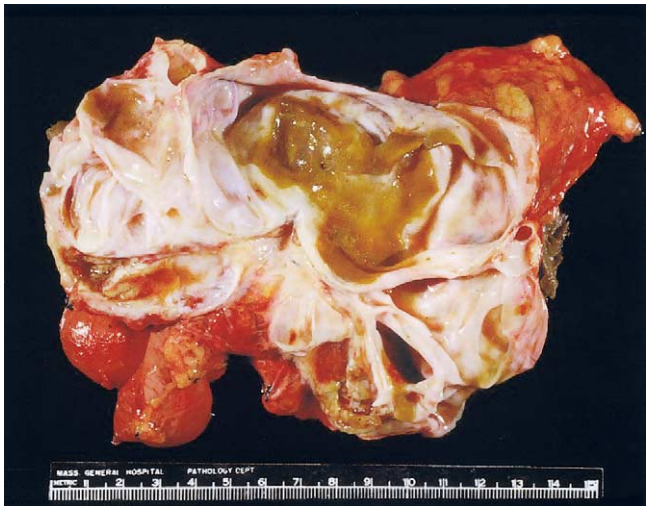

Figure 1. Gross pathology of mucinous cystic neoplasms. Note the presence of thin septations surrounding mucin-filled cystic cavities.

FNA.[14,15] We sought to determine whether cyst fluid analysis with cytology and tumor markers would provide complementary information to EUS imaging alone in patients with pancreatic cyst lesions and thereby improve the diagnostic accuracy of EUS-FNA in the setting of a large, prospective, multicenter study.

Materials and Methods

A multicenter trial, with institutional review board approval at each site, was initiated in July 1999 (see Appendix I). Patients (with or without symptoms) found to have a pancreatic cystic lesion of greater than 10 mm on transabdominal ultrasonography or computed tomography (CT) scanning were eligible. Exclusion criteria included the following: Pro-time (PT-INR) >1.5, partial thromboplastin time (PTT) >50, platelets <50,000, acute pancreatitis, or the presence of a pancreatic abscess. The results of a clinical assessment, EUS exam, cytology, and histology were blindly entered into a central database at Massachusetts General Hospital (MGH). Frozen, undiluted cyst fluid was sent to MGH for tumor marker analysis. The results of the tumor marker concentrations were obtained and reported without knowledge of the clinical, histologic, or EUS results.

EUS Methods

All patients underwent an EUS examination, performed using a linear echoendoscope as previously described.[16] The results of the examination prospectively reported the location, size, and morphology (see below) of the cystic lesion. The cystic lesion was aspirated under EUS guidance using 1 passage of a 19- or 22-gauge needle (Wilson Cook Inc., Winston-Salem, North Carolina; or Mediglobe, Tempe, AZ) occluded with a stylet. An oral quinolone was administered for 2–3 days after the procedure.

Diagnostic Criteria for Cystic Lesions

Morphology. The morphology of the cystic lesion was determined by EUS as previously described.[14,17] The specific morphologic findings of the cystic lesion that were recorded included the presence or absence of (1) an adjacent mass, (2) macrocystic septations (defined by the presence of discrete loculations), (3) honeycombed septations, and (4) a diffusely thickened cyst wall. Cysts with an adjacent mass or macrocystic septations were classified as mucinous cystic neoplasms by EUS morphology. Those with honeycombed septations or a thickened cyst wall were considered nonmucinous by EUS morphology.

Cytology. All cytology analysis was carried out by cytologists at each participating institution. Samples were reported by the home site to be diagnostic or nondiagnostic (because of insufficient cells or contamination). Diagnostic samples were classified as containing cytologic evidence of (1) mucinous epithelium (clusters of benign or malignant glandular cells with cytoplasmic mucin) or (2) nonmucinous epithelium (flat monolayers of small cuboidal cells or inflammatory cells such as pigment-laden macrophages, histiocytes, or leukocytes).

Histology. Primary histologic interpretations of the resected specimens were performed by pathologists at participating institutions, and the reports were reviewed by one of the study pathologists (B.C.). Based on the reports and the WHO tumor classification, the resected cystic lesions were classified as (1) a mucinous cystic neoplasm (benign, borderline, or malignant)[18] or (2) a nonmucinous cystic lesion including serous, inflammatory, and endocrine. Cystic lesions arising from an intraductal papillary mucinous tumor were considered mucinous. Cystic lesions that could not be classified into the categories stated above were classified as "others."

Tumor Markers

Cyst fluid concentrations of CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3 were measured using specific radioimmunoassays as previously reported. The tumor markers CEA, CA 125, and CA 15-3 were measured on an Abbott Diagnostics IMX-MEIA immunodiagnostics analyzer (Abbott Laboratory, Diagnostics Division, Abbott Park, IL).[10] CA 72-4 was measured at Dianon Systems (Stratford, CT) using the BYK-SANGTEC immunoradiometric method. CA 19-9 was measured at Dianon Systems using the FUJIREBIO Inc. (Wilmington, DE) immunoradiometric method. Cyst fluid was not analyzed for amylase, mucin concentration, or viscosity.

Data Collection and Analysis

Analyses were restricted to patients with histologic confirmation of the type of cystic lesion. Only cytology reports with a concluding diagnosis were interpreted as being diagnostic. All other cytology reports were classified as nondiagnostic. For patients with multiple cystic lesions aspirated, the most malignant lesion was selected for analysis, based on histology. The sensitivity, specificity, and accuracy rates (percentage) were determined for morphology and cytology and

Table 1. Patient Characteristics

Types of cystic lesions	Subjects	Age (yr)	Sex		Location of cyst				Size of cyst (mm)			
			Male	Female	Head	Body	Tail	Unknown	0–10	10–20	>20	Unknown
Total evaluable subjects	341	63.2	125	216	156	109	67	9	34	77	207	23
Without histology	229	64.7	84	145	107	72	42	8	27	53	135	14
With histology	112	60.1	41	71	49	37	25	1	7	24	72	9
Surgical resection	95	58.9	32	63	40	31	23	1	6	24	59	6
Surgical biopsy	17	66.5	9	8	9	6	2	0	1	0	13	3
Mucinous (benign)	18	52.0	2	16	2	7	9	0	1	5	10	2
Mucinous (borderline)	8	67.5	6	2	4	1	3	0	1	2	4	1
Mucinous (malignant)	42	66.7	17	25	22	16	4	0	4	7	27	4
Serous	7	65.4	1	6	3	3	1	0	0	1	6	0
Inflammatory	27	54.2	15	12	11	10	5	1	1	5	20	1
Endocrine	5	60.6	3	2	4	0	1	0	0	2	3	0
Other	5	50.6	1	4	3	0	2	0	0	0	4	1

the tumor markers for mucinous (benign and malignant) and nonmucinous cysts (serous, inflammatory, or endocrine). Separate receiver operator characteristic (ROC) curves were plotted using each tumor marker (CEA, CA 72-4, CA 125, CA 19-9, and CA 15-3) to predict a mucinous or a nonmucinous cystic lesion. The area under each ROC curve, a measure of predictive power, was calculated. For tumor markers, cutoff values were selected to maximize the proportion of correct classifications of the cystic lesion. Sensitivity and specificity were calculated using these values. The tumor marker with the greatest area under the ROC curve was selected for comparison with morphology and cytology. Sensitivity, specificity, and accuracy rates were compared using 2 sample tests of proportions.

Results

Three hundred forty-one consecutive patients were enrolled in the trial over 2 years and underwent EUS and FNA. None of the patients had an infective complication of the EUS-guided FNA. Two patients developed mild pancreatitis after the EUS-FNA that resolved within 3 days.

The patient characteristics are presented in Table 1. Patients were predominantly female (63%, $P < 0.001$). Most of the cysts examined (n = 207, 61%) were greater than 2 cm in diameter, and most were located in the head of the pancreas (n = 156, 47%). One hundred twelve of the enrolled patients underwent a resection (n = 95) or a biopsy (n = 17) that yielded histologic confirmation of the cyst type and were included in the analysis. Mucinous cysts accounted for 60% of the cysts. Patients with histologic evidence of the cyst type were younger than those without (60.1 vs. 64.8 years, respectively, $P < 0.01$) but did not differ in proportion of cysts greater than 2 cm (63% vs. 70%, respectively, $P > 0.05$) of cysts located in the head (44% vs. 45%, respectively, $P > 0.05$) or proportion of female patients (63% vs. 63%, respectively, $P > 0.05$). The histology of the mucinous lesions is presented in Table 2. Most (52 of 68, 76%) of the mucinous lesions were mucinous cystic neoplasms, and 29 of 52 (56%) were malignant.

Overall Cyst Fluid Tumor Marker Results

The mean and median cyst fluid CEA concentration for all mucinous cysts (5607 ng/mL and 500 ng/mL, mean and median values, respectively) were greater than the median and mean CEA concentration for all nonmucinous cystic lesions (284 ng/mL and 21 ng/mL, mean and median values, respectively) ($P < 0.0001$ for median values). Mucinous cysts with malignancy (including borderline malignancy) tended to have greater mean concentrations of CEA (8400.5 ng/mL), followed by benign mucinous (683.9 ng/mL), inflammatory (36.8 ng/mL), and serous (2.7 ng/mL) cysts (Figure 2). There was a substantial range of CEA concentrations within each cyst type, particularly in the malignant cysts. The wide range resulted in overlapping values for CEA for each cyst type. The other tumor markers provided even less discrimination between cyst types.

Table 3 presents the sensitivity, specificity, accuracy, and the area under the ROC curve obtained using each tumor marker to predict whether the cysts in the 112 patients were mucinous or not mucinous. The ROC curve area was greatest for CEA (0.79), followed closely

Table 2. Number of Patients with Mucinous Cystic Neoplasms and IPMT: WHO Classification

	Mucinous cystic neoplasm	IPMT	Total
Benign	23	5	28
Borderline	5	9	14
Malignant	24	2	26
Total	52	16	68

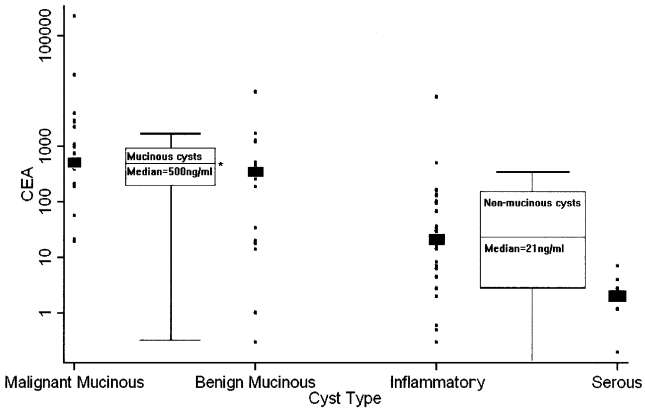

Figure 2. Median (*solid box*) cyst fluid concentration of CEA (log scale) in mucinous (malignant and benign), inflammatory, and serous cysts. Also shown are the median values for all mucinous and all nonmucinous cysts (*open boxes*: indicating 25th–75th percentiles; the *vertical lines* indicate the range of 1.5 times the interquartile value). *$P < 0.0001$ vs. non-mucinous cysts.

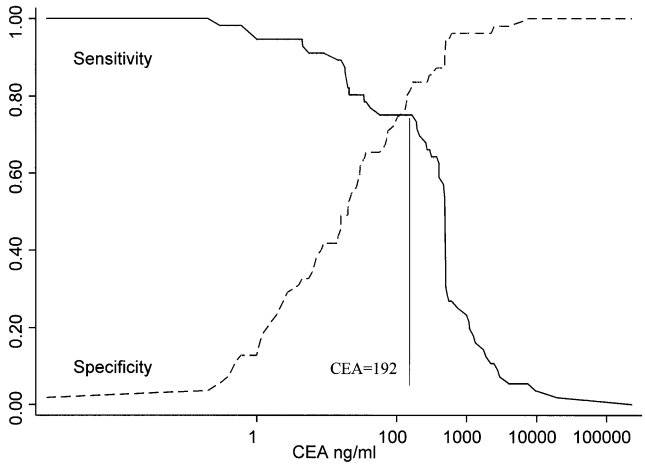

Figure 3. Sensitivity and specificity curves of cyst fluid CEA concentrations (ng/mL; log scale) for differentiating between mucinous and nonmucinous cystic lesions. An optimal cutoff value of 192 ng/mL correlated with the crossover of the sensitivity and specificity curves.

by CA 72-4 (0.72). A sensitivity and specificity curve demonstrated that the optimal cutoff value for CEA corresponded to the intersection of the sensitivity and specificity curves (Figure 3). CEA with a cutoff value of 192 ng/mL provided the greatest accuracy (0.79) for differentiating between mucinous and nonmucinous cysts with moderate sensitivity (0.73) and specificity (0.84).

Results of EUS Morphology

The morphology of the cystic lesions was prospectively determined using interpretation of EUS images (Table 4). Using morphologic criteria for mucinous cysts (macrocystic septations or adjacent mass), mucinous cysts were differentiated from nonmucinous cystic lesions (unilocular, honeycombed, or thickened wall). The sensitivity and specificity of EUS morphology were low (56% and 45%, respectively), resulting in a poor overall accuracy (57 of 112 or 51%). The EUS morphologic finding of "an adjacent mass" was present in 20 of 32 (63%) of malignant cysts (data not shown in Table 4; see example in Figure 4).

Table 3. Accuracy of the Tested Tumor Markers in Differentiating Between Mucinous and Nonmucinous Lesions

Tumor marker	Sensitivity	Specificity	Accuracy	ROC	*P* value[a]	Cut off
CEA	.73	.84	.79	.7930	<.001	192
CA125	.83	.37	.60	.5910	.183	9
CA15-3	.19	.94	.57	.5011	.816	121
CA19-9	.68	.62	.66	.6654	.004	2900
CA72-4	.80	.61	.72	.7423	.001	7

ROC, receiver operator characteristics curve (area); Cut off: calculated optimal cutoff values for each marker (ng/mL).
[a]*P* value: significance vs. chance in predicting a mucinous lesion.

Results of Cytology

The results of cytology were used to categorize cysts into mucinous or nonmucinous types (Table 4). The sensitivity of cytology for diagnosing a mucinous cyst was 19 of 55 or 34.5% with a high specificity rate of 45 of 54 or 83%. However, the overall accuracy (64 of 109 or 59%) was similar to the overall accuracy of EUS morphology (51%). The sensitivity of cytology for diagnosing malignancy in a malignant mucinous cystic lesion was 7 of 32 or 22% (data not shown in Table 4).

Results of Cyst Fluid CEA

Using an optimal cutoff value of 192 ng/mL, the cyst fluid CEA concentration was used to differentiate between mucinous and nonmucinous lesions (Table 4). The sensitivity of cyst fluid CEA for the diagnosis of a mucinous cyst was 42 of 56 or 75.0% for detecting a mucinous cyst with a modest specificity of 46 of 55 or 83.6%. The overall accuracy of CEA (79%) was signifi-

Table 4. Accuracy of the 3 Primary Tests for Differentiating Between Mucinous and Nonmucinous Cystic Lesions

	EUS morphology	Cytology	CEA
Sensitivity	32/57 (56.1%)	19/55 (34.5%)	42/56 (75%)
Specificity	25/55 (45.4%)	45/54 (83.3%)	46/55 (83.6%)
Accuracy	57/112 (50.9%)	64/109 (58.7%)[a]	88/111 (79.2%)[b,c]

[a]Three patients did not have cytology result.
[b]One patient did not have a CEA result.
[c]$P < 0.05$ vs cytology, EUS morphology.

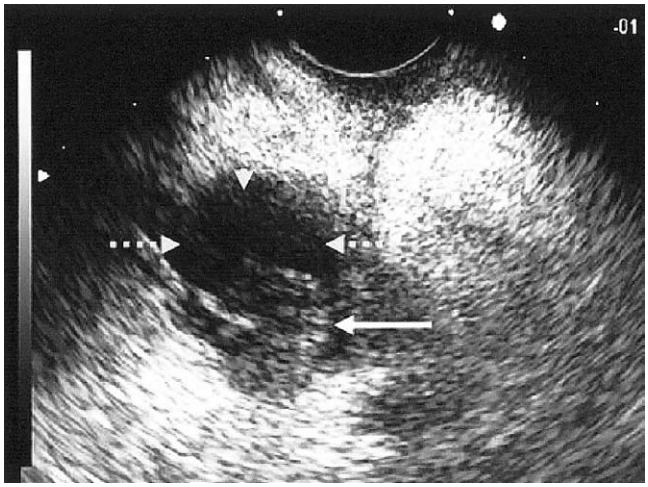

Figure 4. Linear EUS image of a malignant mucinous cystic neoplasm. The cystic lesion (*gray, dashed arrows*) was located in the head of the pancreas and measured approximately 2 cm in diameter. A mass in the wall of the cyst (*white arrow*) provided morphologic evidence of a malignancy.

cantly greater than the accuracy of cytology (59%) or morphology (51%; $P < 0.05$).

Combination Testing

Table 5 compares the performance of various combinations of tests in identifying mucinous cysts. In these combinations, a cyst was classified as mucinous if any of the component tests were positive for the diagnosis of a mucinous lesion. The combination of morphology, cytology, and CEA (second column, Table 5) was more sensitive than CEA alone (91% vs. 75%, respectively, $P = 0.0044$; see Table 4 for sensitivity of CEA alone), but the combination was less specific and produced an ROC curve with a smaller area (0.6107 vs. 0.7930, respectively, $P < 0.0001$; see also Table 3 for ROC area for CEA alone). The ROC curve area for morphology and cytology combined (0.5418) did not differ from that for cytology or morphology alone ($P = 0.5099$ and $P = 0.2464$, respectively). The addition of cytology to CEA did not increase sensitivity ($P = 0.33$) or the area under the ROC curve ($P = 0.3283$), compared to CEA alone.

Discussion

Cystic mucinous neoplasms of the pancreas are composed of a group of cystic tumors that are lined by mucinous, columnar epithelium. The diagnosis of this type of cystic lesion is very important because of the presence of malignancy in some lesions at the time of presentation and the tendency to develop malignancy over time. This feature is highlighted in our highly selected patients by the presence of malignancy or borderline malignancy in 40 of 68 patients with a mucinous cystic lesion. Other investigators have also encountered similar prevalence of malignancy.[19] In contrast, there was no evidence of overt malignancy in the other cysts encountered, although cystic endocrine neoplasms are considered low-grade malignancies. Given the risk of malignancy in mucinous lesions and the excellent prognosis of resected mucinous cystic lesions, many recommend surgical resection for benign and malignant mucinous cystic lesions.[20] For these reasons, we examined the usefulness of various diagnostic tests for differentiating between mucinous cystic lesions and nonmucinous lesions.

An accurate diagnosis of a pancreatic cystic lesion is often difficult because traditional cross-sectional imaging tests cannot provide diagnostic images.[21] EUS has several features that may make it an excellent tool for the imaging of pancreatic cysts. Because the pancreas lies directly adjacent to the stomach, an EUS transducer can be placed in close proximity to the pancreas, and the entire gland can be readily imaged. Ultrasound imaging is well suited for assessment of cystic lesions. EUS can provide detailed images of the wall and septations and adjacent masses that characterize many different types of cysts.[14,17,22] However, despite high-resolution images of pancreatic cystic lesion, EUS alone has not been able to accurately differentiate between benign and malignant cystic neoplasms.[17,23] A recent study by Song et al. suggested that the finding of mural nodules during EUS imaging may aid in identifying mucinous lesions.[24] Our study has confirmed that EUS imaging through the use of strict morphologic criteria is relatively insensitive and nonspecific in differentiating mucinous cystic neoplasms from nonmucinous cystic lesions.

FNA is often used to improve the results of pancreatic imaging. However, CT-guided FNA has been relatively

Table 5. Accuracy of Combination of Tests for Diagnosing Mucinous Cystic Lesions of the Pancreas

	EUS morphology or cytology	EUS morphology or cytology or CEA	Cytology or CEA
Sensitivity[a]	70	91	82
Specificity	38	31	71
Accuracy	54	62	77[b]
Area under ROC curve	0.5418[c]	0.6107[c]	0.7668

[a]The values reported were compared with regression analysis using area under ROC curves and are more accurately termed *areas* rather than percentage.

[b]$P < 0.05$ vs. EUS morphology-cytology, EUS morphology-cytology-CEA.

[c]Area less than CEA alone, $P < 0.0001$; see Table 3 for CEA alone ROC area.

unsuccessful in the diagnostic evaluation of cystic lesions because of the small size and inaccessibility of pancreatic cysts.[25] EUS-guided FNA of solid pancreatic masses has been successful at improving the diagnostic accuracy of EUS imaging alone.[26] Although EUS-guided FNA of pancreatic masses is a highly sensitive test for diagnosing pancreatic malignancy, the results of FNA of pancreatic cysts has not been as successful.[15] Obtaining sufficient cells for diagnostic cytology is often difficult because of the relatively low cellularity of aspirated pancreatic cyst fluid.[9] This study has confirmed the limited utility of FNA when used solely for obtaining cyst fluid cytology and for diagnosing mucinous cysts, with a shown sensitivity of only 34%. However, as expected, the specificity of cytology was quite high (83%), particularly when compared with results of EUS imaging alone (specificity of 45%).

Cyst fluid tumor markers have been evaluated for several years with the hope that secreted markers into the cyst fluid could reflect the type of epithelial lining.[27] It has been postulated that the secretion of tumor antigens by a mucinous epithelium could provide unique markers for mucinous cystic neoplasms.[28] Because serous cystadenomas are lined by a simple cuboidal type of epithelium, markers such as CEA should be absent in the fluid secreted by serous cystadenomas. The ability to distinguish between serous and mucinous cystic lesions using fluid analysis has been demonstrated previously using cyst fluid obtained during surgery or through CT-guided aspiration.[11] This study has confirmed that the cyst fluid concentration of mucinous tumor markers such as CEA and CA 72-4 are present in much higher concentrations in mucinous cystic neoplasms (mean CEA of 5607 ng/mL in mucinous cysts and mean CEA of 284 ng/mL in nonmucinous cysts).[29,30] This study has also confirmed previous reports of low concentrations of cyst fluid CEA in serous cystadenomas.[29,30]

Traditionally, a combination of testing has been used to diagnose mucinous cystic lesions and differentiate them from nonmucinous cystic lesions. Our study has demonstrated that various combinations of morphology and cytology did not provide additional diagnostic accuracy. Instead, the determination of the cyst fluid concentration of CEA alone was found to be highly diagnostic and more accurate than combination testing. Previous investigators have used a similar optimal cutoff value for CEA (400 ng/mL) and demonstrated a sensitivity rate of 57% and a specificity rate of 100% in the differentiation between mucinous and pseudocyst lesions.[30]

In conclusion, this investigation has assessed the diagnostic accuracy of EUS imaging and cyst fluid analysis in differentiating cystic lesions of the pancreas. The investigation was unique because of its size, the number of participating centers, and the comprehensive and centralized, blinded data analysis of many diagnostic criteria. We have found that cyst fluid CEA is more accurate than EUS and cytology in the diagnosis of mucinous cystic lesions. Endoscopists who evaluate cystic lesions of the pancreas should have aspirated cyst fluid analyzed for CEA, particularly if endoscopic drainage is being considered rather than resection.

The patients who were analyzed in this study composed a subset of patients who underwent a surgical resection for a number of reasons, including symptoms, the concern of malignancy, and a lack of a definitive diagnosis. The characteristics of these patients may be different than an unselected population, and the results may not necessarily be applicable to all patients with a pancreatic cystic lesion. The results of cyst fluid CEA analysis (particularly the cutoff values) presented in this investigation may not be applicable if CEA assays with different characteristics are used.

Appendix 1. Members of the CPC Study

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