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Role of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of mass lesions

CHAOQUN HAN[1], RONG LIN[1], QIN ZHANG[2], JUN LIU[1], ZHEN DING[1] and XIAOHUA HOU[1]

Departments of [1]Gastroenterology and [2]Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China

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Abstract. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an accurate technique for sampling the pancreas and mediastinum; however, limited data are available for other mass lesions. The aim of this study was to explore the value of EUS-FNA in the differential diagnosis of all mass lesions. Data from patients who underwent EUS-FNA for the diagnosis of mass lesions, including pancreatic, mediastinal, celiac and retroperitoneal lesions were retrospectively analyzed. The accuracy was calculated by comparing the results of FNA with the results of pathological examination or follow-up surveillances in non-operated cases. A total of 150 cases were included. The location of the mass varied from the pancreas (n=62) to the mediastinum (n=29), gastrointestinal tract (n=36), celiac cavity and retroperitoneum (n=23). The sensitivity and Youden's index of EUS-FNA in the diagnosis of all lesions were 92.97% and 0.93 respectively. The accuracy of diagnosis of pancreatic, mediastinal, gastrointestinal, celiac and retroperitoneal lesions was 85.48, 89.66, 83.33 and 78.23%, respectively. Masses were categorized into parenchymal organs (n=66), luminal organs (n=36) and enlarged lymph nodes (n=33). Lesions in parenchymal organs were likely to be bigger than those in luminal organs (P=0.03) and enlarged lymph nodes (P=0.01). For solid and cystic masses, which constituted 63.3 and 14.7% of the total masses, no significant difference in diagnostic accuracy was observed (P=0.56); however, lesion sizes were significantly different between these two groups (P=0.04) and the majority of cystic masses were identified in women (P=0.03). Malignant lesions were more common in older (P=0.01) and male (P=0.03) patients. In conclusion, EUS-FNA is an effective tool in the diagnosis of unexplained mass lesions; it influences the management of patients by enabling the appropriate treatment to be identified.

Correspondence to: Professor Zhen Ding, Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430022, P.R. China
E-mail: docd720@126.com

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Introduction

Despite advances in diagnostic imaging techniques and the use of tumor markers, even with the development of spiral computed tomography (CT) and positron emission tomography (PET), the differentiation of pancreatic cancer and focal pancreatitis or other mass lesions, such as retroperitoneal or pelvic lesions remains problematic (1-3). Since the first report of endoscopic ultrasound (EUS)-fine needle aspiration (FNA) of the pancreas by Vilmann *et al* (4) in 1992, EUS-FNA has been considered as a standard method for the diagnosis of mass lesions in the pancreas because it is an effective and accurate procedure with a low complication rate (5-8) and, moreover, it provides cytological or pathological confirmation of benign or malignant disease. It has also been recognized as a minimally invasive and maximum accurate diagnostic procedure (7,9). Furthermore, this least invasive procedure is often suitable for use in the endoscopic procurement of tissue from patients with unresectable tumors (10).

While EUS-FNA has been increasingly used as a valuable diagnostic modality for mass lesions, the majority of studies have collectively investigated primary pancreatic and mediastinal lesions, including focal pancreatitis, pancreatic neuroendocrine neoplasms and mediastinal lymphadenopathy (5,10-15), the accuracy of which has previously been presented in the form of a meta-analysis (16-18). However, very few studies have examined other types of mass lesions, such as those affecting the enterocoelia or retroperitoneum, due to the anatomical structural challenges (19,20). Therefore, the aim of the present study was to evaluate the diagnostic accuracy of EUS-FNA and to investigate the associations of diagnostic findings with various types of mass lesions.

Materials and methods

Patients. A total of 150 patients presenting to the Department of Gastroenterology, Union Hospital, Tongji Medical College (Wuhan, China) and undergoing EUS-FNA of mass lesions over a 4-year study period, from June 2010 to March 2014, were enrolled in the study. Suspicions of mass lesions were based on radiological findings or abdominal imaging such as

magnetic resonance imaging (MRI), abdominal CT or transabdominal ultrasound. Targets included gastrointestinal and extra-gastrointestinal mass lesions and peri-gastrointestinal lymph nodes. Patients were excluded if they had a blood coagulation disorder or had used non-steroidal anti-inflammatory drugs or other anticoagulant drugs within 14 days of the EUS-FNA. The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). All patients provided signed informed consent.

EUS technique. EUS was performed using an Olympus Ultrasound Processor (EU-ME1) with a UCT-240 linear endoscope (Olympus America, Inc., Center Valley, PA, USA). FNA was operated under EUS guidance with 0, 5 or 10 ml of suction applied during aspiration with either a 22-gauge or 19-gauge needle (22G Endocoil or 19G Echotip; Cook Endoscopy, Winston-Salem, NC, USA). Needle passes were processed about 1 to 6 times until the operator considered that sample adequacy was achieved. Samples were prepared by EUS assistants trained by cytology technicians and sent to the pathology department for evaluation. EUS-FNA was performed by two well-trained (>1,500 EUS procedures) endoscopists.

Data collection. Data collected included patient demographics (gender, age and mass lesion location) and procedure details (tumor characteristics and number of needle passes). Post-procedure complications were defined as any symptoms requiring emergency department evaluation, including bleeding, pneumothorax, perforation, pancreatitis and other severe complications.

A diagnostic result was defined by cytological or histological findings as EUS-FNA biopsy positive for tumor cells of any type, acid-fast bacillus, mesenchymoma or leiomyoma. Cytological or histological findings of negative for atypical cells (inflammatory cells, phagocytes or epithelial cells), suspicious and not obtaining adequate sample were considered non-diagnostic. All the EUS-FNA results were compared with the gold standard of surgical findings or follow-up examinations in non-operated cases over a minimum period of 6 months and a final diagnosis was determined.

Statistical analysis. Performance characteristics including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy were calculated. Continuous variable results were reported as means with/without standard deviation (SD). Dichotomous variables are shown as percentages with or without 95% confidence intervals (CIs). The χ^2 test was used for comparisons of rates, and means between two groups or three groups were assessed with independent-samples t-tests and one-way analysis of variance, respectively. Statistical analyses were performed with SPSS software, version 19.0 (IBM SPSS, Armonk, NY, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

General characteristics. Data for 150 patients (57 female and 93 male) undergoing EUS-FNA evaluation for mass lesions were entered into a designed database. Study patients were relatively old (mean age, 54.3 years, range, 21-80 years). The mean lesion size was 3.5±1.9 cm (range, 0.4-10 cm). The numbers of pancreatic, mediastinal, gastrointestinal, celiac and retroperitoneal lesions were 62 (41.3%), 29 (19.3%), 36 (24.0%) and 23 (15.4%) cases, respectively. The number of passes performed per patient in this study was between 1 and 6 with a mean of 2.4. The basic characteristics and details of all cases (location and size of the lesions, as well as the results of EUS-FNA) are listed in Table I.

EUS-FNA findings. Adequate specimens for pathological assessment or cytological examination were obtained for 136 patients (90.7%) and 23 (15.3%) cases had indeterminate results (non-diagnostic, atypical or suspicious). The EUS-FNA diagnoses were as follows: 87 (58.0%) had malignant cytology, 3 (2%) were suspicious for neoplasia, 6 (4.0%) had atypical cells and 40 (26.7%) were found to be benign. There were 14 cases (9.3%) where the FNA was non-diagnostic (an inadequate sample was obtained). Of the 23 patients with indeterminate results, 2 patients had surgical pathology and in the remaining 21 cases, the diagnosis was based on clinical follow-up examination. There were no false positive cases or false negative cytological cases. The EUS-FNA findings are detailed in Table II.

Diagnostic value of EUS-FNA. The overall diagnostic rate of EUS-FNA for all lesions was 84.67% (127/150; 95% CI, 78.90-90.44%), and the sensitivity, specificity, PPV, NPV, accuracy and Youden's index for lesions at various locations are presented in Table III. The accuracy for mediastinal lesions was the highest (89.66%); however, celiac and retroperitoneal lesions had a diagnostic accuracy of only 78.2%, which may be due to the presence of vital interferential structures.

The masses were categorized into those associated with parenchymal organs (n=66), luminal organs (n=36) and enlarged lymph nodes (n=33). Parenchymal organs were more likely to have a larger lesion diameter compared with luminal organs (P=0.03) and enlarged lymph nodes (P=0.01). Otherwise, age, number of passes, sensitivity and accuracy were similar among the three categories of masses (P>0.05; Table IV). The accuracy of EUS-FNA in the diagnosis of parenchymal organs, luminal organs and enlarged lymph nodes was 86.36, 83.33 and 87.88% respectively.

Moreover, 95 (63.3%) lesions were considered as solid masses and 22 (14.7%) as cystic masses. There was no statistically significant difference in patient age (P=0.81) and diagnostic sensitivity (P=1.00) between the these two types of mass. The accuracy of diagnosis of solid masses was higher than that of cystic masses (85.26 vs. 77.27%), although with no statistical significance (P=0.56). Furthermore, no correlation was observed with respect to the number of passes (P=0.38). However, lesion size (P=0.04) and gender (P=0.03) had a statistically significant difference between these two groups (Table V). Cystic masses were found to have a larger diameter compared with solid masses (P<0.05). The majority of solid masses were identified in men and cystic masses in women.

Masses were also categorized into malignant and benign masses. The final diagnosis, which was confirmed by the pathological examination or follow-up surveillances, was malignant in 100 cases and benign disease in 50 cases. The most frequently

Table I. Basic information of lesion characteristics for all 150 patients, EUS-FNA results and final diagnosis.

Lesion location	Final diagnosis	Gender, male/female	Mean age (years)	Mean size, (cm)	Mean no of. passes	EUS-FNA results	
						Positive	Negative
Pancreas (n=62)	Pancreatic cancer	25/7	58.28	3.19	2.00	26	6
	Chronic pancreatitis	1/2	51.33	2.34	2.00	3	0
	Autoimmune pancreatitis	2/1	58.00	3.60	2.00	1	2
	Solid pseudopapillary tumor	1/1	44.00	5.50	4.00	1	1
	Pancreatic neuroendocrine neoplasm	2/1	49.00	4.46	2.00	3	0
	Pancreatic tuberculosis	1/1	32.50	4.55	3.00	2	0
	Pancreatic pseudocyst	6/2	50.38	5.63	2.00	8	0
	True pancreatitis cyst	1/2	51.33	3.13	2.00	3	0
	Pancreatic cystadenoma	1/5	56.67	3.82	2.00	6	0
	Total	40/22	54.68	3.73	2.63	53	9
Mediastinum (n=29)	Mediastinal lymph node metastasis of lung cancer	5/3	56.00	3.60	2.14	8	0
	Mediastinal tumor	5/0	61.80	4.40	2.60	5	0
	Lymphoma	2/1	65.00	2.33	3.00	2	1
	Tuberculosis of mediastinal lymph node	3/1	35.25	2.86	2.25	4	0
	Phlogosis of mediastinal lymph node	3/3	54.83	2.28	2.60	4	2
	Sarcoidosis	0/2	52.50	2.95	3.00	2	0
	Nerve sheath tumors	0/1	59.00	3.00	3.00	1	0
	Total	18/11	54.69	2.98	2.46	26	3
Gastrointestinal tract (n=36)	Esophageal cancer	5/0	56.80	1.94	2.00	4	1
	Esophageal leiomyoma	2/1	40.66	3.25	3.00	3	0
	Esophageal tuberculosis	1/2	43.33	1.70	3.33	2	1
	Esophagitis	0/1	59.00	2.20	2.00	1	0
	Esophageal cyst	0/1	61.00	1.20	2.00	0	1
	Physiological thickening (esophagus, stomach and rectum)	4/4	53.75	1.92	2.00	8	0
	Gastric carcinoma	3/1	55.50	2.78	3.00	3	1
	Gastrointestinal stromal tumor	7/0	56.86	6.48	2.33	6	1
	Duodenitis	1/0	68.00	1.00	2.00	1	0
	Rectal carcinoma	3/0	48.33	1.24	4.20	2	1
	Total	26/10	53.31	2.78	2.61	30	6
Enterocoelia and retroperitoneum (n=23)	Lymphoma	1/5	58.67	3.50	1.67	5	1
	Peritoneal tuberculosis	0/1	22.00	3.50	3.00	1	0
	Celiac cyst	2/2	58.00	4.40	2.33	0	4
	Liver cancer	1/1	56.00	4.00	2.00	2	0
	Ewing's sarcoma of soft tissue	0/1	33.00	7.00	2.00	1	0
	Renal carcinoma	1/0	75.00	8.00	1.00	1	0
	Prostatic cancer	1/0	62.00	2.50	2.00	1	0
	Pseudomyxoma peritonei	1/0	68.00	3.70	4.00	1	0
	Nerve sheath tumors	0/1	65.00	4.50	2.00	1	0
	Celiac lymph node metastasis of liver cancer	2/2	46.00	2.25	2.00	4	0
	Omentum metastasis of ovarian cancer	0/1	49.00	2.30	2.00	1	0
	Total	9/14	54.52	3.95	2.13	18	5
All patients (n=150)		93/57	54.33	3.52	2.38	127	23

Enterocoelia lesions exclude pancreatic and gastrointestinal masses. EUS-FNA, endoscopic ultrasound-fine needle aspiration.

Table II. EUS-FNA cytological findings and final diagnoses of targeted mass lesions.

EUS-FNA diagnosis	N	Final diagnosis (n)		Final diagnosis of malignancy type
		Benign	Malignant	
Benign	40	40	0	-
Malignant	87	0	87	See Table I
Atypical	6	2	4	Pancreatic cancer (n=3) and lymphoma in mediastinum (n=1)
Suspicious	3	1	2	Esophageal cancer (n=1) and rectal carcinoma (n=1)
Non-diagnostic	14	7	7	Lymphoma in retroperitoneum (n=1), pancreatic cancer (n=3), solid pseudopapillary tumor (n=1), gastric carcinoma (n=1) and gastrointestinal stromal tumor (n=1)
Total	150	50	100	

EUS-FNA, endoscopic ultrasound-fine needle aspiration.

Table III. Diagnostic accuracy of EUS-FNA evaluated on the basis of surgical findings or follow-up examination.

Lesion location	Lesion size (cm)	No. of passes	Sensitivity (%)	Specificity[a] (%)	PPV (%)	NPV (%)	Accuracy (%)	Accuracy (95% CI)	Youden's index[a]
Pancreas	1.60-8.00	2-6	92.98	-	100.00	0.00	85.48	76.71-94.25	-
Mediastinum	1.10-5.00	2-5	96.30	-	100.00	0.00	89.66	78.58-100.00	-
Gastrointestinal	0.40-7.00	2-6	91.67	100.00	100.00	80.00	83.33	71.15-95.51	0.92
Celiac or retroperitoneal	0.60-9.60	1-4	90.00	-	100.00	0.00	78.23	61.40-95.12	-
Total	0.40-9.60	1-6	92.97	100.00	100.00	47.06	84.67	78.90-90.44	0.93

[a]Specificity and Youden's index could not be calculated for lesions of the pancreas and mediastinum because the number of true negatives could not be determined on the basis of the available data. EUS-FNA, endoscopic ultrasound-fine needle aspiration; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

observed type of malignant mass was pancreatic adenocarcinoma (n=32; 21.3%). Other types of neoplasia included lymph node metastasis of cancer (n=12; 8.0%), lymphoma (n=9; 6.0%) and esophageal tumors (n=5; 3.3%). Older patients (P=0.01) and men (P=0.03) were more likely to have malignant tumors. No association was found between the FNA accuracy of benign (80.00%) and malignant masses (87.00%), with a P-value of 0.26 (Table VI). No complications were identified to be associated with the procedure in any of the 150 patients.

Discussion

Multiple imaging modalities and techniques, including PET, CT, MRI and ultrasound, have been used to evaluate mass lesions; however, small or special lesions pose a diagnostic challenge (21,22). EUS has been demonstrated to be the most significantly advanced procedure, especially for smaller lesions (<3 cm) (23). However, distinguishing malignant from benign etiologies using EUS can be difficult in certain clinical scenarios, such as chronic pancreatitis and pancreatic neoplasm (1). EUS can only provide the tumor location, size, shape, echo and boundary conditions, and is not able to provide a histological diagnosis. EUS-FNA was introduced to aid in the diagnosis and differentiation between lesion types. Distinguishing adenocarcinoma from local pancreatitis has important implications for prognosis and the method of treatment. A review of the literature concerning EUS-FNA of pancreatic lesions reveals a 78-95% sensitivity, 75-100% specificity, 98-100% PPV, 46-80% NPV and 78-95% accuracy (24-26). The present study found that the accuracy of diagnosis of pancreatic lesions was 85.48% (53/62; 95% CI 76.71-94.25%; Table II). However, EUS-guided biopsy was not feasible in all cases (Table I). Nine patients were considered non-diagnostic for pancreatic lesions because the mean number of needle passes was insufficient (2.6 passes) and an adequate sample was not obtained. LeBlanc *et al* (27) recommend that at least seven passes with a fine needle into pancreatic lesions are required to ensure a high degree of certainty for making a correct diagnosis.

Among the patients in the present study, there was one case that was diagnosed as a mass-forming focal chronic pancreatitis (MFP); yet misdiagnosed as pancreatic cancer before surgery or FNA was performed because pancreatic carcinoma could not be absolutely ruled out under EUS (Figs. 1 and 2). Contrast harmonic echo-EUS may increase the accuracy of detection of malignant lesions in difficult cases (patients with chronic pancreatitis or biliary stents) (28,29) and repeat EUS-FNA is able to provide a conclusive diagnosis in the majority of cases (30).

Table IV. Patient characteristics for masses of parenchymal organs, luminal organs and enlarged lymph nodes (n=135).

Characteristic	Parenchymal organs (n=66)	Luminal organs (n=36)	Enlarged lymph nodes (n=33)	P-value
Male	43	26	16	P=0.11
Female	23	10	17	
Mean age (years)	55.14	53.31	53.15	P=0.65
Mean lesion size (cm)	3.78	2.78	2.92	P^a=0.03; P^b=0.01
Mean no. of passes	2.52	2.61	2.30	P=0.70
Sensitivity (%)	93.44	91.67	96.67	P=0.73
Specificity (%)	-	100.00	-	-
PPV (%)	100.00	100.00	100.00	-
NPV (%)	0.00	80.00	0.00	-
Accuracy (%)	86.36	83.33	87.88	P=0.85

Unlabeled P-values were determined for comparison of the parenchymal organs, luminal organs and enlarged lymph nodes patient groups. [a]P-value determined for comparison of parenchymal organs and luminal organs. [b]P-value determined for comparison of parenchymal organs and enlarged lymph nodes. Parenchymal organs include all pancreatic, hepatic, renal and prostatic lesions. Luminal organs comprise all gastrointestinal masses. Diseases of enlarged lymph nodes are constituted by lymphoma, mediastinal lymph node metastasis of lung cancer, celiac lymph node metastasis of liver cancer, sarcoidosis, tuberculosis and phlogosis of mediastinal lymph node. Certain specificity percentages and P-values could not be calculated because the number of true negatives could not be determined on the basis of available data. PPV, positive predictive value; NPV, negative predictive value.

Table V. Comparison of lesions and clinical characteristics in patients with final diagnoses of solid and cystic masses (n=150).

Characteristic	Solid masses (n=95)	Cystic masses (n=22)	P-value
Male	67	10	P=0.03
Female	28	12	
Age (years), mean ± SD	54.79±12.49	54.10±10.12	P=0.81
Lesion size (cm), mean ± SD	3.36±1.84	4.20±2.35	P=0.04
No. of passes, mean ± SD	2.63±1.41	2.14±0.38	P=0.38
Sensitivity (%)	92.41	89.47	P=1.00
Specificity (%)	100.00	-	-
PPV (%)	100.00	100.00	-
NPV (%)	57.14	0.00	-
Overall accuracy (%)	85.26	77.27	P=0.56

P-values were determined for comparison of solid masses and cystic masses. Cystic masses included pancreatic pseudocyst, true pancreatitis cyst, pancreatic cystadenoma, esophageal cyst and celiac cyst. Solid masses included other lymphadenectasis and cystic diseases. Certain specificity percentages and P-values could not be calculated because the number of true negatives could not be determined on the basis of available data. PPV, positive predictive value; NPV, negative predictive value; SD, standard deviation.

Mediastinal lesions (lymph nodes) may be caused by lymphoma, sarcoidosis or cancer metastasis. As there are various potential types of pathogenesis, blind treatment, such as surgery, may be an unnecessary burden for a patient. EUS-FNA can provide important information for the further management of patients. In the present study, the diameters of mediastinal lesions were 1.1-5.0 cm, and the sensitivity and accuracy of the EUS-FNA were 96.30 and 89.66%, respectively, which is concordant with previously reported data (14). However, the most inadequate specimens for pathological assessment or cytological examination were obtained for celiac and retroperitoneal lesions (5/23, 21.74%). Four cases were celiac cysts. A study conducted by Maleki *et al* (31) showed that the primary tumor site for such tumors included the colon or rectum, urinary bladder, prostate and ovary, with EUS-FNA exhibiting 87% sensitivity and a diagnostic accuracy of 90%. The accuracy determined in the present study was lower (78.23%). This may be due to the presence of vital interferential structures or the operating distance; power conduction may not have been uniform, and the needle may have failed to penetrate the mass. A further prospective study with a large numbers of patients is necessary to confirm these results. Real-time onsite cytopathology to increase the diagnostic yield and reduce the number of indeterminate or unsatisfactory samples from EUS-FNA may solve this problem (32-34).

Table VI. Comparison of lesions and basic characteristics in patients with final diagnoses of benign and malignant masses.

Lesion type	Mean age (years)	Male	Female	Lesion size (cm)	Mean no. of passes	Sensitivity (%)	Specificity (%)	Accuracy (%)
Benign (n=50)	50.54	25	25	3.87	2.74	91.43	100.00	80.00
Malignant (n=100)	56.22	68	32	3.20	2.35	93.55	-	87.00
P-value	0.01	0.03		0.08	0.16	0.98	-	0.26

P-values were determined for comparison of benignant and malignant masses. Malignancy included clearly and potentially malignant tumors, such as gastrointestinal stromal tumor. Benign included non-malignant conditions. Certain specificity percentages and P-values could not be calculated because the number of true negatives could not be determined on the basis of available data. PPV, positive predictive value; NPV, negative predictive value.

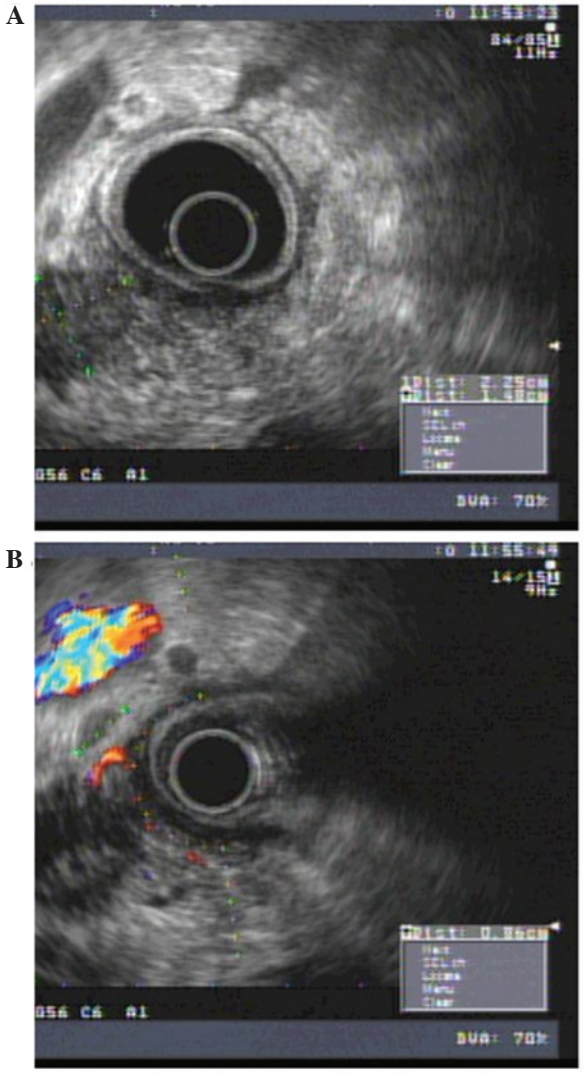

Figure 1. Endoscopic ultrasound (EUS) was suggestive of pancreatic cancer preoperatively because the ultrasonographic features of mass-forming focal chronic pancreatitis (MFP) are similar to those of pancreatic carcinoma and could not be absolutely excluded. Under EUS, the pancreatic body and tail were observed to be significantly narrowed (diameter <1 cm). (A) There was a low echo lesion at the head of pancreas (2.3x1.5 cm), breaking through the pancreatic envelope, and (B) a 1.1 cm enlarged lymph node.

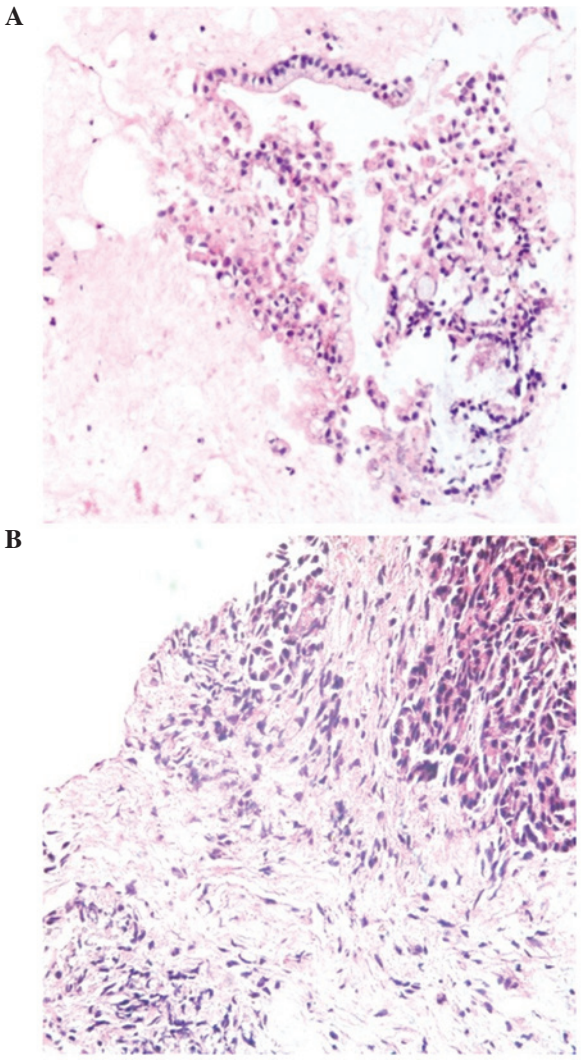

Figure 2. Histological examination of the cells obtained from the fine needle biopsy helped to distinguish between benign and malignant lesions. (A) Endoscopic ultrasound-guided-fine needle aspiration confirmed the pancreatic lesion was mass-forming focal chronic pancreatitis [MFP: hematoxylin and eosin (H&E) staining, magnification, x200]. (B) Postoperative pathology also confirmed that the pancreatic lesion was MFP (H&E staining, magnification, x200).

In addition to use as a diagnostic technique, EUS-FNA has also been developed as a therapeutic means, such as for use in celiac plexus neurolysis, pseudocyst drainage, radiation therapy, the delivery of antitumor agents and bile duct drainage (35,36). The total complication rate across the

reported studies concerning EUS-FNA ranges from 0 to 2.0% (37-39). With the exception of some instances of mild abdominal discomfort, no complications associated with EUS-FNA were observed in the 150 patients in the present study.

In conclusion, EUS-FNA has emerged as a powerful modality for acquiring cytology results from types of lesion diseases. The results of the present study demonstrated that EUS-FNA provides an incomparable superiority for the investigation of various masses and is able to diagnose suspected neoplastic lesions with a high sensitivity and specificity. Furthermore, it is a safe procedure with low complication rates, although more high-quality, larger-scale and prospective studies are required.

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