

ORIGINAL ARTICLE

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Predictors of Malignancies in Patients with Inconclusive or Negative Results of Endoscopic Ultrasound-guided Fine-needle Aspiration for Solid Pancreatic Masses

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Background/Aims: This study analyzed the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for pancreatic solid masses in patients with or without chronic pancreatitis as well as the clinical parameters relevant to a malignancy when EUS-FNA was negative or inconclusive.

Methods: A total of 97 patients, who underwent EUS-FNA for solid pancreatic masses over 2 years at a single institution, were evaluated. All patients underwent EUS-FNA for 3-5 passes with 22 or 25 G needles without an on-site cytopathologist. The final diagnosis was obtained by surgery or compatible clinical outcomes for a more than 12 month follow-up. The diagnostic yields in the patients with or without chronic pancreatitis were compared and the histories and laboratory data relevant to pancreatic ductal adenocarcinoma (PDAC) or pseudo-tumor were analyzed.

Results: The final diagnoses were adenocarcinoma in 88 patients (90.7%) and inflammatory pseudo-tumor in 9 (9.3%). The results of EUS-FNA were adenocarcinoma (74), suspicious (7), atypical (5), negative (10), and inadequate specimen (1). The diagnostic accuracies were 76.9% and 91.6% in patients with or without chronic pancreatitis, respectively. Among the 23 cases with non-diagnostic results of EUS-FNA, PDAC was finally diagnosed in 5 out of 7 suspicious, 3 out of 5 atypical, and 5 out of 10 negative cytology cases. The clinical parameters related to a pseudo-tumor were a history of alcohol consumption and pancreatitis, and normal alkaline phosphatase levels.

Conclusions: The diagnostic accuracy of pancreatic masses in the background of chronic pancreatitis was low. When EUS-FNA produced inconclusive results, the histories of alcohol consumption, pancreatitis, and serum levels of alkaline phosphatase are useful for making a final diagnosis. (*Korean J Gastroenterol* 2018;71:153-161)

Key Words: Pancreatic cancer; Chronic pancreatitis; Endosonography; Fine needle aspiration

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is charac-

terized by hypovascular lesions and extensive interstitial fibrosis. These features are helpful for a presumptive diagnosis by abdominal imaging; however, a pathology diagnosis

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is necessary to determine the therapeutic plans. Endoscopic ultrasound (EUS) is useful for specific image features and a definitive diagnosis can be made with EUS-guided fine-needle aspiration (EUS-FNA).¹⁻³ On the other hand, a diagnosis of PDAC in the background of chronic pancreatitis is still challenging because extensive fibrosis leads to inadequate sampling and incorrect targeting.^{1,2} The diagnostic accuracy of EUS-FNA for PDAC was 85-90%^{1,3} in patients with a normal background, which decreased to 54-74% in those with chronic pancreatitis.^{4,5} Because the diagnostic power of EUS-FNA for pancreatic solid masses was specific, the presence of malignant cells can be diagnosed easily as PDAC. On the other hand, it was difficult to determine whether follow-up or surgical resection were required when the results of EUS-FNA were negative or inconclusive, such as atypical or suspicious.^{1,3}

Various methods, such as lengthening of the passages of FNA, performing a core biopsy instead of cytology, pathology studies by an on-site pathologists, or repeated FNA on different days are recommended to improve the diagnostic accuracy.^{1,6-8} In addition, the patient's characteristics are also helpful for clinical decision making, when the cytology data are negative or inconclusive. The weight loss, elevated serum levels of cancer antigen (CA) 19-9, smoking history, no history of pancreatitis or alcohol intake, and evidence of a bile duct obstruction were relevant to a pancreatic malignancy. On the other hand, the proportions of inconclusive results, final diagnosis of these patients, and relevant clinical parameters have been inconsistent in many studies.^{5,9-13}

This study examined the diagnostic yields of EUS-FNA for pancreatic solid masses in patients with or without chronic pancreatitis. In addition, the clinical parameters relevant to a final diagnosis were determined when EUS-FNA was non-diagnostic.

SUBJECTS AND METHODS

1. Patients

Ninety-nine patients were admitted to Chungbuk National University Hospital from May 2013 to May 2015 for solid masses in the pancreas. The patients' medical records were reviewed retrospectively. The demographics, including age, sex, presenting symptoms such as abdominal pain, jaundice, weight loss, and fever, and habits regarding alcohol intake and smoking, were recorded. Alcohol consumption or smok-

ing habit were positive for patients with current chronic heavy drinkers (average total alcohol intake of ≥ 60 g/day) or regular current smokers (≥ 1 pack/day), respectively. Liver function tests, serum glucose, and serum CA 19-9 at admission were collected. All patients underwent an abdominal computerized tomography scan before EUS-FNA. Chronic pancreatitis was diagnosed based on the following criteria, which is applicable to the Korean population: the presence of at least one finding among irregular main duct dilatation and atrophy, the presence of pancreatic duct stones, protein plugs, or pancreatic parenchymal calcification by an abdominal computerized tomography scan.¹⁴ A final diagnosis was made by the surgical pathology or by compatible clinical findings during a follow-up of more than 12 months or until death. Stable imaging, benign pathology, or survival for 12 months after EUS-FNA was considered benign. The diagnosis of a malignancy was based on a positive pathology, local invasion, and metastasis on imaging, or death within 12 months from cancer-associated causes.

2. EUS-FNA

Two experienced endoscopists performed this procedure without an on-site cytopathologist. EUS was conducted using linear EUS (GF-UCT240-AL5; Olympus, Tokyo, Japan). FNA was performed for 3-5 passes with 22 or 25 G needles (Echotip; Wilson-Cook, Winston Salem, NC, USA) for lesions in the body/tail or uncinate/head of the pancreas, respectively.¹⁵ The fanning technique and suction method were applied. The stomach and duodenum were sites of needle passage for lesions in the body/tail and uncinate/head of the pancreas, respectively. The stylet was introduced to the needle, and the extruded material was placed onto glass slides for a primary inspection. The aspirated material was smeared carefully onto glass slides and fixed in a 96% alcohol solution for a cytology examination. The smear on slides were performed on-site. Diff-Quik histological staining (Baxter Healthcare, Deerfield, NY, USA), Papanicolaou staining, and cell blocks with hematoxylin and eosin stains were prepared in the cytology laboratory.

3. Cytology interpretation

One experienced pathologist interpreted all the Papanicolaou staining and cell blocks. The cytological findings were categorized as 'inadequate', 'negative', 'atypical', 'suspicious', and

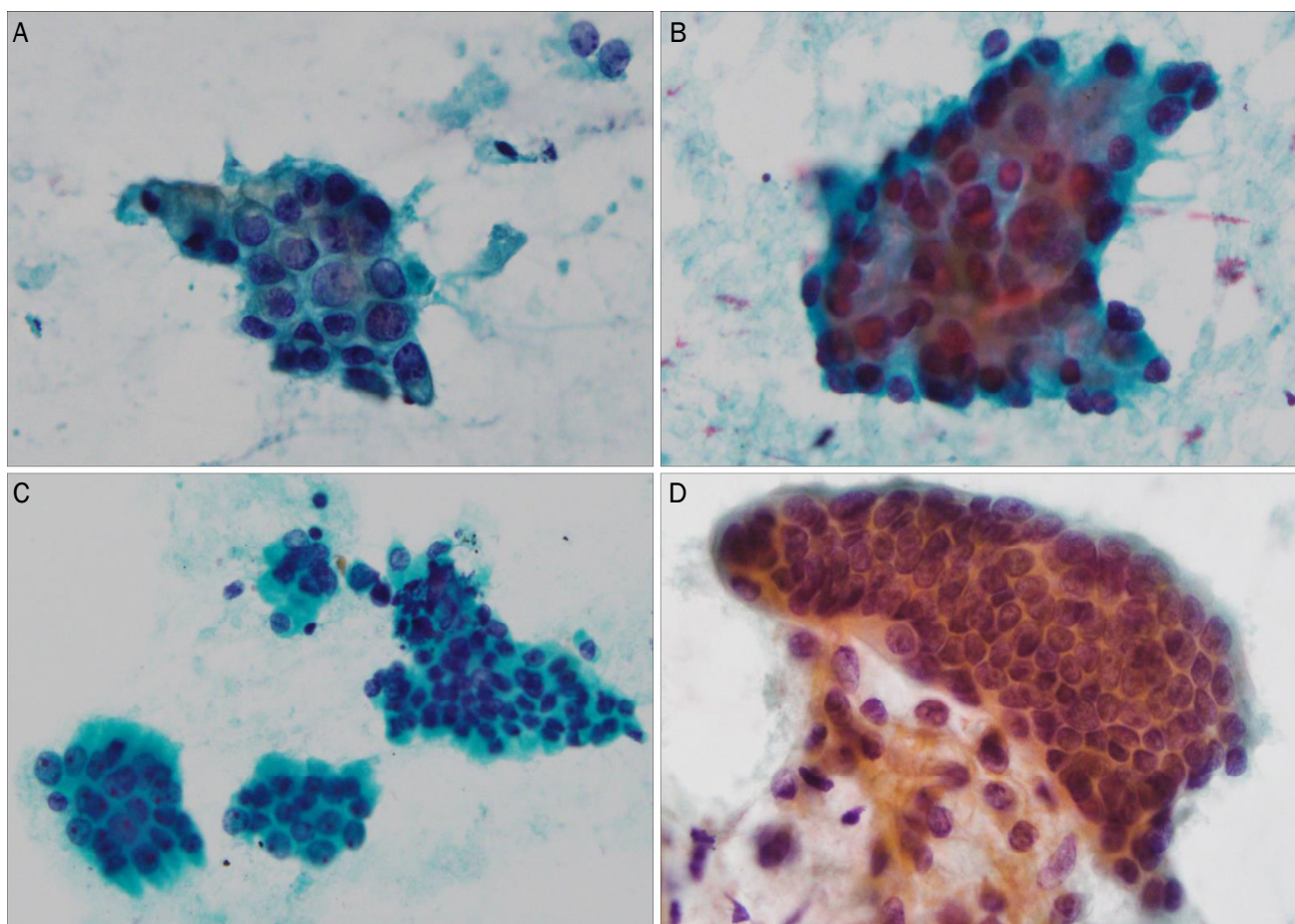


Fig. 1. Representative images of the pancreatic cytology (papanicolaou staining, magnification $\times 400$). (A) Positive for a malignancy. (B) Suspicious for a malignancy. (C) Atypical cells. (D) Negative for a malignancy.

'malignant'.¹⁶ The 'suspicious' category is defined as atypical cells severe enough to suspect a PDAC, but the quantity of cells is insufficient to prove positive for a malignancy. The 'atypical' category is that the level of atypical cells is more than that of benign or reactive, but insufficient for a diagnosis of the 'suspicious' category (Fig. 1). The atypical or suspicious cytology results were interpreted as negative or neoplasms, respectively.

4. Clinical parameters for predictors of malignancy

Patients with negative or inconclusive results in EUS-FNA for PDAC, were selected. The clinical parameters relevant to PDAC or pseudo-tumors were analyzed. Patients with a PDAC or pancreatic pseudo-tumor were compared using the demographic data, history of alcohol or smoking, presenting symptoms, and laboratory data (Fig. 2).

5. Statistical analysis

The diagnostic yields of EUS-FNA for pancreatic masses, including sensitivity, specificity, and overall accuracy, were assessed. The data were analyzed with SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). The continuous variables are presented as the mean \pm standard deviation and the two groups were compared using a Mann-Whitney U test. The categorical variables were compared using a chi square test or Fisher's exact test. p-values less than 0.05 were considered significant.

RESULTS

1. Patient characteristics of pancreatic solid mass

Among the ninety-nine patients who underwent EUS-FNA for pancreatic solid masses, two patients, one with neuroendocrine tumor and the other with a metastasis, were excluded. The final diagnoses were done by surgery in 7

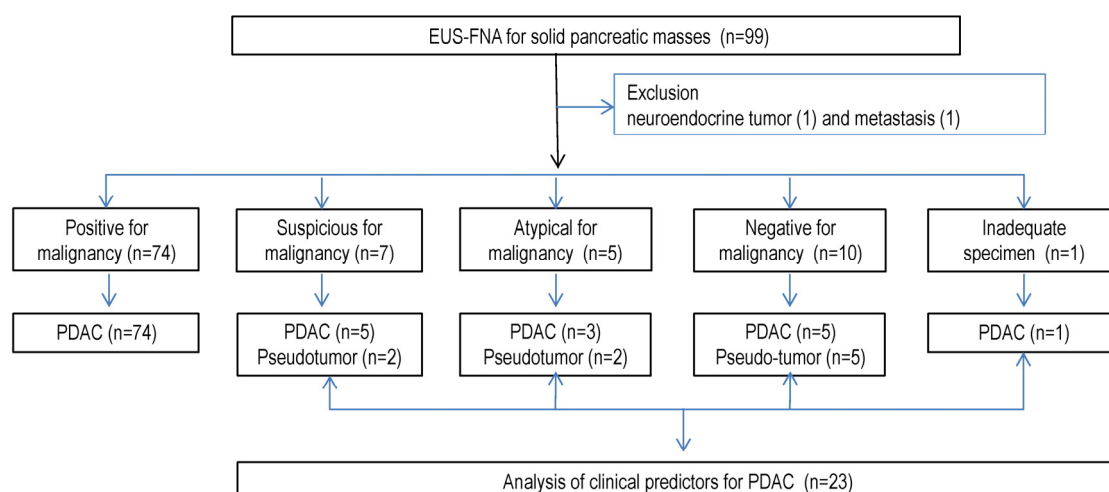


Fig. 2. Flow chart of the diagnostic process. Of the 99 patients who underwent EUS-FNA, each patient with a neuroendocrine tumor and metastasis on the pancreas was excluded. Twenty-three patients with negative or non-diagnostic EUS-FNA were included in the analysis of the clinical parameters relevant to pancreatic cancers or pseudo-tumors. EUS-FNA, endoscopic ultrasonography guided fine needle aspiration; PDAC, percentages of pancreatic ductal adenocarcinoma.

Table 1. Characteristics of Patients with Pancreatic Masses

Parameters	Total (n=97)	Chronic pancreatitis		p-value
		No (n=84)	Yes (n=13)	
Mean age±SD	67.6±10.6	69.1±9.7	57.9±11.6	0.005
Male:Female	66:31	55:29	11:3	0.214
Symptoms				0.797
Abdominal pain	73 (75.3)	62 (73.8)	11 (84.6)	
Weight loss	9 (9.3)	8 (9.5)	1 (7.7)	
Jaundice	6 (6.2)	5 (6.0)	1 (7.7)	
Fever	6 (6.2)	6 (7.1)	0 (0.0)	
Uncontrolled hyperglycemia	3 (3.1)	3 (3.6)	0 (0.0)	
Alcohol drinking	15 (15.5)	8 (9.5)	7 (53.8)	0.001
Smoking	18 (18.5)	15 (17.9)	3 (23.1)	0.703
Laboratory data				
Glucose ≥126 mg/dL	57 (58.8)	50 (59.5)	7 (53.8)	0.767
CA 19-9 ≥37 U/L	69 (71.1)	61 (77.2)	8 (61.5)	0.299
ALT (IU/L) ≥1.5×UNL	24 (24.7)	20 (23.8)	4 (30.8)	0.730
ALP (IU/L) ≥220 U/L	39 (42.9)	35 (44.3)	4 (33.3)	0.545
Total bilirubin (mg/dL) ≥2	12 (12.4)	9 (10.7)	3 (23.1)	0.201
Mass locations				0.002
Pancreatic head	46 (47.4)	34 (40.5)	12 (92.3)	
Pancreatic body	23 (23.7)	23 (27.4)	0 (0.0)	
Pancreatic tail	28 (28.9)	27 (32.1)	1 (7.7)	
Mass size (cm)	3.4±1.3	3.5±1.3	2.7±0.7	0.049
Diameter of CBD ≥7 mm	18 (32.7)	18 (40.0)	0 (0.0)	0.021
Diameter of PD ≥3 mm	43 (51.2)	35 (48.0)	8 (72.7)	0.264
Final diagnosis				<0.0001
PDAC	88 (90.7)	82 (97.6)	6 (46.2)	
Pseudo-tumor	9 (9.3)	2 (2.4)	7 (53.8)	

Values are presented as n (%) unless otherwise indicated.

SD, standard deviation; CA, cancer antigen; ALT, alanine aminotransferase; UNL, upper normal limit; ALP, alkaline phosphatase; CBD, common bile duct; PD, pancreatic duct; PDAC, pancreatic ductal adenocarcinoma.

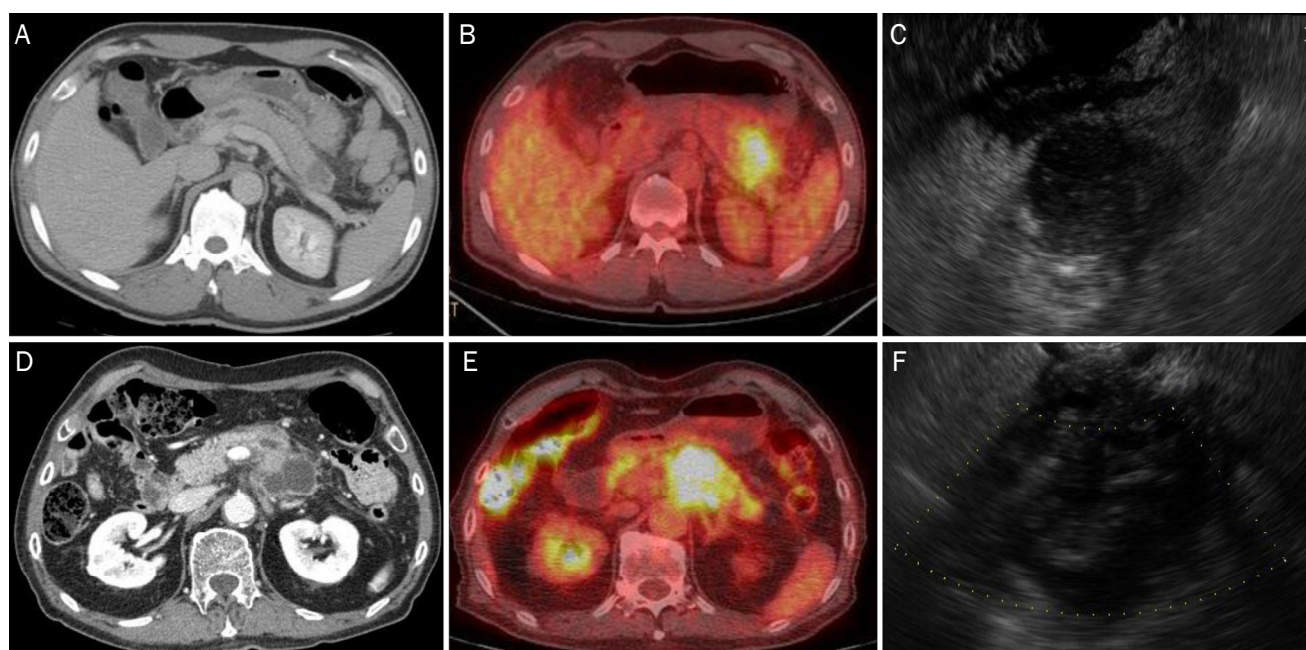


Fig. 3. Representative images of a pseudo-tumor (A-C) and pancreatic adenocarcinoma (D-F) in the setting of chronic pancreatitis. (A, D) Abdominal computed tomography scan. (B, E) Positron emission tomography-computed tomography scan. (C, F) Endoscopic ultrasound guided fine needle aspiration.

Table 2. Results of EUS-FNA and Final Diagnosis in 97 Patients with Pancreatic Solid Masses

EUS-FNA	PDAC (n=88)	Pseudo-tumor (n=9)	Total (n=97)
Malignancy	74 (84.1)	0 (0.0)	74 (76.3)
Suspicious	5 (5.7)	2 (22.2)	7 (7.2)
Atypical	3 (3.4)	2 (22.2)	5 (5.2)
Negative	5 (5.7)	5 (55.6)	10 (10.3)
Inadequate	1 (1.1)	0 (0.0)	1 (1.0)

Values are presented as n (%).

EUS-FNA, endoscopic ultrasonography guided fine needle aspiration; PDAC, pancreatic ductal adenocarcinoma.

(7.2%) patients and a clinical follow-up in 90 (92.8%) patients. Ninety-seven patients (male [M]:female [F], 66:31; mean age, 67.6 years) including 13 patients with chronic pancreatitis (13.4%) (M:F, 11:2; mean age, 57 years), and 84 patients without chronic pancreatitis (86.6%) (M:F, 55:29; mean age, 69 years) were enrolled (Table 1). The presenting symptoms upon admission were abdominal pain (75.3%), weight loss (9.3%), jaundice (6.2%), fever (6.2%), and uncontrolled hyperglycemia (glycosylated hemoglobin $\geq 7\%$, 6.2%). Patients with chronic pancreatitis had a history of alcohol consumption, were younger, and had a smaller mass located in the pancreas head with a normal common bile duct diameter compared to those without pancreatitis. The final diagnosis was PDAC in 88 (90.7%) patients and inflammatory pseudo-tumor in 9 (9.3%) patients (Fig. 3). PDAC was diag-

nosed in 6 (46.2%) and 82 (97.6%) patients with or without pancreatitis, respectively.

2. Diagnostic accuracy and factors related with diagnostic yields

EUS-FNA revealed a malignancy in 74 patients, suspicions of a malignancy in 7 patients, atypical in 5 patients, and negative in 10 patients. One sample was inadequate for interpretation because of the poor cellularity (Table 2). No complications were encountered during the procedures. The sensitivity, specificity, and diagnostic accuracy in the presence or absence of pancreatitis were 83.3%, 71.4%, and 76.9%; and 91.4%, 100%, and 91.6%, respectively (Table 3). The group contained 32 patients with non-diagnostic cytology, 7 patients with 'suspicious' findings, 5 patients with 'atypical'

Table 3. Diagnostic Accuracy of EUS-FNA with or without Chronic Pancreatitis

Results	Chronic pancreatitis		Total (n=97)
	No (n=84)	Yes (n=13)	
True positive	74	5	79
True negative	2	5	7
False positive	0	2	2
False negative	7	1	8
Indeterminate	1	0	1
Sensitivity	91.4 (83.2-95.8) ^a	83.3 (43.7-97.0) ^a	90.8 (82.9-95.3) ^a
Specificity	100.0 (34.2-100.0) ^a	71.4 (35.9-91.8) ^a	77.8 (45.3-93.7) ^a
Accuracy (%)	91.6	76.9	89.6

^aPercent (95% confidence interval).**Table 4.** Predictors of Malignancy in Patients with Inconclusive or Negative EUS-FNA for Solid Pancreatic Masses

Parameters	PDAC (n=14)	Pseudo-tumor (n=9)	p-value
Mean age±SD	65.4±10.0	58.7±15.5	0.215
Male:Female	10:4	7:2	1.000
Symptoms			0.392
Abdominal pain	8 (57.1)	8 (88.9)	
Weight loss	1 (7.1)	0 (0.0)	
Jaundice	2 (14.3)	0 (0.0)	
Fever	1 (11.1)	1 (11.1)	
Uncontrolled hyperglycemia	2 (14.3)	0 (0.0)	
Alcohol drinking	1 (7.1)	5 (55.6)	0.018
Smoking	1 (7.1)	4 (44.4)	0.056
Chronic pancreatitis	1 (7.1)	7 (77.8)	0.001
Laboratory data			
Glucose ≥126 mg/dL	9 (64.3)	6 (66.7)	1.000
CA 19-9 ≥37 U/L	11 (84.6)	3 (37.5)	0.056
ALT (IU/L) ≥1.5×upper normal limit	4 (28.6)	2 (22.2)	1.000
ALP (IU/L) ≥upper normal limit	8 (66.7)	1 (12.5)	0.028
Total bilirubin (mg/dL) ≥2	2 (14.3)	2 (22.2)	1.000

Values are presented as n (%) unless otherwise indicated.

EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; SD, standard deviation; PDAC, pancreatic ductal adenocarcinoma; CA, cancer antigen; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

findings, and 10 patients with 'negative' findings. PDAC was finally diagnosed in 5 out of 7 'suspicious' cases, 3 out of 5 'atypical' cases, and 5 out of 10 'negative' cases.

3. Clinical parameters related with malignancy

PDAC revealed less alcohol consumption (7.1% versus 55.6%, $p=0.018$), less chronic pancreatitis (7.1% versus 77.8%, $p=0.001$), and frequent elevated alkaline phosphatase levels (66.7% versus 12.5%, $p=0.028$) compared to pseudo-tumors. Elevated CA 19-9 levels and a non-smoking history were related to PDAC; however, the findings were not statistically significant. There were no differences in age, sex, presenting symptoms, and serum bilirubin levels (Table 4). The percentages of PDAC were 71.4%, 80%, 20%, and 0% ac-

cording to the number of clinical parameters of 0, 1, 2, and 3, respectively (Fig. 4). The percentage of PDAC in patients with low risk (≥ 2) and high risk (< 2) malignancies were 16.7% and 76.5%, respectively.

DISCUSSION

This study showed that the diagnostic accuracy of EUS-FNA for pancreatic solid masses in the presence of coexisting pancreatitis was lower than those without pancreatitis. 'Suspicious' or 'atypical' categories by EUS-FNA were more frequent in patients with chronic pancreatitis than in those without it. When the EUS-FNA results were negative or inconclusive, the histories of alcohol consumption, pancreatitis,

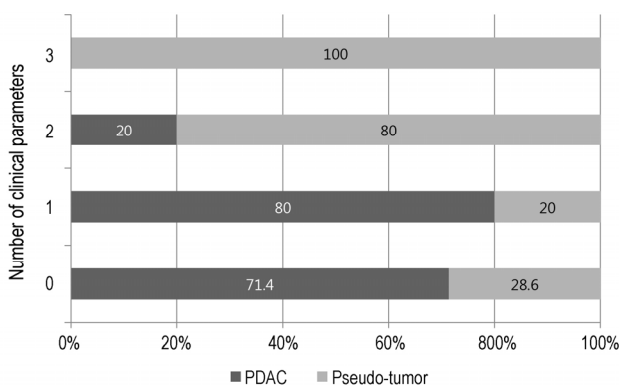


Fig. 4. Percentages of PDAC or pseudo-tumors according to the number of clinical parameters relevant to pseudo-tumors (alcohol drinking, history of pancreatitis, normal alkaline phosphatase level). The percentages of PDAC were 71.4%, 80%, 20%, and 0% according to the number of clinical parameters of 0, 1, 2, and 3, respectively. PDAC, pancreatic ductal adenocarcinoma.

and serum levels of alkaline phosphatase were helpful for diagnosing pseudo-tumors or PDAC.

EUS-FNA of the pancreatic lesions has been reported to be a reliable and minimally invasive method for evaluating solid masses.^{3,17} The diagnostic yields of EUS-FNA were improved in recent years in prospective multicenter studies¹⁷ compared to remote studies.¹⁸ EUS-FNA for pancreatic masses in the setting of a normal pancreas showed high sensitivity (85-90%) and high specificity (94.6-96.7%), positive likelihood ratio of 15.2 (95% confidence interval [CI], 8.5-27.3), and negative likelihood ratio of 0.17 (95% CI, 0.13-0.21).^{1,3}

On the other hand, the sensitivity of EUS-FNA was only 54-74% when sampling solid pancreatic masses in the setting of chronic pancreatitis,^{1,4,5} which was lower than in those without it.^{2,3} Chronic pancreatitis makes it difficult to target and interpret the cytology.^{1,2} A conglomeration of pancreatitis-induced lobulations may mimic a pancreatic mass and the presence of acoustic shadowing from a calcified stone may undermine the visibility of a neoplasm. Furthermore, the coexistence of collateral vasculature in patients with severe chronic pancreatitis makes the process of FNA more challenging. In addition, the cytology features that may mimic a malignancy in chronic pancreatitis are occasional atypical cells that include enlarged, single cells with large nuclei, degenerative vacuoles, and occasional mitosis.⁸ This study showed that the diagnostic accuracy of EUS-FNA of solid lesions in a normal pancreas was excellent, reaching 91.6%. Nevertheless, the accuracy was 76.9% in patients with chron-

ic pancreatitis. The sensitivity and specificity of EUS-FNA in diagnosing solid pancreatic masses underlying chronic pancreatitis were 83.3% and 71.4%, respectively.

The results of EUS-FNA were interpreted as the categories of 'non-diagnostic', 'negative', 'atypical', 'suspicious', and 'positive/malignant' by the Papanicolaou Society of Cytopathology guidelines.¹⁶ 'Suspicious' was interpreted as a malignancy and 'atypical' as pseudo-tumor.¹⁶ If 'atypical' and 'suspicious' cytology results were included to determine true neoplasms, the sensitivity increases to 91% (95% CI, 90-92); however, the specificity is decreased to 94% (95% CI, 93-96).¹³

The indeterminate categories of 'atypical' and 'suspicious' continue to be the most difficult for clinicians to interpret and manage. The proportions of 'suspicious' or 'atypical' cases were different in various studies. Previous studies reported that the frequency of the 'atypical' cases was 1-14%,^{19,20} and that of 'suspicious' cases was 3-5%.^{13,19} These wide variations between studies were attributed to on-site cytopathologists, reference standards, study type, and mass size and site.²⁰ This study showed similar frequencies of 'suspicious' (7.2%) and 'atypical' (5.2%) categories compared to previous studies. The frequency of the indeterminate category has been reported to be 20-35% among chronic pancreatitis patients.^{13,21} This study showed that the proportions of indeterminate categories are higher in patients with chronic pancreatitis than in those without it (30.8% versus 9.5%, $p=0.053$).

The percentage of pancreatic cancer in patients with suspicious or atypical categories showed wide variations. Previous studies reported that 25-100% of the atypical category and 73-96% of the suspicious category had been finally diagnosed with pancreatic carcinoma.^{13,20,21} This data was similar to previous data; 5 out of 7 (71.4%) suspicious and 3 out of 5 (60%) atypical cytology were PDAC.

In addition to EUS-FNA, the clinical characteristics may have a complimentary role to accurately diagnose pancreatic solid lesions. Many studies reported that the clinical parameters are useful for determining a malignancy when EUS-FNA showed inconclusive results. Old age, female gender, alcohol abstinence, jaundice, abdominal pain, weight loss, CA 19-9 level, hyperbilirubinemia, presence of a mass, dilation of the pancreatic duct, obstruction of the bile duct, no smoking history, diabetes, and no history of pancreatitis, have been re-

ported as factors relevant to a malignancy. On the other hand, these factors were different in other studies. Weight loss has been reported to be a strong indicator of a malignancy in patients with a mass in the suspicious category.¹³ In addition, age <50 years, male gender, African race, and the absence of jaundice were significantly associated with chronic pancreatitis not malignancy.⁵ Another study of the malignancy risk stratification of pancreatic masses in the setting of chronic pancreatitis reported that female gender, mass location at the pancreatic body, more than one mass number, hyperbilirubinemia (>7 $\mu\text{mol/L}$), and CA 19-9 (>37 U/mL) were associated with a malignancy.¹² Increased CA 19-9 was highly specific (97%) for a malignancy in older jaundiced patients, or when the preoperative level was greater than 150 U/dL.^{9,10} Elevated alkaline phosphatase and CA 19-9 were related to a malignancy.^{5,9-12} These results reflect a higher prevalence of chronic pancreatitis in younger male patients.¹⁹ Male gender and alcohol consumption were related to chronic pancreatitis.⁵ This study showed that a history of alcohol consumption and pancreatitis, and normal levels of alkaline phosphatase were related to pseudo-tumors. There were no differences in tumor locations, gender, clinical symptoms, or bilirubin levels between pancreatic cancer and pseudo-tumor. In addition, smoking history was slightly related to pseudo-tumors, not PDAC. Because most patients with chronic pancreatitis have drinking and smoking habits, smoking was more related to a pseudo-tumor. When the parameters were applied to 'negative' or 'inconclusive' categories, most patients with more than 2 parameters were diagnosed with pseudo-tumors.

This study had some limitations. Although there was a relatively long follow-up period, only a small percentage of cases (7.2%) were diagnosed by surgery, and most cases were diagnosed by a clinical follow-up. In addition, the number of patients with accompanying chronic pancreatitis was insufficient to compare the diagnostic yields to those without it. On the other hand, the percentage of patients presenting with pancreatic solid lesions in the background of pancreatitis was 23.5-25%,^{5,9} which was similar to this study.

In conclusion, cases categorized as 'negative' or 'indeterminate' on EUS-FNA, which showed clinical features relevant to a malignancy, have a high possibility of PDAC. Under these conditions, repeated FNA or surgical resection may be more helpful instead of a close follow-up. Therefore, the clinical parameters play a role in the complimentary data for clinical de-

cision making.

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