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RETROSPECTIVE STUDY

Evaluation of diagnostic cytology *via* endoscopic naso-pancreatic drainage for pancreatic tumor

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Abstract

AIM: To evaluate the usefulness of cytology of the pancreatic juice obtained *via* the endoscopic naso-pancreatic drainage tube (ENPD-C).

METHODS: ENPD was performed in cases where a diagnosis could not be made other than by using endoscopic retrograde cholangiopancreatography and in cases of pancreatic neoplasms or cystic tumors, including intraductal papillary mucinous neoplasm (IPMN) suspected to have malignant potential. 35 patients (21 males and 14 females) underwent ENPD between January 2007 and June 2013. The pancreatic duct was imaged and the procedure continued in one of ENPD-C or ENPD-C plus brush cytology (ENPD-BC). We checked the cytology result and the final diagnosis.

RESULTS: The mean patient age was 69 years (range, 48-86 years). ENPD-C was performed in 24 cases and ENPD-C plus brush cytology (ENPD-BC) in 11 cases. The ENPD tube was inserted for an average of 3.5 d. The final diagnosis was confirmed on the basis of the resected specimen in 18 cases and of follow-up findings at least 6 mo after ENPD in the 18 inoperable cases. Malignancy was diagnosed in 21 cases and 14 patients were diagnosed as having a benign condition. The ratios of class Ⅴ/Ⅳ:Ⅲ:Ⅱ/Ⅰ findings were 7:7:7 in malignant cases and 0:3:11 in benign cases. The sensitivity and specificity for all patients were 33.3% and 100%, respectively. The cytology-positive rate was 37.5% (6/16) for pancreatic cancer. For IPMN cases, the sensitivity and specificity were 33% and 100%, respectively.

CONCLUSION: Sensitivity may be further increased by adding brush cytology. Although we can diagnosis cancer in cases of a positive result, the accuracy of ENPD-C remains unsatisfactory.

Key words: Endoscopic naso-pancreatic drainage; Pancreatic juice; Cytology; Pancreatic cancer; Intraductal papillary mucinous neoplasm

Core tip: This study was performed to evaluate the usefulness of cytology of the pancreatic juice obtained *via* the endoscopic naso-pancreatic drainage tube (ENPD-C). We retrospectively investigated 35 patients with pancreatic disease. ENPD-C was performed in 24 cases and ENPD-C plus brush cytology (ENPD-BC) in 11 cases. The sensitivity and specificity for all patients were 35% and 100%, respectively. The cytology-positive rate was 37.5% (6/16) for pancreatic cancer and 33% (1/3) for intraductal papillary mucinous cancer. Sensitivity may be further increased by adding brush cytology. We can diagnosis cancer in cases of a positive result (class Ⅴ/Ⅳ) but the accuracy of ENPD-C remains unsatisfactory.

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INTRODUCTION

The early diagnosis of malignant pancreatic disease is very difficult and, as a result, it is usually only discovered at an advanced stage. Patients with malignant pancreatic disease, especially pancreatic ductal adenocarcinoma (PDAC), have a poor prognosis, and therefore we perform a pathological examination in cases where disease is suspected in order to make a diagnosis as early as possible and to select the optimal treatment strategy. Advancements in imaging techniques, such as computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), have improved the diagnosis rate, but pancreatic tumors are still generally detected too late for effective treatment. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has recently been employed and now plays a key role in the diagnosis of pancreatic cancer. However, if a mass cannot be detected by imaging, it is correspondingly difficult to diagnose an early pancreatic carcinoma in situ by pathological examination.

Some researchers[1,2] reported that pancreatic juice could be obtained repeatedly *via* an endoscopic naso-pancreatic drainage (ENPD) tube and that this was useful for making a definitive diagnosis of small pancreatic tumors. Furthermore, EUS-FNA is not generally used for cystic tumors in Japan because infectious complications, bleeding and dissemination in a patient with a pancreatic cystic tumor have been reported[3-5]. Diagnosis by cytology and brush cytology using an ENPD tube guided by endoscopic retrograde cholangiopancreatography (ERCP) has also been reported, but with variable rates of detection[6-14]. A few reports have also described the cytology findings of pancreatic juice in cases of branched type intraductal papillary mucinous neoplasm (IPMN)[15]. In this retrospective study, we assessed the diagnostic potential of cytology of pancreatic juice obtained *via* ENPD (ENPD-C) and ENPD-C with brush cytology (ENPD-BC) for the diagnosis of pancreatic neoplasms, including IPMN.

MATERIALS AND METHODS

ENPD was performed in cases where a diagnosis could not be made other than by using ERCP and in cases of pancreatic neoplasms or cystic tumors suspected to have malignant potential. Accordingly, 35 patients (21 males and 14 females) at Showa University Hospital underwent ENPD between January 2007 and June 2013. This procedure was performed by 8 experienced endoscopists. The mean patient age was 69 years (range, 48-86 years) (Table 1). ERCP was performed using a duodenoscope (JF260V; Olympus Medical Systems, Tokyo, Japan). In all cases, we were able to insert a cannula (MTW ERCP catheter; MTW Endoscopy, Wesel, Germany) and a guide-wire (VisiGlide™; Olympus Medical Systems, Tokyo, Japan, or Jagwire™; Boston Scientific, Natick, Mass, United States).

Table 1 Characteristics of patients undergoing endoscopic naso-pancreatic drainage tube and endoscopic naso-pancreatic drainage plus brush cytology

Daiagnostic ENPD (n = 35)	
Age (yr)	69 (48-86)
Sex, M/F	21:14
ENPD-BC (n)	11
Frequency of brush in ENPD-BC (range)	1 (1-2)
Frequency of pancreatic juice cytology in ENPD-BC (range)	4 (2-5)
ENPD-C (n)	24
Frequency of ENPD-C (range)	3 (1-5)

Thirty-five patients underwent the cytology of pancreatic juice obtained *via* endoscopic naso-pancreatic drainage tube (ENPD-C) and ENPD-C with brush cytology (ENPD-BC). M/F: Male/female.

The pancreatic duct was imaged and the procedure continued in one of the following ways: (1) ENPD-BC: In cases of stenosis of the main pancreatic duct, we performed brush cytology (10 single strokes) from the distal tip to the proximal end of the stenosis using a cytology brush (RX Cytology Brushes™; Boston Scientific, Natick, Mass, United States). This was performed in 11 cases. Ultimately, we inserted 5Fr ENPD tubes (Nasal Pancreatic Drainage Set; Cook Medical Inc Endoscopy, Winston-Salem, NC, United States) into the main pancreatic duct; and (2) ENPD-C: After imaging the pancreatic duct, we inserted an ENPD tube into the main pancreatic duct without performing brush cytology in 24 cases.

After steps 1 or 2, we collected the pancreatic juice and submitted it for analysis on the same day or on the following day. Pancreatic juice was obtained *via* the ENPD tube that was inserted for an average of 3.5 d (range, 1-5 d) per patient. All pancreatic juice specimens contained sufficient cells for cytological diagnosis. We occasionally performed additional endoscopic sphincterotomy (EST) in cases of bile duct stenosis or a common bile duct stone, and endoscopic papillosphincterotomy (EPST) was performed in cases of a pancreatic stone. Samples were submitted for cytological examination as soon as possible after collection and the examination tubes contained saline and heparin as rapid on-site specimen evaluation was not possible. If sufficient pancreatic juice could not be obtained by gravity drainage, the specimen was instead obtained by suction. We evaluated the following: (1) the accuracy of cytological analysis of pancreatic juice obtained from pancreatic tumors using ENPD-C and ENPD-BC; (2) the rate of malignancy detected by cytological analysis in cases of pancreatic cancer; (3) the difference in the rate at which cancer was

Table 2 Diagnostic, surgical methods and final diagnosis of pancreatic diseases

		No.
Operable	Pancreaticoduodenectomy	10
	Distal pancreatectomy	3
	Total pancreatectomy	1
	Palliative operation or exploratory laparotomy	4
Inoperable		17
Cancerous	Pancreatic cancer	16
	IPMN-CAN	3
	Others	2
Non-cancerous	IPMN-BEN	8
	Chronic pancreatitis	5
	Others	1

In 18 operable cases, the final diagnosis was confirmed on the basis of the resected specimen. In the 17 inoperable cases, it was diagnosed by follow-up findings at least 6 mo after endoscopic naso-pancreatic drainage (ENPD). The diagnosis of pancreatic ductal adenocarcinoma derived from the intraductal papillary mucinous neoplasm (IPMN-CAN) was only confirmed pathologically in consecutive lesions. We defined IPMN without the potential of cancer as IPMN-BEN.

detected between samples collected by ENPD-C and ENPD-BC; (4) the accuracy of cytological analyses of pancreatic juice for IPMN; and (5) the number and type of complications.

The final diagnosis was based on the surgically resected specimen or on imaging findings in inoperable cases. The diagnosis of PDAC derived from the IPMN (IPMN-CAN) was only confirmed pathologically in consecutive lesions because the distinction between IPMN-CAN and PDAC concomitant with the IPMN is sometimes difficult[15]. Total pancreatectomy was performed in 1 case (2.9%), pancreatoduodenectomy (PD) was performed in 10 cases (28.6%), distal pancreatectomy was performed in 3 cases (8.6%), and palliative surgery was performed in 4 cases. The remaining 17 patients did not undergo surgery (Table 2). The cases diagnosed as being pancreatic cancer included 5 cystic lesions, all of which were classified as IPMN without the potential of cancer (IPMN-BEN). Specimens were categorized using Papanicolaou classification: class Ⅰ, absence of atypical or abnormal cells; class Ⅱ, atypical cytology but no evidence of malignancy; class Ⅲ, cytology suggestive of, but not conclusive for malignancy; class Ⅳ, cytology strongly suggestive of malignancy; and class Ⅴ, cytology conclusive for malignancy. Eight pathologists and 7 cytologists reviewed the cytological examinations of the 35 patients. Cases classified as class Ⅳ/Ⅴ were considered positive, those classified as class Ⅲ were considered borderline-positive, and those classified as class Ⅰ/Ⅱ were considered negative. Class Ⅲ cytology could not be defined as malignant and was therefore considered negative for the determination of sensitivity and specificity. Complications were assessed according to Cotton's classification[16]. Statistical analyses were performed using the Student's t test, χ^2 test or the Fisher exact test, as appropriate. For all tests, $P < 0.05$ was considered significant. All measurements are presented as the median value.

Table 3 Sensitivity and specificity of pancreatic juice cytology

Cytology	Positive	Negative		Total
	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	7	7	7	21
Non-cancerous	0	3	11	14

The sensitivity and specificity for all patients were 33.3% and 100%, respectively.

RESULTS

The final diagnosis was confirmed on the basis of the resected specimen in 17 cases and on the basis of follow-up findings at least 6 mo after ENPD in the 17 inoperable cases (Table 2). EST was performed in 3 cases and EPST in 4 cases. An ENPD tube was inserted for a median of 3.5 d (range, 1-5 d).

Accuracy of cytological analyses of pancreatic juice obtained by ENPD-C and ENPD-BC in patients with pancreatic tumors

The final diagnosis in 21 cases was of pancreatic malignancy, of which 7 were positive, 7 were false positive, and 7 were negative on ENPD-BC or ENPD-C. The remaining 14 cases found to be benign based on surgical specimens were negative on cytological analysis. Accordingly, the sensitivity and specificity were 33.3% and 100%, respectively, and the accuracy of cytological analysis of pancreatic juice for pancreatic tumors was 60.0%. Although finally diagnosed as benign, cytological analysis of pancreatic juice yielded 3 false-positive results (Table 3).

Rate of malignancy detection by cytological analysis in pancreatic cancer

Sixteen patients were diagnosed as having pancreatic cancer. Cytology results were positive in 6 of these cases, resulting in an accuracy of 37.5%. Five cases of pancreatic cancer were considered to involve a pancreatic cystic lesion. Most pancreatic cancers were located in the pancreatic head (Ph) (12/16, 75.0%), only 1 tumor was located in the body (Pb), and 3 tumors were located in the tail (Pt). The median tumor size was 30 mm (range, 15-54 mm) and the median main pancreatic duct size was 3.5 mm (range, 1-10 mm) (Table 4).

Comparison between the sensitivities of ENPD-C and ENPD-BC

ENPD-BC and ENPD-C was performed in 11 and 24 cases, respectively. In the ENPD-BC group, of the 8 malignant cases, 4 showed positive results (class Ⅴ/Ⅳ) on cytology and 4 showed negative results on cytology [class Ⅲ (3 cases)/Ⅱ/Ⅰ]. In the ENPD-C group, of the 13 malignant cases, 4 showed positive results on cytology (class Ⅴ/Ⅳ) and 9 showed negative results on cytology [class Ⅲ (4 cases)/Ⅱ/Ⅰ]. None of the non-malignant cases showed positive results (class Ⅴ/Ⅳ) on cytology. Thus,

Table 4 Location and size of pancreatic cancer

	Pancreatic cancer
Total	16
Location	
Ph	12
Pb	1
Pt	3
Size (range)	30 mm (15-54 mm)
Main pancreatic duct size (range)	3.5 mm (1-10 mm)

Ph: Head of pancreas; Pb: Body of pancreas; Pt: Tail of pancreas. Most pancreatic cancers were located in the pancreatic head (Ph) (12/16, 75.0%).

the overall sensitivity of ENPD-C and ENPD-BC was 30.8% and 50%, respectively (Table 5).

Accuracy of cytological analysis in patients with IPMN

Three cases of IPMN-CAN were diagnosed on the basis of resected specimens (1 case of branch duct IPMN (BD-IPMN) and 2 cases of main duct IPMN (MD-IPMN)). There were also 8 cases of IPMN-BEN (6 of BD-IPMN and 2 of MD-IPMN). Two IPMN-CANs were located in the Ph and the other was located in the Pt. The median IPMN-CAN size was 43 mm (range, 32-75 mm) and the median IPMN-BEN size was 17.5 mm (range, 10-61 mm), although these differences were not statistically significant (P = 0.081). Mural nodules were observed in all IPMN-CAN cases and in 3 IPMN-BEN cases, but again this difference was not statistically significant (P = 0.182). The diameter of the main pancreatic duct was 6 mm (range, 4-17 mm) in IPMN-CAN cases and 5 mm (range, 3-15 mm) in IPMN-BEN cases (P = 0.530) (Table 6). Cytological examination of pancreatic juice without brush cytology was only performed during ERCP because no stenosis was observed in the main pancreatic duct. One of the 3 IPMN-CAN cases and 2 of the 8 IPMN-BEN cases were classified as class Ⅲ. The sensitivity and specificity of the cytological diagnosis of IPMN was 33% and 100%, respectively, when class Ⅲ cases were considered negative (Table 5).

Complications

The major complication associated with ERCP is post-ERCP pancreatitis[17], although there was only 1 case of post-ERCP pancreatitis in this study (2.9%) in a patient diagnosed as having serous cyst adenoma including non-cancerous cells, located in the Pt. The pancreatitis in this case was relatively mild and resolved after the patient received a nil-by-mouth regimen for a few days. No other complications (such as hemorrhage, cholangitis and perforation) were observed.

DISCUSSION

The number of diagnostic ERCPs has reduced recently with improvements in CT, magnetic resonance imaging and EUS, and the sensitivity, specificity and accuracy of EUS-FNA has been shown to be 85%, 98% and 88%, respectively[5,18], the latter being considerably higher than that of ERCP (18%-70%)[6-8,19-23]. However, it has been reported that cytodiagnosis *via* ENPD can be useful in cases of small pancreatic tumors[1,2]. On occasion, we have not been able to detect small pancreatic tumors due to technical problems, and in these cases, brush cytology and pancreatic juice cytology using ERCP were necessary. However, a number of complications can occasionally arise after ERCP and, according to Vandervoort *et al*[24], its use is followed by pancreatitis in 21% of cases. To date, ERCP for pancreatic cancer diagnosis has been limited to cases in which it is difficult to distinguish between malignant and benign disease by any other modality, complicated by jaundice, cholangitis or an unclear image of the main pancreatic duct by noninvasive examination. When drainage is necessary, it is used for diagnosis and treatment. In our hospital, we perform pancreatic juice cytology and brush cytology using ENPD as necessary, and in the study we report here, there were false-positive cases (class Ⅲ), 7 among the cancer cases and 3 among the non-cancer cases, with an overall sensitivity and specificity of 33.3% and 100%, respectively. In the analysis, false-positive (class Ⅲ) cases were included in the negative group, because these cannot be definitively shown to be malignant. However, if cancer is possible, it might be considered worthwhile to repeat the examination or to perform an operation in order to avoid treatment being given too late. The management of these cases with class Ⅲ findings is a difficult clinical problem. There have been many reports of improved accuracy resulting from changes in the method used to collect pancreatic juice. One of these involved using a catheter or brush cytology and has been reported to result in a sensitivity of 33%-76%[7,9,10] or 30%-84.7%, respectively[11-14]. The sensitivities of ENPD-C and ENPD-BC in these studies were similar at 30.8% and 50%, respectively, but sensitivity may be improved if brush cytology is added to ENPD-C.

The diagnostic utility of ENPD for IPMN is yet to be established as to date, there have only been a few reports on its use[3,25,26]. In the International Consensus Guideline 2012 for the management of IPMN and MCN of the pancreas, routine ERCP for sampling of fluid or brushings in IPMN is not recommended[15]. Hirono *et al*[27] reported that the rate of positive cytology (class Ⅴ/Ⅳ) findings for IPMN-CAN was 11.1%. Another study of a large patient series showed that a carcinoembryonic antigen level greater than 30 ng/mL was a potential diagnostic marker for malignant BD-IPMN. Molecular analysis of cells in pancreatic juice includes an examination of the K-ras codon 12 point mutation, the p53 mutation[28], CD44 expression[29,30] and telomerase activity[30]. Proteomics can also be used to differentiate pancreatic cancer from pancreatitis[31]. However, the diagnostic potential of most of these methods is yet to be established. In our study, using ENPD to diagnose 12 cases of IPMN yielded a sensitivity of 33% and a specificity of 100%. These findings need to be considered with some caution as the study included relatively few cases and was retro-

Table 5 Sensitivity and specificity of endoscopic naso-pancreatic drainage tube with brush cytology and endoscopic naso-pancreatic drainage tube, pancreatic juice cytology and characteristics of intraductal papillary mucinous neoplasm

ENPD-BC (Sensitivity: 50%; Specificity: 100%)	Positive	Negative		Total
11 cases	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	4	3	1	8
Non-cancerous	0	1	2	3
ENPD-C (Sensitivity: 30.8%; Specificity: 100%)	Positive	Negative		Total
24 cases	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	4	4	5	13
Non-Cancerous	0	3	8	11
Cytology in IPMN patients (Sensitivity: 33%; Specificity: 100%)	Positive	Negative		Total
	Class Ⅴ/Ⅳ	Class Ⅲ	Class Ⅱ/Ⅰ	
Cancerous	1	1	1	3
Non-cancerous	0	2	6	8

IMPN: Intraductal papillary mucinous neoplasm.

Table 6 Characteristics of intraductal papillary mucinous neoplasm

	IPMN-CAN	IPMN-BEN	*P* value
Total	3	8	
Main duct type	2	2	-
Branch duct type	1	6	
Position			
Ph, Pb, Pt	2, 0, 0	3, 1, 1	-
Pb + Pt	1	1	
Ph + Pt		1	
Ph + Pb + Pt		1	
Size (range)	43 mm (32-75 mm)	17.5 mm (10-61 mm)	0.081[1]
Mural nodule + (%)	3 (100%)	3 (33%)	0.1818[2]
Main pancreatic duct size (range)	6 mm (4-17 mm)	5 mm (3-15 mm)	0.5298[1]

[1]Mann-Whitney *U* test; [2]χ^2 test. None of the differences between the two intraductal papillary mucinous neoplasm (IPMN) groups were significant ($P \geq 0.05$).

spective, but the sensitivity and specificity achieved were similar to those when using pancreatic juice cytology for diagnosing pancreatic tumors and IPMN.

As mentioned above, ERCP is associated with a number of complications, the most common of which is pancreatitis. Cotton *et al*[17] likewise reported that complications (4.0%) were associated with ERCP, including pancreatitis (2.6%) and bleeding (0.3%), identified on follow-up investigations performed over a period of 12 years. In general, post ERCP pancreatitis occurred in 1%-40% of cases and hyperamylasemia was detected in 70% of cases[16]. Vandervoort *et al*[24] reported that pancreatitis occurred in 21% of cases after pancreatic cytology, whilst Ryan *et al*[11] found that it occurred in only 3.2% of cases. These complication rates therefore seem to be study dependent.

Complications for one of the other important modalities for pancreatic solid tumors, EUS-FNA biopsy, occur in only 1%-2% of cases[32]. Pancreatic mass lesions are a suitable indication for EUS-FNA biopsy because of the high diagnostic accuracy and low rate of complications[5]. As the complication rate of ERCP was higher than that of EUS-FNA, it is difficult to argue that ENPD-C and ENPD-BC should be first-line choices. However, they become necessary when a mass cannot be detected by EUS or if the patient has obstructive jaundice or cholangitis requiring drainage. In these cases, we found that ERCP using ENPD for pancreatic diseases including IPMN was an effective alternative. However, additional care is needed when cases are found to be borderline positive, as it is in the case of main pancreatic duct stenosis.

ENPD proved to be a safe technique, but the accuracy with which malignant tumors were detected by cytodiagnosis was low, making further improvements necessary, especially for cases with a border-line positive result. Despite the inclusion of only a small number of cases, the sensitivity and specificity when using pancreatic juice cytology were similar for pancreatic masses and IPMN. Sensitivity may be further increased by adding brush cytology for cases in which there is stenosis of the pancreatic duct. This procedure may not be the first choice of the diagnosis, but we suggest and reconfirm that it is available as one choice of the safe diagnosis method.

COMMENTS

Background

The early diagnosis of malignant pancreatic disease is very difficult. If a small mass cannot be detected by imaging, it is correspondingly difficult to diagnose an early pancreatic carcinoma in situ by pathological examination. Some researchers reported the usefulness of cytology of pancreatic juice obtained repeatedly *via* an endoscopic naso-pancreatic drainage (ENPD) tube.

Research frontiers

The accuracy of the cytology *via* ENPD is uneven in each report. In addition, there are few articles about ENPD for pancreatic neoplasm, including IPMN. Therefore, the authors assessed the diagnostic potential of cytology of pancreatic juice obtained *via* ENPD (ENPD-C) and ENPD-C with brush cytology (ENPD-BC) for the diagnosis of pancreatic neoplasms, including IPMN.

Innovations and breakthroughs

Recent reports have highlighted the importance of more accurate diagnosis for pancreatic tumor before treatment because there is rarely the case of benign disease. The studies suggest that this diagnostic procedure is usable and available if a mass cannot be detected by imaging. Furthermore, this is useful because the sensitivity and specificity in cases of branched type IPMN were similar for pancreatic cancer.

Applications

ENPD proved to be a safe technique, but the accuracy with which malignant

tumors were detected by cytodiagnosis was low, making further improvements necessary, especially for cases with a border-line positive result. Despite the inclusion of only a small number of cases, the sensitivity and specificity when using pancreatic juice cytology were similar for pancreatic masses and IPMN. Sensitivity may be further increased by adding brush cytology for cases in which there is stenosis of the pancreatic duct. This procedure may not be the first choice of the diagnosis, but it is suggested and reconfirmed that it is available as one choice of the safe diagnosis method.

Peer review

This manuscript is about evaluating the usefulness of cytology of the pancreatic juice obtained *via* the ENPD-C. This is an interesting paper that warrants publication.

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