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Optimal indication of endoscopic retrograde pancreatography-based cytology in the preoperative pathological diagnosis of pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is extremely useful for pathological diagnosis of pancreatic ductal adenocarcinoma (PDAC); however, puncturing is difficult in some cases, and there is a risk of needle tract seeding. This study evaluated the indications for endoscopic retrograde pancreatography-based (ERP)-based cytology for the preoperative diagnosis of PDAC.
Methods: This study included 267 patients with PDAC who underwent preoperative ERP. The diagnostic performance of ERP-based cytology for PDAC was evaluated based on the sample collection method (pancreatic juice cytology [PJC] during ERP, brush cytology, PJC via endoscopic nasopancreatic drainage [ENPD] catheter), lesion site (pancreatic head, body/tail), and lesion size (≤10 mm, 10–20 mm, >20 mm), and compared with the diagnostic performance of EUS-FNA.
Results: The overall sensitivity of ERP-based cytology was 54.9%; sensitivity by the sampling method was 34.7% for PJC during ERP, 65.8% for brush cytology, and 30.8% for PJC via an ENPD catheter. The sensitivity of EUS-FNA was 85.3%. Brush cytology and PJC via an ENPD catheter were performed more often in pancreatic body/tail lesions than in head lesions ($P = 0.016$ and $P < 0.001$, respectively), and the overall sensitivity of ERP-based cytology was better for body/tail lesions (63.2% vs. 49.0%, $P = 0.025$). The sensitivities of ERP-based cytology and EUS-FNA in diagnosing PDAC ≤10 mm were 92.3% and 33.3%, respectively. Post-ERP pancreatitis was observed in 22 patients (8.2%) and significantly less common with ENPD catheters ($P = 0.002$).
Conclusions: ERP-based cytology may be considered the first choice for pathological diagnosis of PDAC ≤10 mm and in the pancreatic body/tail.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a malignancy with very poor prognosis and an overall 5-year survival rate of less than 10% [1]. In contrast, the 5-year survival rates for Union for International Cancer Control stage 0 (in situ) cases and cases with tumors with a diameter <10 mm, which account for most stage IA cases, are 85.8% and 80.4%, respectively [2]. Early diagnosis and treatment can be expected to significantly improve prognosis; however, very few PDAC are diagnosed at an early stage [3]. In addition to early detection, a major issue for improving prognoses

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography; MPD, main pancreatic duct; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; PJC, pancreatic juice cytology; ENPD, endoscopic nasopancreatic drainage; ERP, endoscopic retrograde pancreatography.

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is the efficient diagnosis of PDAC.

Characteristic imaging findings of PDAC include tumors with poor contrast enhancement on computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), and localized stenosis of the main pancreatic duct (MPD) [4]. If these findings are present, PDAC should be kept in mind while proceeding with the diagnosis; however, because inflammatory diseases and other pancreatic tumors can present with similar findings [5], a pathological diagnosis is recommended whenever possible to obtain a definitive diagnosis [6].

Pathological diagnostic methods for PDAC include endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and endoscopic retrograde cholangiopancreatography (ERCP)-based sampling. The diagnostic performance of EUS-FNA is very good [7] and is therefore the first technique to be considered for the pathological diagnosis of PDAC. However, approximately 10% of cases are false negatives, and EUS-FNA is difficult to perform in some cases because of the use of oral antithrombotic agents, a tendency for bleeding, or blood vessels interfering with the puncture route. In addition, there have been a few reports of needle tract seeding [8], which is a complication that cannot be ignored. ERCP-based sampling includes pancreatic juice cytology (PJC), brush cytology in areas of pancreatic or bile duct stenosis, and biopsy of the pancreatic or bile duct. Recently, the usefulness of collecting pancreatic juice using an endoscopic nasopancreatic drainage (ENPD) catheter for the early diagnosis of PDAC has been reported [9]. Although there have been several reports on the diagnostic performance of ERCP-based sampling for PDAC, there were large variations in the results [10–12], and few studies have compared the diagnostic performance of multiple sampling methods.

The objective of this study was to retrospectively examine the performance of endoscopic retrograde pancreatography (ERP)-based cytology and EUS-FNA in the preoperative pathological diagnosis of PDAC and to determine the indications for ERP-based cytology and optimal sampling methods.

2. Materials and methods

2.1. Patients

The subjects were 267 patients with PDAC who underwent preoperative ERP at Hiroshima University Hospital between January 2010 and December 2020. When potentially-resectable PDAC was suspected on contrast-enhanced CT during the study period, pathological examination was performed after evaluation of the tumor by EUS. The procedure for pathological diagnosis was to first perform ERP-based cytology, regardless of the location and diameter of the tumor, followed by EUS-FNA 2–5 days later. EUS-FNA was not performed in cases in which the lesion could not be visualized as a mass or cancer had already been diagnosed using ERP-based cytology. Ideally, the decision to perform EUS-FNA should take place after receiving all results of ERP-based cytology, but due to some restrictions on the length of hospital stay, a certain number of patients underwent EUS-FNA before all ERP-based cytology results were available. In patients with unresectable PDAC due to distant metastasis or being locally advanced, EUS-FNA was first selected for pathological diagnosis, and these cases were excluded from this study.

Written informed consent was obtained from all patients and their families before ERCP and EUS-FNA were performed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hiroshima University Hospital (approval No. E–691).

2.2. ERP-based cytology

ERCP was performed using a video duodenoscope (JF-260V or TJF-260V; Olympus Medical Systems, Tokyo, Japan). The ERP-based cytology was performed as follows: A cannula for contrast enhancement was intubated deep into the pancreatic duct, and pancreatography was performed to fully investigate the pancreatic duct. Next, pancreatic juice was collected by suction from the cannula (PJC during ERP). After breaking through the pancreatic duct stenosis with a guide wire, a brush device (RX Cytology Brush; Boston Scientific Corp., Marlborough, MA, USA) was inserted up to the stenosis to perform brush cytology. Finally, if the lesion was in the pancreatic head or body, the distal end of the ENPD catheter was placed upstream of the stenosis (Fig. 1) to collect pancreatic juice that came out naturally or when pancreatography was performed with the ENPD catheter the next day (PJC via ENPD catheter). The ENPD catheter used was a 5-Fr Flexima (Boston Scientific Corp.) or a 4- or 5-Fr ENPD catheter (Gadelius Medical, Tokyo, Japan). Other ERCP-based samplings include brush cytology in an area of bile duct stenosis and biopsy of the pancreatic or bile duct. Since the bile duct sampling methods can only be performed for pancreatic head cancer, they were excluded from this study. Biopsy of the pancreatic duct has not been performed at our institution because it is difficult to safely insert biopsy forceps into the main pancreatic duct of pancreatic body and tail. Cytology was assessed using the Papanicolaou classification [13], with classes IV and V being malignant. If pancreatic duct epithelial cells could not be collected, or if the cells were degenerated and could not be assessed, the sample was deemed unacceptable. All ERCP-related procedures were performed under conscious sedation of the patient with intravenous administration of midazolam alone or midazolam plus pentazocine.

2.3. EUS-FNA

EUS-FNA was performed using linear EUS (GF-UCT240 AL-5 or GF-UCT260; Olympus Medical Systems). Specimens were collected by performing 10–20 strokes inside the lesion while applying 10 mL negative pressure with a 22- or 25-G puncture needle. The procedure ended once the sample was confirmed visually. The collected samples were submitted for both cytology and histology; samples with a malignant result in either were diagnosed as malignant. EUS-FNA was performed under conscious sedation with intravenous administration of midazolam.

2.4. Outcomes

The primary outcome measure was the diagnostic performance of ERP-based cytology and EUS-FNA for PDAC. In addition, diagnostic performance was compared between lesions in the pancreatic head and body/tail, and between tumor sizes $\leq$10 mm, 10–20 mm, and >20 mm. The secondary outcome measure was the incidence of complications using ERP-based cytology. Complications were assessed based on symptoms and blood test results from 2 h and the following day (complete blood count, C-reactive protein, and serum pancreatic amylase). CT was performed when there was a possibility of serious complications, such as acute pancreatitis. The severity of post-ERP pancreatitis was determined based on the Cotton classification [14].

2.5. Statistical analysis

All statistical analysis was performed using JMP pro 14.2.9 (SAS Institute Inc., Cary, NC, USA). The chi-squared test and Fisher's exact

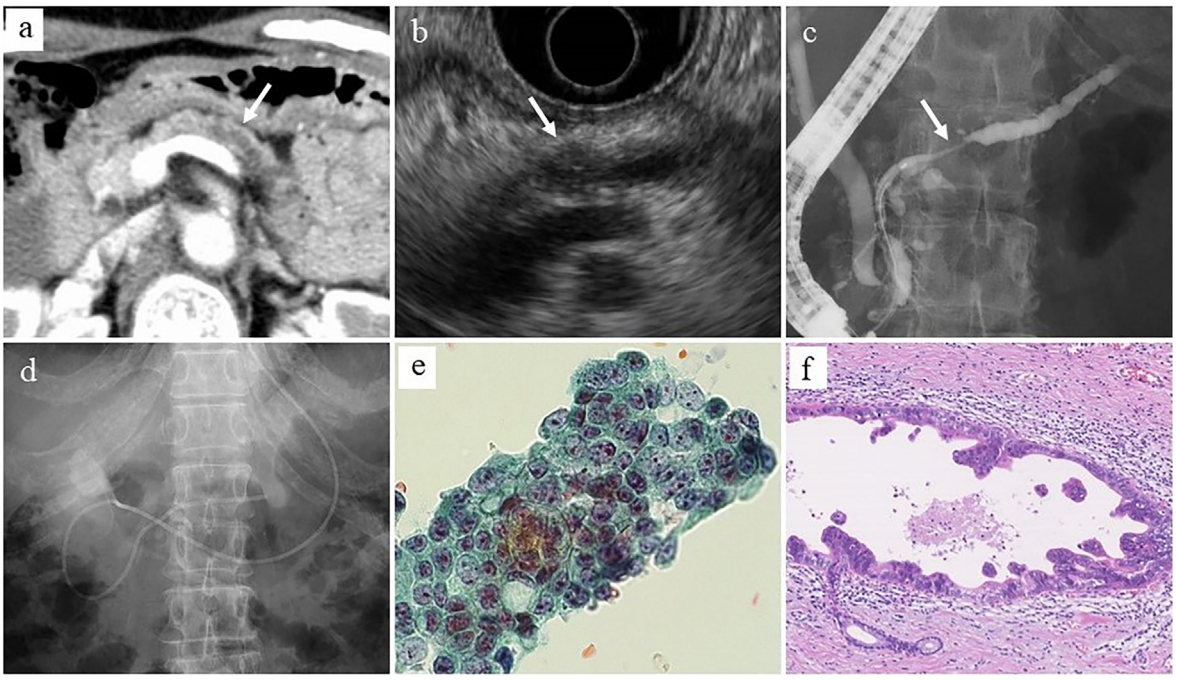

Fig. 1. A 68-year-old woman with minimally invasive pancreatic ductal adenocarcinoma
(a) Computed tomography shows dilatation of the main pancreatic duct (MPD) from the pancreatic body to tail, but no tumor is found on the duodenal side (arrow); (b) Endoscopic ultrasonography shows a hypoechoic area on the duodenal side of the dilated MPD (arrow), but no obvious mass; (c) Endoscopic retrograde pancreatography shows stenosis in the MPD of the pancreatic body (arrow). Aspirated pancreatic juice cytology (PJC) and brush cytology were performed; (d) An endoscopic nasopancreatic drainage (ENPD) catheter is placed and repeated PJCs are performed; (e) Adenocarcinoma cells are detected by PJC via an ENPD catheter; (f) Histopathological findings show minimally invasive pancreatic ductal adenocarcinoma consistent with the stenosis of the MPD.

test were used for 2-group comparisons of diagnostic performances based on the sample collection method and tumor site. The diagnostic performances based on tumor size were compared among the three groups using a Bonferroni adjustment for multiple comparison. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. Patient characteristics

Table 1 shows the characteristics of the 267 patients with PDAC. Their median age was 70 years (range: 37–88 years); 141 were men, and 126 were women. The pancreatic lesion site was in the head in 160 cases (59.9%), the body in 59 cases (22.1%), and the tail in 48 cases (18.0%). The median tumor size was 28 mm (range: 0–90 mm), with 13 cases ≤10 mm (4.9%), 57 cases 10–20 mm (21.3%), and 197 cases >20 mm (73.8%).

ERP was performed in all cases, and ERP-based cytology was possible in 253 cases (94.8%). PJC during ERP was used in 196 patients (73.4%), brush cytology in 111 patients (41.6%), and PJC via ENPD catheter in 195 patients (73.0%). PJC via ENPD catheter was performed a mean 3.2 times, with a median of 2 times (range: 1–10). Two or more ERP-based sampling methods were used in 174 patients (65.2%). EUS-FNA was performed in 177 patients (66.3%). Both ERP-based cytology and EUS-FNA were performed in 165 patients (61.8%). The surgical procedure was pancreatoduodenectomy in 161 cases, distal pancreatectomy in 96 cases, total pancreatectomy in 9 cases, and middle pancreatectomy in 1 case. Neoadjuvant chemotherapy was administered to 72 patients (27.0%). The pathological stage was 0 in 3 cases, IA in 17 cases, IB in 21 cases, IIA in 47 cases, IIB in 146 cases, III in 28 cases, and IV in 5 cases.

Table 1
Clinical profiles of 267 patients with resected PDAC.

Characteristics	Values
Age (years)	70 (37–88)
Sex (male to female)	141 : 126
Location of the tumor	
Head	160 (59.9%)
Body	59 (22.1%)
Tail	48 (18.0%)
Size of the tumor (mm)	28 (0–90)
≤10 mm	13 (4.9%)
10–20 mm	57 (21.3%)
>20 mm	197 (73.8%)
ERP performed	267 (100%)
ERP-based cytology performed	253 (94.8%)
PJC during ERP	196 (73.4%)
Brushing cytology	111 (41.6%)
PJC via ENPD catheter	195 (73.0%)
Combination of either two sampling methods	174 (65.2%)
Number of PJC via ENPD catheter	2 (1–10)
EUS-FNA performed	177 (66.3%)
Both ERP-based cytology and EUS-FNA performed	165 (61.8%)
Surgical procedure	
Pancreatoduodenectomy	161 (60.3%)
Distal pancreatectomy	96 (36.0%)
Total pancreatectomy	9 (3.4%)
Middle pancreatectomy	1 (0.4%)
Neoadjuvant chemotherapy	72 (27.0%)
Pathological stage †	
0/IA/IB/IIA/IIB/III/IV	3/17/21/47/146/28/5

Data are expressed as number (percentage) or median (range).† Japan Pancreatic Society General Rules for the Study of Pancreatic Cancer, 7th edition; PDAC, pancreatic ductal adenocarcinoma; ERP, endoscopic retrograde pancreatography; PJC, pancreatic juice cytology; ENPD, endoscopic nasopancreatic drainage; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

Table 2
Diagnostic performance of PDAC based on sampling method.

Sampling method	Adequate samples	Sensitivity
ERP-based cytology	–	54.9% (139/253)
PJC during ERP	89.8% (176/196)	34.7% (68/196)
Brush cytology	99.1% (110/111)	65.8% (73/111)
PJC via ENPD catheter	69.5% (435/626)	30.8% (60/195)
Combination of either two sampling methods	–	62.0% (108/174)
EUS-FNA	98.3% (174/177)	85.3% (151/177)
Both ERP-based cytology and EUS-FNA	–	92.1% (152/165)

ERP, endoscopic retrograde pancreatography; PJC; pancreatic juice cytology; ENPD, endoscopic nasopancreatic drainage; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

3.2. Diagnostic performance of PDAC based on sampling method

Table 2 shows the diagnostic performance of PDAC based on the sample collection method. The rate of acceptable sample collection was 89.8% (176/196) for PJC during ERP, 99.1% (110/111) for brush cytology, 69.5% (435/626) for PJC via ENPD catheter, and 98.3% (174/177) for EUS-FNA. The overall sensitivity of ERP-based cytology was 54.9% (139/253), and the sensitivity of the sampling method was 34.7% (68/196) for PJC during ERP, 65.8% (73/111) for brush cytology, and 30.8% (60/195) for PJC via ENPD catheter. The sensitivity was 62.0% (108/174) when two sampling methods were combined. The sensitivity of EUS-FNA was 85.3% (151/177), and that of patients who underwent both ERP-based cytology and EUS-FNA was 92.1% (152/165).

3.3. Comparison of diagnostic performance based on the location and size of the tumor

Table 3 shows the diagnostic performance of ERP-based cytology and EUS-FNA based on the tumor site. Brush cytology was performed significantly more often for lesions in the pancreatic tail and body compared to those in the head: 54/107 (50.5%) vs. 57/160 (35.6%) ($P = 0.016$). PJC via ENPD catheter was also performed more often in the pancreatic body/tail vs. the head: 93/107 (86.9%) vs. 102/160 (63.8%) ($P < 0.001$). In contrast, EUS-FNA was performed for significantly more lesions in the pancreatic head than in those in the body/tail: 119/160 (74.4%) vs. 58/107 (54.2%) ($P < 0.001$). No differences in the sensitivity of PDAC diagnosis were observed based on the sampling method, although the overall sensitivity of ERP-based cytology was significantly higher for tumors in the pancreatic body/tail than for those in the head (63.2% vs. 49.0%, $P = 0.025$). In contrast, the sensitivity of EUS-FNA did not differ significantly between the pancreatic head and the body/tail.

Table 4 shows the diagnostic performances of ERP-based cytology and EUS-FNA based on tumor size. No significant differences were observed in the frequency of the sampling methods between the three groups of tumor sizes. There was a significant difference in the overall sensitivity of PDAC diagnosis with ERP-based cytology among the three groups ($P = 0.015$), and the sensitivity was significantly higher in tumors ≤10 mm than in those 10–20 mm and >20 mm ($P = 0.012$ and 0.024, respectively). In the comparison by sampling method, there was no significant difference in sensitivity among three groups. The sensitivity was 100% (10/10) in cases ≤10 mm when two or more sampling methods were combined. There was also a significant difference in the sensitivity of EUS-FNA among the three groups ($P < 0.001$). EUS-FNA was only performed on 6 PDAC patients with tumors ≤10 mm (42.9%), and the sensitivity was significantly lower than that for tumors 10–20 mm and >20 mm ($P = 0.012$ and 0.021, respectively). In addition, the frequency of intraductal spread along the MPD was evaluated by tumor size in 195 patients who did not receive neoadjuvant chemotherapy. Intraductal spread along the

Table 3
Comparison of diagnostic sensitivity based on the location of the tumor.

Sampling method	Head (n = 160)	Body/tail (n = 107)	*P* value
ERP-based cytology	49.0% (72/147)	63.2% (67/106)	0.025
PJC during ERP	33.6% (39/116)	36.3% (29/80)	0.704
Brush cytology	57.9% (33/57)	74.1% (40/54)	0.073
PJC via ENPD catheter	28.4% (29/102)	33.3% (31/93)	0.459
Combination of either two sampling methods	55.2% (48/87)	69.0% (60/87)	0.061
EUS-FNA	83.2% (99/119)	89.7% (52/58)	0.254
Both ERP-based cytology and EUS-FNA	90.7% (98/108)	94.7% (54/57)	0.546

ERP, endoscopic retrograde pancreatography; PJC; pancreatic juice cytology; ENPD, endoscopic nasopancreatic drainage; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

Table 4
Comparison of diagnostic performance based on the size of the tumor.

Sampling method	≤10 mm (n = 13)	10–20 mm (n = 53)	20 mm< (n = 201)	*P* value
ERP-based cytology	92.3% (12/13)	48.0% (24/50)	54.2% (103/190)	0.015
PJC during ERP	22.2% (2/9)	21.6% (8/37)	38.7% (58/150)	0.108
Brush cytology	85.7% (6/7)	56.5% (13/23)	66.7% (54/81)	0.343
PJC via ENPD catheter	58.3% (7/12)	34.1% (15/44)	27.3% (38/139)	0.072
Combination of either two sampling methods	100% (10/10)	56.8% (21/37)	60.6% (77/127)	0.036
EUS-FNA	33.3% (2/6)	91.7% (33/36)	85.9% (116/135)	<0.001
Both ERP-based cytology and EUS-FNA	100% (6/6)	94.1% (32/34)	91.2% (114/125)	0.655

ERP, endoscopic retrograde pancreatography; PJC; pancreatic juice cytology; ENPD, endoscopic naso-pancreatic drainage; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration.

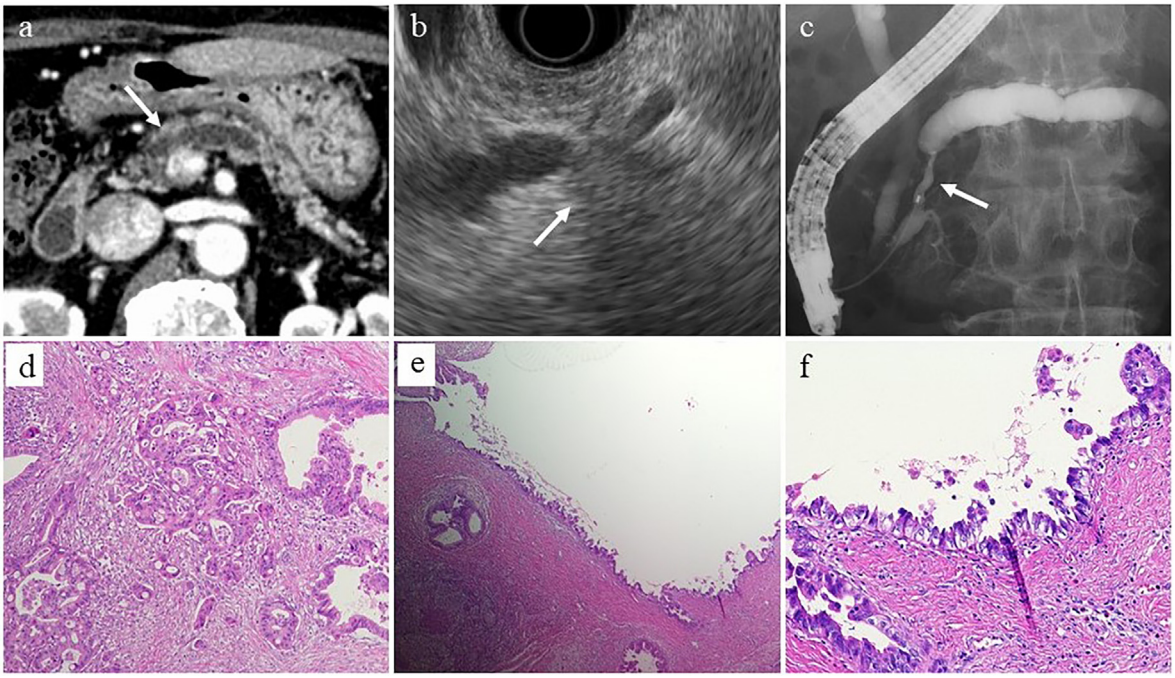

Fig. 2. A 72-year old man with pancreatic ductal adenocarcinoma with intraductal spread along the main pancreatic duct
(a) Computed tomography shows dilatation of the main pancreatic duct (MPD) from the pancreatic head to tail, but no tumor is found on the duodenal side (arrow); (b) Endoscopic ultrasonography shows an irregular hypoechoic mass with a diameter of 10 mm in the pancreatic head (arrow); (c) Endoscopic retrograde pancreatography shows stenosis in the MPD of the pancreatic body (arrow). (d) Histopathological findings show well differentiated tubular adenocarcinoma; (e, f) Intraductal spread along the MPD was observed approximately 10 mm toward the pancreatic tail side.

MPD was observed at 76.9% (10/13), 44.7% (17/21), and 14.6% (21/144) in the groups with tumor diameters ≤10 mm, 10–20 mm, and >20 mm, respectively (Fig. 2).

3.4. Complications

The incidence of complications in patients who underwent ERP was 8.2% (22/267), all of which were acute pancreatitis. All patients were mild cases and improved with conservative treatment. Table 5 shows the risk factors for acute pancreatitis development in this study. The incidence of pancreatitis was significantly higher in women than in men (11.9% vs. 5.0%, $P = 0.040$). In addition, the incidence of pancreatitis was significantly lower in patients who underwent PJC via ENPD catheter than in those who did not (5.1% vs. 16.7%, $P = 0.002$). The only complication observed with EUS-FNA was 1 case of pancreatic fistula. The median postoperative overall survival for patients with pancreatic body/tail cancer was 34 months for those who underwent EUS-FNA and 67 months for those who did not, and there was no significant difference between the two groups ($P = 0.376$ by log-rank test).

Table 5
Risk factors of post ERP pancreatitis.

Parameters	Pancreatitis incidence (%)		*P* value
	Present	Absent	
Age ≤70 years	7.9% (10/126)	8.5% (12/141)	0.865
Female sex	11.9% (15/126)	5.0% (7/141)	0.040
Pancreas head cancer	8.1% (13/160)	8.4% (9/107)	0.934
Tumor size ≤10 mm	15.4% (2/13)	7.9% (20/254)	0.291
PJC during ERP	8.2% (16/196)	8.5% (6/71)	0.940
Brush cytology	7.2% (8/111)	9.0% (14/156)	0.605
PJC via ENPD catheter	5.1% (10/195)	16.7% (12/72)	0.002

ERP, endoscopic retrograde pancreatography; PJC; pancreatic juice cytology; ENPD, endoscopic nasopancreatic drainage.

4. Discussion

EUS-FNA has been reported to have excellent diagnostic performance [7] and be extremely safe [15], and is thus the first option for the pathological diagnosis of PDAC. The present study also found that the diagnostic performance of EUS-FNA was generally better than that of ERP-based cytology, and the incidence of complications was very low at 0.6%. However, EUS-FNA could not be performed in many cases of PDAC when the tumor size was ≤10 mm, and the sensitivity was low in these cases (33.3%). According to Haba et al. [16], the sensitivity of EUS-FNA in diagnosing malignant pancreatic tumors ≤10 mm was 73.1%, and a multivariate analysis found that tumor diameter was an independent factor affecting the accuracy rate. In contrast, in the present study, the sensitivity of ERP-based cytology in PDAC tumors of ≤10 mm was very good (92.9%). It has been reported that EUS-FNA complications are more likely to occur in small tumors [17], which suggests that ERP-based cytology may be the first method to be considered for the pathological diagnosis of lesions that are ≤10 mm in diameter.

In the present study, the diagnostic performance of ERP-based cytology for PDAC ≤10 mm was significantly better than that for those >10 mm, which is believed to be due to the excellent performance of brush cytology and PJC via ENPD catheters. Nakaizumi et al. [18] reported that the sensitivity of PJC was highest in patients with tumors <20 mm diameter. They also suggested that fibrosis on the tumor margins, obstruction of the MPD, and decreased exocrine pancreatic function due to tumor growth can make it difficult for cancer cells to flow into the MPD. However, Takasawa et al. [19] found that intraductal spread along the MPD was significantly more common in pTS1 cases (histologically ≤2 cm in diameter) than in pTS2 cases (>2 cm and <4 cm in diameter) or larger (45% vs. 13%). In this study, 77% of PDAC patients with a tumor diameter ≤10 mm showed intraductal spread along the MPD, and there was a negative correlation between tumor diameter and the rate of intraductal

spread along the MPD. The high rate of intraductal spread along the MPD is believed to explain the higher sensitivity of ERP-based cytology for smaller PDAC tumors.

In this study, ERP-based cytology had better sensitivity for pancreatic body/tail cancers than for head cancer. While the sensitivity of the sampling methods did not differ significantly based on lesion site, two or more sampling methods were used in significantly more pancreatic body/tail cancers than in pancreatic head cancers (81% vs. 54%, $P < 0.001$), suggesting that the ability to combine multiple sampling methods increases the sensitivity for pancreatic body/tail cancers. While the MPD pathway in the pancreatic body/tail is straight, it is quite tortuous in the pancreatic head. When the MPD is obstructed by cancer in the pancreatic head, the pancreatic duct pathway cannot be confirmed, making it difficult to insert a guidewire upstream of the pancreatic duct. This might have made it more difficult to perform brush cytology and PJC using an ENPD catheter.

EUS-FNA is a safe procedure, with a recent prospective multicenter study reporting a complication rate of 1.2% in solid pancreatic masses [15]. However, there have been some reports of needle tract seeding from EUS-FNA [8], which is a complication that must be considered in cases where radical resection is possible. Yane et al. [20] reported a 3.4% incidence of needle tract seeding after EUS-FNA in patients with PDAC who underwent distal pancreatectomy. Although EUS-FNA has been reported to not affect the long-term prognosis after surgery [21,22], needle tract seeding could become a greater concern if the prognoses of PDAC cases that undergo surgery improve in response to the recent introduction of preoperative chemotherapy [23,24] and advancements in postoperative adjuvant chemotherapy [25,26]. ERP-based cytology, which has no risk of seeding, may therefore be a good choice for patients suspected of having resectable pancreatic body/tail cancer.

The greatest concern with ERCP is acute pancreatitis. Acute pancreatitis is the most common complication of ERCP and can be fatal in severe cases; thus, the application of ERCP needs to be considered carefully. The incidence of acute pancreatitis associated with ERCP diagnosis of PDAC has been reported to be 2.5% [27–29]. In the present study, 8.2% of the patients developed pancreatitis after ERP, although all cases were mild. Our analysis of the risk factors of post-ERP pancreatitis showed that the incidence was significantly lower in patients who underwent PJC via ENPD catheter, which suggests that placement of an ENPD catheter might have suppressed the development of pancreatitis. Mouri et al. [30] reported that using a small-diameter (4 Fr) catheter could reduce the incidence of post-ERCP pancreatitis without compromising the sampling rate. Although pancreatic duct stents have been reported to be useful in preventing post-ERCP pancreatitis [31,32], ENPD catheter placement allows the pancreatic duct to drain upstream of the stenosis. Another advantage is that there is no risk of blockage from food residues, which is possible with pancreatic duct stents. When performing ERP for the pathological diagnosis of PDAC, placing an ENPD catheter may be considered, since it might suppress the development of acute pancreatitis.

This study had several limitations. First, this was a retrospective study. Second, there was some patient selection bias, because the decision regarding which sampling method to use was left to the discretion of the attending physician. In the future, large-scale prospective studies will be needed to clarify the diagnostic performance of ERP-based cytology by sampling method, tumor site, and tumor size.

In conclusion, ERP-based cytology may be considered first for diagnosing small PDACs of $\leq$10 mm. In addition, ERP-based cytology may be considered before performing EUS-FNA in cases of suspected resectable pancreatic body/tail cancer, since it has relatively good diagnostic performance for pancreatic body/tail cancer, and EUS-FNA carries a risk of needle tract seeding.

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