Original Article

Can Endoscopic Ultrasound-Guided Fine Needle Aspiration Offer Clinical Benefit for Tumors of the Ampulla of Vater? -An Initial Study

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Abstract:
Objective: No previous studies have described endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) only for intra-ampullary lesions of the papilla of Vater. We aimed to examine whether EUS-FNA can be used to diagnose such lesions.

Methods: This study included a subset of 10 consecutive patients in whom EUS-FNA targeted the ampulla of Vater. All the patients underwent biopsy and/or brushing cytology under endoscopic retrograde cholangiopancreatography (ERCP) prior to EUS-FNA. The final diagnosis was based on pathological examinations of specimens obtained by surgical resection or clinical follow-up more than 1 year in case of evidence of benign lesions.

Results: Tissues from the ampulla of Vater could be obtained by EUS-FNA for all 10 patients. The final diagnosis was papillitis (n = 7) and intra-ampullary carcinoma (n = 3). Carcinoma of the ampulla of Vater showed neither exposure on the duodenal mucosal surface nor invasion to the pancreas. The diagnostic accuracy of surface biopsy with duodenoscopy, and intra-ampullary biopsy and/or brush cytology with ERCP and/or intra-ampullary biopsy after endoscopic sphincterotomy (EST) in distinguishing between benign and malignancy was 70%. The diagnostic accuracy of EUS-FNA was 100%. No complications associated with EUS-FNA were encountered in this study.

Conclusion: EUS-FNA for ampulla of Vater may be safely and accurately performed, and should be considered as a diagnostic modality before EST.

Keywords:
ampulla of Vater; endoscopic ultrasound; fine needle aspiration, intra-ampullary carcinoma; carcinoma of ampulla of Vater; papillitis

INTRODUCTION

The widespread use of cross-sectional imaging and esophagogastroduodenoscopy has contributed to increasing detection of abnormalities at the ampulla of Vater, in minimally symptomatic or asymptomatic patients. Various mass lesions including both benign and malignant, may be present at the ampulla of Vater, such as papillitis, carcinoma, and carcinoid tumors.[1-3] Endoscopic findings suggesting carcinoma of the ampulla of Vater include spontaneous bleeding, erosion, ulceration, surface friability, or induration of the enlarged ampulla.[4] However, the endoscopic abnormality seen in both benign lesion such as papillitis and intra-ampullary-type carcinoma, particularly non-exposed type and early stage T1 or T2 lesions,[5] is often only swelling of the ampulla of Vater. The differential diagnosis in such cases with an enlarged ampulla, but without any other visible abnormality is challenging.

In addition the accuracy rates for identifying carcinoma of the ampulla of Vater by endoscopic biopsy are not particularly high.[6-8] The accuracy rates are even lower for

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Received: 2012-05-24; Accepted: 2012-06-28
doi: 10.7178/eus.02.006

intra-ampullary-type carcinoma because of the normal overlying mucosa. To improve the diagnostic yield several reports have suggested that endoscopic biopsies be done after an endoscopic sphincterotomy (EST).[7, 9-10] When differentiating between benign and malignant tumors of the ampulla of Vater is difficult, endoscopic snare papillectomy may also be considered.[11] However, the complication rates associated with this technique are high.[12-14]

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an established diagnostic method for obtaining submucosal tissue samples from diverse types of lesions.[15-17] However, only a few reports have described EUS-FNA for tumors of the ampulla of Vater.[18-19] And no previous studies have described EUS-FNA only for intra-ampullary lesions of the papilla of Vater.

The present study therefore examined whether EUS-FNA could be useful as a diagnostic modality for lesions at the ampulla of Vater, particularly in identifying intra-ampullary-type carcinoma of the ampulla of Vater.

PATIENTS AND METHODS

Patients

Between January 1998 and April 2011, a total of 2332 EUS-FNA procedures were carried out at Aichi Cancer Center Hospital, Nagoya, Japan. Among these procedures, the present study retrospectively included a subset of 10 consecutive patients (7 men, 3 women; mean age: 66.9 ± 3.0 years; mean follow-up: 802.25 ± 145.3 days) who underwent EUS-FNA for tumor-like lesions detected as low-echoic areas at the ampulla of Vater on EUS. The enlarged ampulla of Vater was found alone in all 10 patients endoscopically. The size of the ampulla of Vater, common bile duct (CBD), and main pancreatic duct (MPD) were measured on EUS.

We firstly performed surface biopsy with duodenoscopy, and then, intra-ampullary biopsy and brushing cytology with endoscopic retrograde cholangiopancreatography (ERCP) and/or EUS-FNA. If these results were not malignant, then we would proceed to intra-ampullary biopsy after EST.

The final diagnosis was based on pathological examination of specimens obtained by surgical resection and clinical follow-up. If the signs of malignancy were absent at the end of follow-up (disease regression or no evidence of disease progression), carcinoma of the ampulla of Vater was ruled out.

All the patients were provided with written informed consents to all procedures associated with the study.

EUS-FNA technique

We used standard EUS-FNA technique, as previously described.[16-17] The ampulla was imaged at a frequency of 7.5 MHz using a convex linear-array echoendoscope (GF-UGT240; Olympus Optical, Tokyo, Japan) connected to an ultrasound device (Aloka Prosound a-5 and -10; Aloka, Tokyo, Japan), and a 22-G needle (NA-10J or NA-11J-KB; Olympus Optical) or 25-G needle (EchoTip-Ultra Needle; Cook Medical, Limerick, Ireland) was used for the aspiration. The aspirated material was separated into one part each for cytopathological evaluation and cell-block preparation. The material aspirated from all the 10 patients was immediately evaluated (Diff Quick Staining) by a cytopathologist and/or cytotechnologist for rapid diagnosis.[17]

Statistical analysis

Continuous variables are expressed as mean and range. The Chi-square analysis and Mann-Whitney *U* test for independence were used to compare the incidences and concordance of both groups. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics (Tab. 1)

The chief complaint of all the patients was asymptomatic and they were detected of abnormality of the ampulla of Vater by esophagogastroduodenoscopy at health check. Between carcinoma and benign lesions, there were no significant differences of the diameter of CBD ($P = 0.07$), the diameter of MPD ($P = 0.68$), the size of mass lesions ($P = 0.61$), the number of biopsies ($P = 0.17$), and the number of FNA passes ($P = 0.05$). Finally, 3 patients were diagnosed with carcinoma of the ampulla of Vater, and 7 patients were diagnosed with papillitis. T stage of all the patients with carcinoma of the ampulla of Vater was T2 according to TNM classification[5], but carcinoma was not exposed on the duodenal mucosal surface.

Results of diagnosis by biopsy and/or brush cytology and EUS-FNA (Fig. 1)

Based on surface biopsy and/or brush cytology and/or intra-ampullary biopsy with ERCP, only 1 patient was suspected to have malignancy; however, EUS-FNA and intra-ampullary biopsy after EST found no malignancy in this patient, and the final diagnosis was papillitis. Among the remaining 9 patients diagnosed with no malignancies based on surface biopsy and/or intra-ampullary biopsy and/or brush cytology, 6 patients were diagnosed without malignancies by EUS-FNA. Among these 6 patients, 5 patients were also diagnosed to have no malignancies after intra-ampullary biopsy after EST. In 1 patient, ERCP could not be performed. All of these 6 patients were finally diagnosed with papillitis on clinical follow-up and surgical resection. The remaining 3 patients, in whom malignancies could not be diagnosed based on surface biopsy and/or intra-ampullary biopsy with ERCP and/or brush cytology, were finally diagnosed with adenocarcinoma by EUS-FNA followed by surgical resection (Fig. 2, 3).

Diagnostic yield of biopsy and/or brush cytology and EUS-FNA: benign vs. malignant (Tab. 2)

Brush cytology led to a false-positive result for 1 patient

Table 1. Patients characteristics

No	Age/ Gender	Final diagnosis	Brushing cytology	EST	Number of biopsies	Number of FNA passes	Size (mm)	CBD (mm)	MPD (mm)	Repeat FNA/ Biopsy (number)	Follow-up period (d)
1	74/M	Carcinoma (operation)	+	-	4	3	10.0	13.2	7.0	-	616
2	68/M	Carcinoma (operation)	+	-	4	3	13.3	18.0	2.0	-	1164
3	67/M	Carcinoma (operation)	+	-	5	5	9.0	12.0	3.0	-	462
4	61/F	Papillitis (follow-up)	+	+	4	2	12.3	7.0	3.0	3 / 3	789
5	56/M	Papillitis (follow-up)	-	-	6	2	13.0	6.0	3.0	1 / 1	547
6	71/M	Papillitis (follow-up)	-	+	5	2	10.0	8.2	5.1	4 / 5	1978
7	77/M	Papillitis (follow-up)	+	+	8	3	16.0	12.4	4.2	3 / 4	624
8	81/M	Papillitis (operation)	+	+	10	2	12.0	18.0	3.0	-	744
9	50/F	Papillitis (follow-up)	+	+	4	3	10.0	5.0	2.0	1 / 2	489
10	64/M	Papillitis (follow-up)	+	+	6	2	11.0	8.0	4.2	3 / 4	609

EST: endoscopic sphincterotomy; FNA: fine needle aspiration; CBD: common bile duct; MPD: main pancreatic duct.

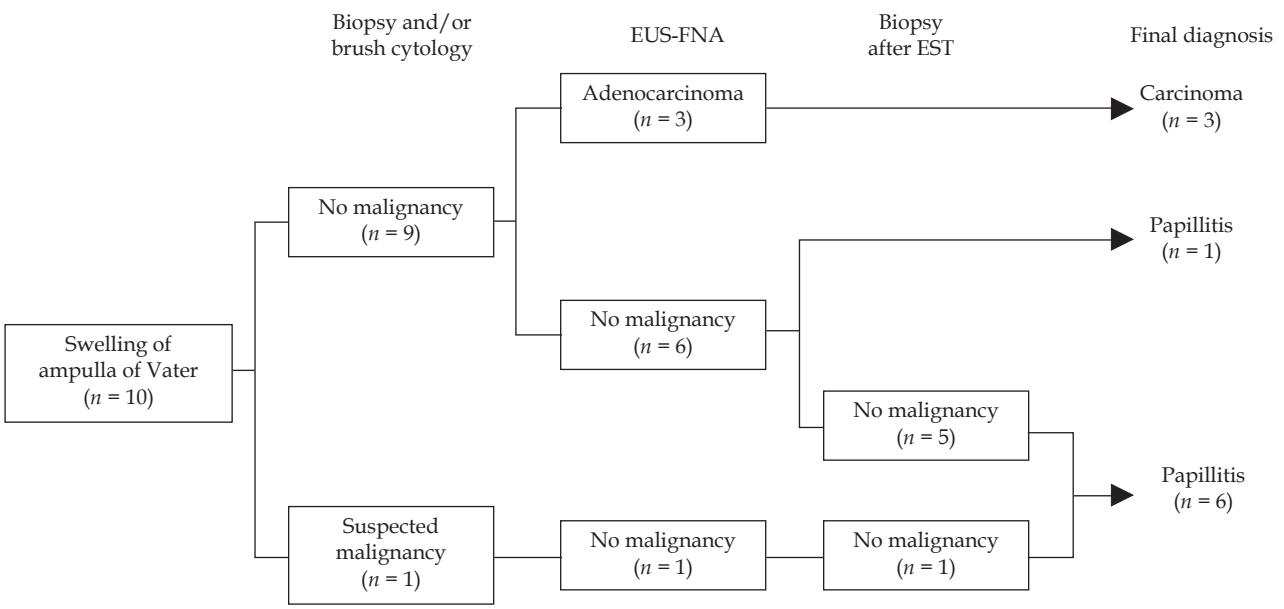

Figure 1. Figure 1 shows results of diagnosis by biopsy and/or endoscopic ultrasound-guided fine needle aspiration following identification of swelling of the ampulla of Vater.

and false-negative results for 3 patients. On the other hand, results of EUS-FNA showed no false-positives or false-

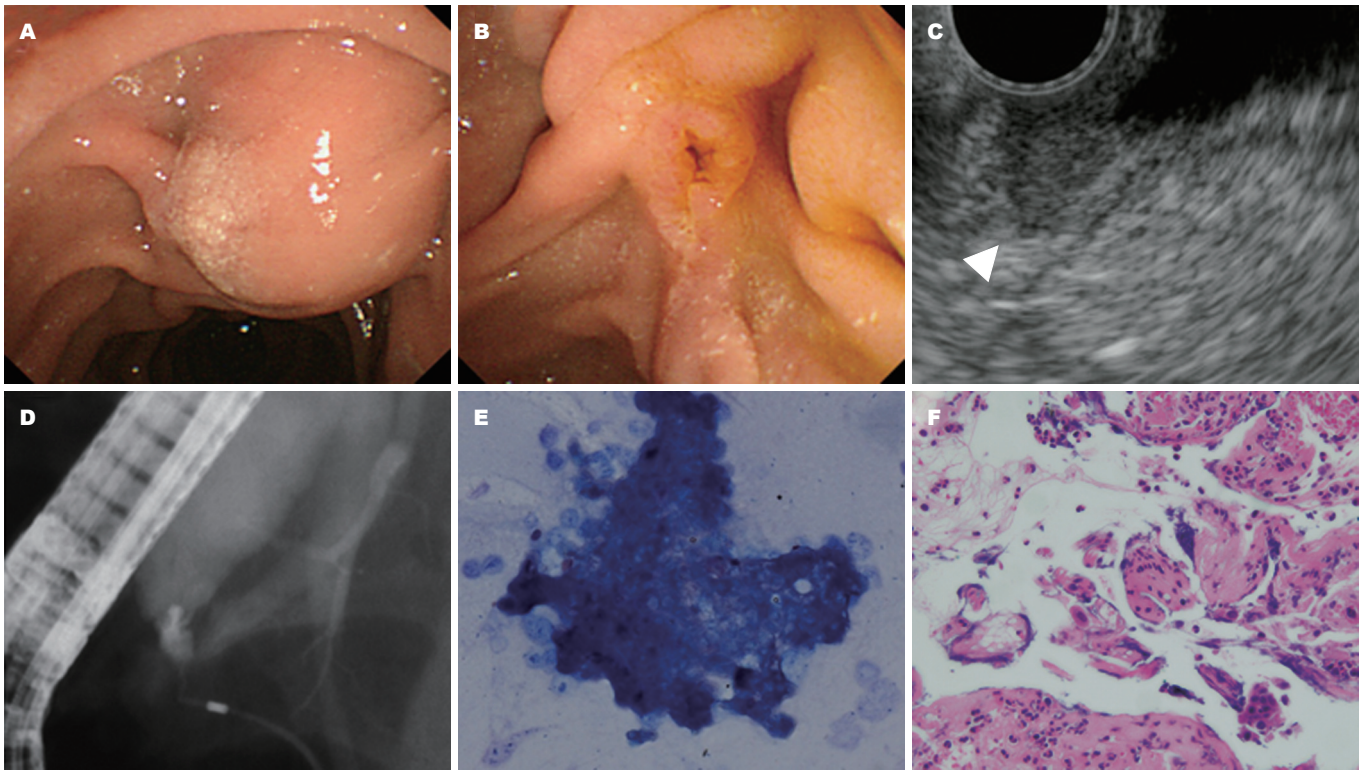

Figure 2. Endoscopic findings showed swelling of the ampulla of Vater (Fig. 2A, B). Endoscopic ultrasound showed a low echoic mass extending to the common bile duct (CBD), and the distal part of the CBD was stenosed by ERCP (Fig. 2C, D). Brush cytology and biopsy showed no malignancy (Fig. 2D, E).

Table 2. Diagnostic yield intra-ampullary biopsies and/or brushing cytology and EUS-FNA: malignant *vs.* benign

	Final diagnosis	
	Malignant (n = 3)	Benign (n = 7)
Diagnsosis by intra-ampullary biopsies and/or blushing cytology under ERCP and after EST		
Malignant	0 (TP)	1 (FP)
Benign	3 (FN)	6 (TN)
Diagnosis by EUS-FNA		
Malignant	3 (TP)	0 (FP)
Benign	0 (FN)	7 (TN)

EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; ERCP: endoscopic retrograde cholangiopancreatography; TP: true-positive; FP: false-positive; TN: true-negative; FP: false-negative.

negatives. The overall accuracy of intra-ampullary biopsies and/or brush cytology with ERCP and after EST was 70%, with a sensitivity of 0%, a specificity of 86%, a positive predictive value (PPV) of 0%, and a negative predictive value (NPV) of 67%. However, the overall accuracy of EUS-FNA was 100%, with a sensitivity, specificity, PPV, and NPV of 100%.

Complications

No complications were associated with EUS-FNA and intra-ampullary biopsy and/or brush cytology with ERCP and EST. However, groups undergoing intra-ampullary biopsy and/or brush cytology under ERCP and EST showed hyperamylasemia (365.8 ± 163.9 IU/L) as compared with the group receiving EUS-FNA (85.1 ± 13.8 IU/L) (P = 0.041).

DISCUSSION

The accuracy rates for endoscopic biopsies of carcinoma of the ampulla of Vater are 62%-85%.[6-8] Even for endoscopic biopsies obtained after EST, the accuracy rates only reach 80%.[7] One reason for this is the various histological grades of cellular atypia, which might increase in deeper tissues.[6-7] Therefore, when biopsies are performed, it is important to

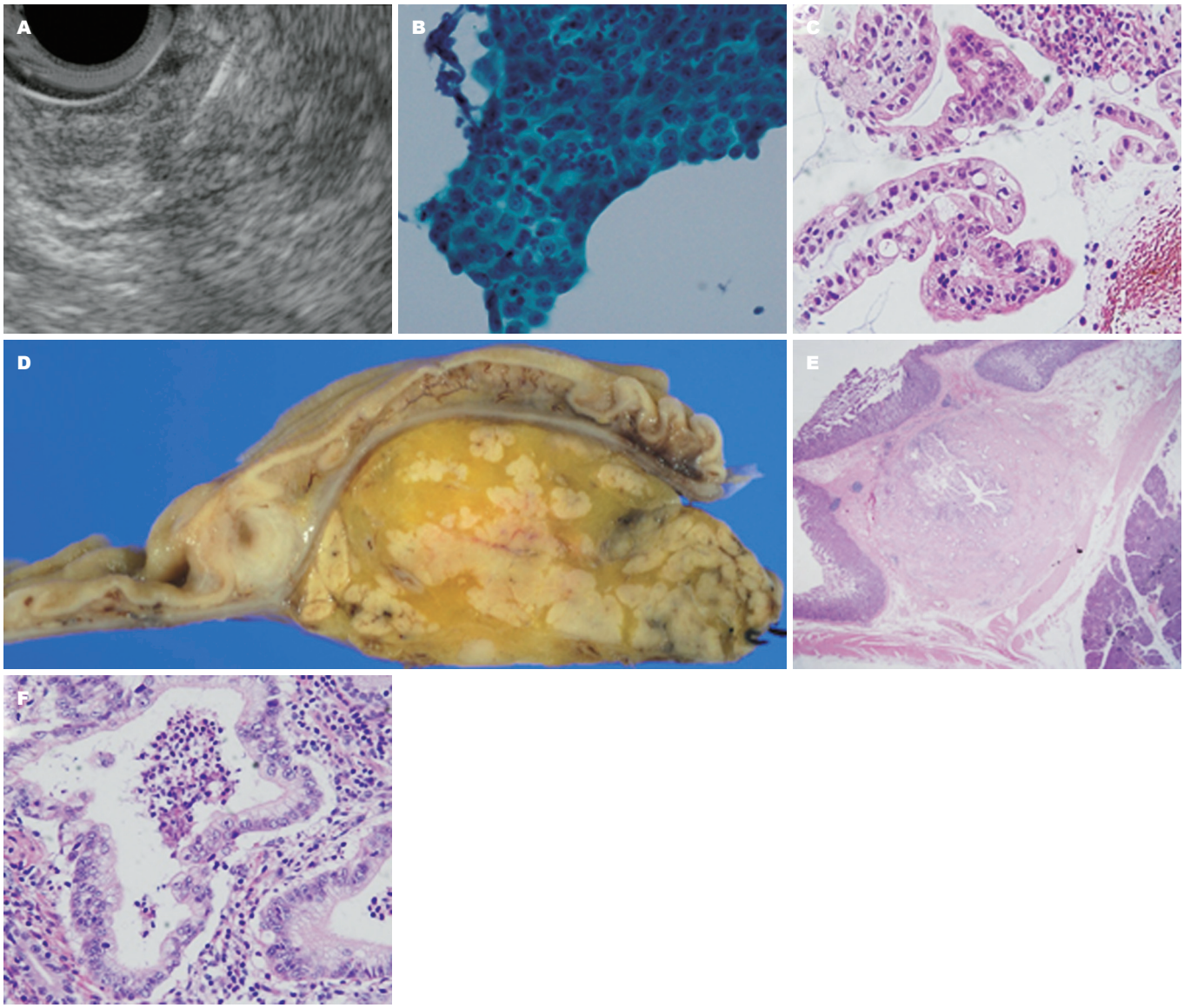

Figure 3. This patient underwent EUS-FNA (Fig. 3A). Endoscopic ultrasound-guided fine needle aspiration indicated malignancy (Fig. 3B, C). At a later date, this patient underwent surgical operation. Final diagnosis was intra-ampullary-type carcinoma of ampullary of Vater (Fig. 3D, E, F).

obtain samples from tissue deeper than the mucosa.

On the other hand, overall, EUS-FNA samples can be obtained from submucosal tissues with a sensitivity of 64%-94%, a specificity of 93%-100%, and an accuracy of 76%-95% for pancreatic lesions.[15-17] Only two reports of EUS-FNA for the ampulla of Vater have been published. Chang *et al*,[18] in an abstract for an invited paper from the University of California, reported an accuracy of 35% (7/20). On the other hand, Defrain *et al*[19] investigated 35 patients with suspected primary ampullary lesions, reporting a sensitivity of 82.4%, a specificity of 100%, and an accuracy of 88.8%. However, the precise endoscopic findings for the ampulla of Vater and T factor were not described in those reports. We considered that EUS-FNA should be evaluated for intra-ampullary lesions that seem difficult to diagnose using standard methods. The present study was thus planned to clarify the benefits for patients who could not be diagnosed by intra-ampullary biopsy and/or brush cytology with ERCP in addition to conventional endoscopic biopsy. No previous studies have described EUS-FNA only for intra-ampullary lesions of the papilla of Vater, and this study revealed the benefits of EUS-FNA for such lesions. To our knowledge, the present study might be the first.

In the present study, adequate tissue samples were obtained by EUS-FNA for all the 10 patients with intra-ampullary lesions of the papilla of Vater. Furthermore, no complications were observed in either the EUS-FNA group or the biopsy and/or brush cytology group, although

hyperamylasemia was significantly seen among biopsy and/or brush cytology group and EST group as compared with the EUS-FNA group.

However, it has the possibility that carcinoma could be missed by both techniques. Although the gold standard treatment may be surgery, it is also an undeniable fact that this procedure is greatly invasive for patients. Therefore, if results of EUS-FNA or intra-ampullary biopsy after EST were not malignant, it may be an option to carefully perform clinical follow-up with repeated EUS-FNA and intra-ampullary biopsy.

Several limitations must be considered when the results of this investigation are interpreted. First, since the intra-ampullary carcinoma is a relatively rare tumor, the study included a small number of cases. Second, the design was retrospective with information only from a single tertiary center. A large-scale study is thus needed to confirm the clinical impact of EUS-FNA for lesions of the ampulla of Vater, particularly in terms of intra-ampullary lesions.

In conclusion, EUS-FNA for the ampulla of Vater may be safely and accurately performed. If the diagnosis is inconclusive for tumor of the ampulla of Vater with conventional biopsy and/or brush cytology, EUS-FNA should be considered before biopsy after EST. That is because tumor confirmation on EUS may become difficult after EST.

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