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Usefulness of endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of pancreatic cancer

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Background. Endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) has come into widespread use, mainly in Western countries, as an efficient and safe method for the cytologic or histologic diagnosis of pancreatic cancer. However, it still has received relatively little attention in Japan. To evaluate the clinical status of EUS-FNAB in Japan, we retrospectively analyzed the results with regard to the ability of EUS-FNAB to diagnose pancreatic cancer, as well as its safety. ***Methods.*** A total of 52 patients (37 male, 15 female; mean age, 62.5 years; range, 33–85 years) with focal pancreatic lesions underwent EUS-FNAB at our group of hospitals in one region of Japan. Final diagnosis was confirmed by histologic examination of surgical specimens or clinical follow-up. ***Results.*** The final diagnoses were malignant tumors in 32 patients and benign ones in 20. Insertion of the needle into the lesion was successful in 50 of the 52 patients (96.2%). Adequate specimens were obtained by EUS-FNAB from 47 of the 50 pancreatic lesions (94.0%). With five false-negative and no false-positive results, the accuracy, sensitivity, specificity, and positive and negative predictive values were 89.4%, 82.1%, 100%, 100%, and 79.2%, respectively. No complications occurred. ***Conclusions.*** EUS-FNAB is an efficient and safe method for the histologic diagnosis of pancreatic cancer. It should be considered as one of the indispensable modalities for the histological diagnosis of pancreatic cancer in Japan, as it is in Western countries.

Key words: EUS-FNAB, pancreatic cancer, histologic diagnosis

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Introduction

Despite various advances in diagnostic imaging, including endoscopic ultrasonography (EUS), it is still difficult to make a reliable qualitative diagnosis of pancreatic cancer.[1] Unlike patients with other gastroenterological diseases, nonsurgical tissue sampling is difficult in patients with pancreatic disease. Therefore, some patients with pancreatic lesions may undergo invasive treatment for suspected cancer without definite histologic evidence. Lee[2] reported that 8% of radical pancreatic resections without preoperative histologic diagnosis were finally diagnosed as benign disease. Van Gulik et al.[3] found that 6% of 220 pancreatoduodenectomies performed on the suspicion of pancreatic head cancer were actually for benign inflammatory diseases. To avoid such unnecessary surgery, it is very important to establish minimally invasive methods for obtaining a preoperative histologic diagnosis. In patients with inoperable cancer, making a histologic diagnosis is also important for selecting treatment methods such as chemotherapy and radiotherapy, and for determining the prognosis.

In 1992, Vilmann et al.[4] reported the EUS-guided fine-needle aspiration biopsy (EUS-FNAB) method. This method was expected to be useful for collecting specimens to make a definite diagnosis when determining the therapeutic strategy for intramural gastrointestinal lesions and tumors of nearby organs. EUS-FNAB has since come into widespread use, mainly in Europe and North America, as an efficient and safe method for the histologic diagnosis of nonepithelial gastrointestinal lesions and pancreaticobiliary disease.[5–8] However, the use of EUS-FNAB for pancreatic lesions has received little attention and the procedure has only been performed at a limited number of Japanese institutions, due to insufficient availability of equipment and possible complications.[9,10] To clarify the clinical status of EUS-FNAB in Japan, we retrospectively analyzed the

results obtained at our group of hospitals in one region of Japan, to determine the ability of EUS-FNAB to diagnose pancreatic cancer, as well as its safety.

Patients and methods

Patients

The subjects were 52 patients with pancreatic lesions and parapancreatic diseases who underwent EUS-FNAB at Yamaguchi University Hospital, Kokura Memorial Hospital, Saiseikai Yamaguchi Hospital, Shuto General Hospital, Shinkoga Hospital, Ube Industries Central Hospital, Hikari City Hospital, Yamaguchi Rosai Hospital, and Shimonoseki City Hospital during the 33 months from July 2000 to March 2003. In this period, we had 118 patients with pancreatic cancer, 153 with chronic pancreatitis, and 59 with pancreatic cystic lesions. The indication for EUS-FNAB was a pancreatic lesion seen initially on other imaging studies. The inclusion criteria included patients with a clinical suspicion of pancreatic cancer who were referred for a diagnosis, as well as those who had an established diagnosis of pancreatic cancer who were referred for further staging. In this study, if a pancreatic cystic lesion was strongly suspected as malignant from other imaging studies, we did not perform EUS-FNAB. The patients' ages ranged from 33 to 85 years, with an average age of 62.5 years. The male/female ratio was 37:15. The subjects comprised 39 patients with solid pancreatic lesions, 11 with cystic pancreatic lesions, and 2 with enlargement of parapancreatic lymph nodes. The lesion was located in the head of the pancreas in 41 patients, the pancreatic body in 4, the pancreatic tail in 5, and the parapancreatic region in 2. The lesion was less than 2 cm in greatest diameter in 5 patients, 2 cm to less than 4 cm in 30 patients, and 4 cm or more in 17 patients (Table 1). The present study was approved by the Institutional Review Board of each hospital, and informed consent was obtained from all patients.

Methods

Prior to the performance of EUS-FNAB, the platelet count, prothrombin time, and partial thromboplastin time were measured to confirm the absence of a bleeding tendency. One well-trained endoscopist (S.R.) performed EUS-FNAB in all patients. Examination was always done with the patient under sedation with intravenous midazolam. The echoendoscope was a 7.5-MHz convex scanning GF-UC30P or GF-UC2000P-OL5 (Olympus Optical, Tokyo, Japan), and a 22-gauge NA-10J-1 or NA-11J-KB needle (Olympus Optical) or a 22-gauge Echotip needle (Wilson Cook, Salem, NC, USA) was used for sample collection. Specimens were subjected to conventional cytologic and histologic studies. Rapid cytologic examination (Diff-Quik stain; International Reagents, Kobe, Japan)[11] was also performed as needed.

The technique of EUS-FNAB was largely the same as that already reported.[6] First, the lesion was identified on B-mode imaging, followed by confirmation of the absence of vessels in the target area in the color Doppler mode. Then, while the angle and site of needle insertion was confirmed, the catheter was advanced to immediately above the mass. After determination of the correct direction, an aspiration needle was introduced into the lesion. The stylet of the needle was removed, and a 20-ml syringe was attached to create suction. While negative pressure was maintained, the needle was moved back and forth 10 to 20 times within the lesion. The pressure was released before the needle was removed from the lesion. Part of the sample thus obtained was used to prepare smears on glass slides, and cytologic examination was performed after staining with Papanicolaou stain and Geimsa stain. Another part of the specimen was fixed in formalin and stained with hema-

Table 1. Characteristics of pancreatic mass lesions evaluated using EUS-FNAB

	Types of mass lesions			
	Solid lesions	Cystic lesions	Lymph nodes	Total
Locations				
Pancreatic head	32	9	0	41
Pancreatic body	4	0	0	4
Pancreatic tail	3	2	0	5
Around the pancreas	0	0	2	2
Mass size				
<2 cm	3	1	1	5
2 cm to <4 cm	23	6	1	30
≥4 cm	13	4	0	17
Total	39	11	2	52

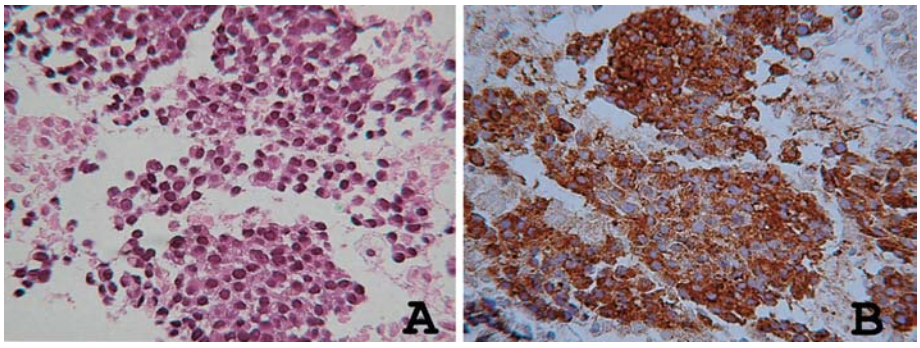

Fig. 1. A Histologic findings of a pancreatic tumor, obtained by endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB), showing acinar cell adenocarcinoma. **B** Immunostaining, showing positivity for α-fetoprotein in carcinoma cells. **A** H&E ×400. **B** ×400

toxylin and eosin (H & E) for conventional histologic examination. Histologic diagnosis was carried out according to the *Classification of pancreatic carcinoma* of the Japan Pancreas Society.[12] If necessary, a diagnosis was made after immunostaining for α-fetoprotein (Fig. 1B), chromogranin, synaptophysin, amylase, and other items. EUS-FNAB was continued until sufficient material was obtained with a maximum of five needle insertions (mean, 2.6). For the cystic lesions, we also analyzed pancreatic enzymes and tumor markers in the cystic fluid. The final diagnosis of all our pancreatic cystic lesions was confirmed by clinical follow-up.

The final diagnosis in each patient was based on the results of histologic examination of surgical specimens or clinical follow-up of more than 9 months. The final diagnosis after surgery (21 patients) or follow-up for 9 months or more (31 patients) was pancreatic ductal carcinoma in 29 patients, acinar cell carcinoma in 2, bile duct cancer in 1, chronic pancreatitis in 8, benign pancreatic cyst in 10, and pancreatic abscess in 2.

For EUS-FNAB, patients underwent hospitalization for at least 1 day and were observed for the development of any changes or symptoms of possible complications.

Results

Insertion of the needle into the lesion was successful in 50 of the 52 patients (96.2%). Of the 2 patients for whom the method failed, 1 had undergone partial gastrectomy with Billroth-II reconstruction, so the echoendoscope could not approach the lesion. In the other patient, the procedure was abandoned because of the presence of a major blood vessel in the path of the needle puncture. The lesions of the 50 patients who could be tested ranged in size from 1.2 to 7 cm (mean, 3.3 cm). Specimens suitable for examination were collected in 47 of the 50 patients, so the successful sampling rate was 94.0% (47/50). With regard to tumor diameter, the sampling rate was 100% (5/5) for lesions less than 2 cm, 93.1% (27/29) for lesions of 2 to less than 4 cm, and 93.8% (15/16) for lesions of 4 cm or more, with the differences not being significant. In the 3 patients whose samples were unsuitable for diagnosis, only blood clots were collected and no tumor parenchyma was obtained.

Table 2. EUS-FNA cytologic and/or histologic diagnosis of pancreatic mass lesions compared with the final diagnosis of cancer

		Final diagnosis	
		+	–
EUS FNA cytology and/or histology	+	23	0
	–	5	19

+, Malignant involvement; –, benign

When the pathologic diagnosis made by EUS-FNAB was compared with the final diagnosis in relation to the differentiation of benign from malignant disease in the 47 patients from whom assessable specimens were collected, no patient had a false-positive diagnosis. In other words, all patients who were positive for cancer on EUS-FNAB had cancer lesions at the final diagnosis. However, five patients were negative for cancer on EUS-FNAB but had a final diagnosis of cancer, i.e., five patients had false-negative results. The overall accuracy of diagnosis was 89.4%, the sensitivity of cancer diagnosis was 82.1%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 79.2% (Table 2).

Among the five patients with small lesions, less than 2 cm, one cystic lesion was clinically benign but the patient wished to make sure that the lesion was not a cancer. Another lesion was an enlarged lymph node close to the pancreatic head. In this patient, the EUS-FNAB diagnosis was benign, and we followed-up this patient as having chronic pancreatitis. The other three small lesions were tumors associated with the presence of chronic pancreatitis. In one of these patients, with an EUS-FNAB result of benign, we followed-up the patient as having chronic pancreatitis. The other two patients, with EUS-FNAB results of malignant, received curative operations, without the complication of dissemination.

In this study, the diagnosis before and after EUS-FNAB changed in 11 patients. Among these 11 patients, five with chronic pancreatitis and three with benign cyst avoided having an unnecessary operation. One patient with acinar cell adenocarcinoma received chemotherapy. Two patients with pancreatic cancer received an operation.

Monitoring for 1 day after EUS-FNAB and laboratory tests revealed no complications such as pancreatitis, hemorrhage, infection, or perforation in any of the patients. Intraoperative examination and clinical follow-up showed no evidence of cancer dissemination due to this examination.

Discussion

The application of a convex or linear echoendoscope has recently made pancreatic FNAB possible under EUS control.[4] Unlike a conventional radial echoendoscope, these endoscopes produce images parallel to the long axis, making it possible to follow needle movements in real time. If the Doppler mode is added, it becomes possible to avoid vessels. However, EUS-FNAB is not widely used in Japan. The reasons for this may be the following three points: (1) there is a lower incidence of alcoholic pancreatitis and tumor-forming pancreatitis in Japan than that in Europe or North America. Such diseases, which are difficult to differentiate from pancreatic cancer, are relatively uncommon in Japan. (2) Physicians are relatively conservative about performing chemotherapy and radiotherapy for inoperable pancreatic cancer. (3) Physicians are concerned about tissue sampling by EUS-FNAB because of the risk of procedural complications, including the peritoneal dissemination of tumor cells.

Previous reports, mainly from Western countries, on EUS-FNAB for pancreatic lesions[5–9] have stated that the sensitivity and accuracy were 64%–92% and 85%–95%, respectively. In the present study, the differentiation of benign from malignant pancreatic lesions using EUS-FNAB showed a sensitivity of 83.3% and an accuracy of 90.5%, which were equal to the results obtained with extracorporeal ultrasound (US)-FNAB or computed tomography (CT)-FNAB (sensitivity, 66.7%–98.3%; accuracy, 71.8%–98.3%).[13–15] There were no false-positive results in the present series; therefore, it seems that EUS-FNAB is useful to avoid unnecessary surgery. The diagnosis of malignancy by EUS-FNAB provides a solid basis for determining the therapeutic strategy for the patient with pancreatic cancer.

On the other hand, false-negative results occurred in five patients. Possible causes of a false-negative result include the heterogeneous interior of some tumors (because pancreatic cancer frequently shows extensive fibrosis) and sampling error. Of the five patients with false-negative results, four were stages I and II, and one was stage IV; all five had chronic pancreatitis. Some previously published reports on this subject noted a similar rate of false-negative FNAB results. In these series, the presence of chronic pancreatitis appeared to be responsible for this.[16,17] To reduce false-negative results, it may be necessary to perform rapid cytologic examination by methods such as Diff-Quik staining,[11] to confirm that suitable material was collected, or to use a Trucut needle to obtain biopsy specimens.[16,17] We think histologic diagnosis is useful in addition to cytologic diagnosis, because the diagnosis of well-differentiated adenocarcinoma of the pancreas may often be difficult based on the interpretation of cytologic specimens alone. In this study, all the specimens were subjected to both cytologic and histologic studies. We also used immunostaining for two cases of acinar cell adenocarcinoma, and it was very useful for reaching precise diagnoses. In light of the rate of progression of pancreatic cancer, repeat EUS-FNAB may be considered after 1 month or so if the tumor shows a tendency to grow. Considering that 20.8% (5/24) of pancreatic lesions diagnosed as benign by EUS-FNAB are actually malignant, such patients require careful follow-up and confirmation by other imaging methods.

The rate of complications associated with EUS-FNAB is reported to be 0.5%–2.0%,[5,18,19] which is similar to the complication rate of 0–0.5% associated with CT-FNAB.[13–15] The complications associated with EUS-FNAB include infection, hemorrhage, perforation at sites of cancer-induced stenosis, pancreatitis, and peritoneal dissemination. The incidence of these complications has been reported to be significantly higher when biopsy is performed for cystic disease.[18,19] Hence, in addition to the prophylactic administration of antibiotics and the use of an aseptic technique, we should be careful in determining the indications for this procedure. The most dangerous potential complication is the peritoneal dissemination of cancer cells along the needle track after EUS-FNAB, but only one such case has been reported to date. Hirooka et al.[10] detected peritoneal dissemination after EUS-FNAB in a patient with an intraductal papillary mucinous tumor. On the other hand, Fornari et al.[20] reported that peritoneal dissemination occurred in only 1 of 10766 patients who underwent extracorporeal US-FNAB at 33 institutions. The shorter needle track for EUS-FNAB than for extracorporeal US-FNA suggests an even lower likelihood of peritoneal dissemination. Also, when carcinoma of the pancreatic head is sampled from the duodenum, dissemination will have very little effect on prognosis because the needle track is included within the area of surgical resection. Johnson et al.[21] divided 32 patients with resectable pancreatic cancer into groups with and

without preoperative FNAB and noted no significant differences between the two groups of patients (total, 32 patients) either with regard to positivity for cancer by peritoneal washing cytology or in the incidence of peritoneal dissemination. Matsumoto et al.[9] compared 40 patients who had undergone EUS-FNA with 14 patients who had not and reported no significant differences between the two groups of patients with regard to the incidence of ascites. However, because EUS-FNAB is a relatively new technique and the number of patients studied is limited, the issue of peritoneal dissemination is still controversial. Thus, we should always keep this problem in mind and be careful when deciding on the indication for EUS-FNAB.

According to our experience, it was possible to identify pancreatic cancer cells in sections of tissue obtained by EUS-FNAB, but it was difficult to rule out pancreatic cancer in apparently benign lesions. Thus, the indication for EUS-FNAB of pancreatic lesions seems to be pancreatic cancer that is clinically unresectable and requires histologic diagnosis before the start of radiotherapy and chemotherapy. In such cases, a pathological diagnosis is required and, because effective treatment methods for pancreatic cancer are not yet established, histologically based analysis of the efficacy and safety of multidisciplinary therapy is essential. On the other hand, when EUS-FNAB was performed for clinically resectable mass lesions of the pancreas, some false-negative results occurred. Considering the possible danger of tumor-cell dissemination, EUS-FNAB examination does not seem to be indicated for such lesions. However, if the lesion is located in the pancreatic head and can be approached by the transduodenal route, which involves a lower risk of peritoneal dissemination, and when histologic diagnosis is important for determining the therapeutic strategy, EUS-FNAB may be performed with caution. Regarding cystic lesions, if cancer is suspected from other imaging studies, caution should be used when deciding to perform EUS-FNAB, because dissemination has been reported.

In conclusion, from our experience with patients in one region of Japan, EUS-FNAB is an efficient and safe method for the histologic diagnosis of pancreatic cancer. Therefore, EUS-FNAB should be considered as one of indispensable tools for the histologic diagnosis of pancreatic cancer in Japan, as it is in Western countries.

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