—Original Article—

Histopathological evaluation of needle tract seeding caused by EUS-fine-needle biopsy based on resected specimens from patients with solid pancreatic masses: An analysis of 73 consecutive cases

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ABSTRACT

Background and Objectives: EUS-guided fine-needle biopsy (EUS-FNB) is considered a safe and useful method for preoperative diagnosis of resectable solid pancreatic masses. However, needle tract seeding (NTS) after EUS-FNB has recently been reported, which may affect long-term outcome. The aim of this study was to evaluate NTS after EUS-FNB. **Materials and Methods:** We reviewed 73 resected cases that underwent preoperative EUS-FNB for a pancreatic tumor from April 2014 to March 2016 and evaluated the utility and adverse events of EUS-FNB based on consecutively resected pathological specimens. **Results:** The final diagnoses were pancreatic ductal adenocarcinoma ($n = 67$), neuroendocrine neoplasm ($n = 5$), and acinar cell carcinoma ($n = 1$). The diagnostic accuracy of preoperative EUS-FNB was 98.6%. Clinical adverse events were observed in 4.1% of cases (bleeding, $n = 2$; acute pancreatitis, $n = 1$) and abnormal pathological findings in 4.1% (NTS, $n = 2$; acute focal pancreatitis, $n = 1$). **Conclusions:** Although EUS-FNB is useful for preoperative diagnosis of pancreatic tumors, we may need to reconsider the risk of NTS and use of EUS-FNB in patients with a resectable solid pancreatic mass unless the tract itself is planned to be resected.

Key words: EUS-fine-needle biopsy, needle tract seeding, pancreatic cancer

INTRODUCTION

EUS-fine-needle biopsy (FNB) is used to diagnose solid pancreatic masses.[1,2] In general, preoperative EUS-FNB for resectable solid pancreatic masses has high accuracy with overall sensitivity of 89% and specificity of 96%,[1] allowing optimal therapy. However, EUS-FNB has been

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reported to have an overall morbidity rate of 0.98% and a mortality rate of 0.02%,[2] and complications such as infection, bleeding, perforation, and pancreatitis may be inevitable. In particular, needle tract seeding (NTS) caused by EUS-FNB has been attracting attention since it was first reported by Paquin *et al.* in 2005[3] because of its potential effect on long-term outcome in patients with resectable solid pancreatic masses. Although El Haji and Al-Haddad found no significant association between EUS-FNB and an increased rate of recurrence of gastric or peritoneal cancer,[4] there have been several recent case reports on NTS after EUS-FNB.[3,5-16] Interestingly, almost all of these cases involved patients undergoing distal pancreatectomy. Therefore, EUS-FNB is thought to be risky in terms of NTS regardless of the prognosis.

To date, NTS after EUS-FNB has been investigated using diagnostic imaging methods such as computed tomography (CT) and magnetic resonance imaging in the postoperative follow-up period to detect metastatic lesions resulting from NTS. Therefore, in distal pancreatectomy, the actual NTS rate after EUS-FNB is not known because the gastric wall through which the puncture route passes is not resected. In contrast, in pancreatoduodenectomy (Whipple procedure), the area surrounding the needle tract is usually resected together with the pancreatic lesion. However, NTS after EUS-FNB has not been evaluated based on consecutively resected pathological specimens in which both preoperative EUS-FNB and resection were performed in patients with solid pancreatic masses.

The aim of this study was to evaluate the NTS rate after EUS-FNB based on histopathological findings as "histological adverse events" in patients undergoing resection of solid pancreatic masses.

MATERIALS AND METHODS

We retrospectively reviewed 73 resected consecutive cases in which preoperative EUS-FNB for a pancreatic tumor was performed at our institution between April 2014 and March 2016. We evaluated the utility and adverse events of EUS-FNB based on the whole resected pathological specimens. We investigated sex, age, tumor size, tumor location, puncture route, median interval between EUS biopsy and pancreatic surgery, operative procedure, margin status, histological grade, pathological stage according to the Union for International Cancer Control (UICC) classification, and use of adjuvant chemotherapy. This study was approved by our Institutional Review Board (No. T2020-0056).

Preoperative EUS-fine-needle biopsy procedure

EUS-FNB was performed using a curved linear array echoendoscope (GF-UCT240 or GF-UCT260; Olympus Medical Systems, Tokyo, Japan) and end-cut type needle under moderate sedation. All FNB punctures were performed by experts in the EUS-FNB procedure. The pancreatic mass was visualized under EUS. After careful evaluation, including assessment of the regional vasculature using the color Doppler function, the pancreatic mass was punctured through the transgastric or transduodenal route. Next, the stylet was removed and suction was applied with a 20-mL syringe under negative pressure at the first puncture. If there was extensive macroscopic blood contamination, a slow pull technique or no suction was applied at the second puncture. The needle was moved to-and-fro within the pancreatic mass >10 times using the fanning technique. The obtained tissue specimens were immediately fixed in 10% neutral-buffered formalin solution for histological examination by releasing the syringe and reinserting the stylet. The number of FNB passes was decided according to the visible macroscopic core, defined as white or yellow pieces of obtained tissue with apparent bulk, without rapid on-site evaluation. Basically, 2 FNB passes were performed; however, an additional puncture was performed if the tissue specimens obtained by the 2 FNB passes were considered insufficient for pathological diagnosis.

Histopathological evaluation

All surgically resected specimens were fixed in 10% buffered formalin and stained with hematoxylin and eosin (HE) by routine procedures. In addition to routine HE staining, histochemical and immunohistochemical staining were performed as appropriate. Histological diagnoses, including tumor size, type, and growth pattern, depth of invasion, lymphatic permeation, vascular invasion, perineural invasion, and lymph node metastasis, were made based on the 2019 World Health Organization classification of digestive system tumors by a single pathologist (HY). TNM staging was performed according to the TNM Classification of Malignant Tumors of the UICC. The histopathological diagnosis and findings from EUS-FNB of each tumor were reviewed by the same pathologist (HY). Who was blinded to the clinical findings. After reviewing the EUS-FNB images and the location of

the puncture (stomach or duodenum), the route of puncture of the resected specimen was confirmed pathologically. NTS was defined as a continuum between the puncture route and the tumor.

Definition of clinical adverse events during EUS-fine-needle biopsy and follow-up

Clinical adverse events were defined as a reduction in hemoglobin (>2.0 g/dL) or clinically visible bleeding after EUS-FNB. Patients were usually followed up in our hospital at 3-month intervals if there were no specific medical problems. At each visit, imaging studies were performed to check for recurrence.

RESULTS

Data of 73 patients who underwent preoperative EUS-FNB for a solid pancreatic mass at our institution between April 2014 and March 2016 were analyzed. The final diagnoses were pancreatic ductal adenocarcinoma (PDAC; *n* = 67), neuroendocrine neoplasm (*n* = 5), and acinar cell carcinoma (*n* = 1) [Table 1].

Table 1. Final diagnosis

Final diagnosis	*N*
Patients, *n*	73
Pancreatic ductal adenocarcinoma	67
Neuroendocrine neoplasm	5
Acinar cell carcinoma	1

Patient and tumor characteristics are shown in Table 2. The characteristics of the adenocarcinomas are summarized in Table 3. Mean age was 67.2 ± 10.2 years and 61.6% of the patients (45/73) were male. Mean lesion size was 30.0 mm, 54.8% of the lesions (40/73) were located in the head of the pancreas, and 45.2% (33/73) were in the body or tail. Of the 67 adenocarcinomas, 50 (74.6%) were classified as IIB according to the 7th UICC classification. The median interval between the initial EUS biopsy and pancreatic surgery was 35.0 days. The most common type of surgery was pancreatoduodenectomy. The R0 resection rate was 67.2% (45/67). Adjuvant chemotherapy was given in 92.5% of these patients (62/67).

The puncture route for EUS-FNB was transduodenal in 53.8% of cases (36/67) and transgastric in 46.2% (31/67). Preoperative EUS-FNB sampling was adequate in 98.6% of cases (72/73) and diagnostic accuracy was 100% (98.6% by intention-to-treat analysis) [Table 2].

EUS-FNB-related adverse events are shown in Table 4. The clinical adverse event rate was

Table 2. Patient and tumor characteristics

	Total	PDAC	NET/acinar
Patients, *n*	73	67	6
Sex, male/female, *n*	45/28	43/24	2/4
Age (years), mean±SD	67.2±10.2	68.0±10.0	59.7±7.1
Tumor size (mm), median (range)	30.0 (7-140)	34.0 (12.5-75)	26.5 (7-140)
Tumor site (head/body-tail), *n* (%)	40 (54.8)/33 (45.2)	37 (55.2)/30 (44.8)	2 (33.3)/4 (66.6)
Puncture route, TG/TD, *n* (%)	34 (46.5)/39 (53.5)	31 (46.2)/36 (53.8)	2 (33.3)/4 (66.6)
Needle passes, median (range)	3.17 (2-5)	3.21 (2-5)	3.17 (2-4)
Needle size (25G/22G/20G), *n* (%)	14 (19.2)/56 (76.7)/3 (4.1)	12 (18.0)/52 (77.5)/3 (4.5)	2 (33.3)/3 (50.0)/1 (16.7)
Interval duration (days), median (range)	35.0 (6-304)	34.5 (6-304)	54.7 (34-110)
Sampling adequate, *n* (%)	72 (98.6)	66 (98.5)	6 (100)
Diagnostic accuracy, *n* (%)	73 (100)	67 (100)	6 (100)

Acinar: Acinar cell carcinoma; NET: Neuroendocrine tumor; PDAC: Pancreatic ductal adenocarcinoma; SD: Standard deviation; TG: Transgastric; TD: Transduodenal

Table 3. Characteristics of adenocarcinomas

Characteristics of adenocarcinomas	*n* (%)
Type of surgery, SSPPD/PPPD/DP/TP/partial, *n* (%)	7 (10.4)/29 (43.3)/28 (41.8)/3 (4.5)/0 (0)
Outcomes, R0/R1/R2, *n* (%)	45 (67.2)/22 (32.8)/0 (0)
Peritoneal recurrence, *n* (%)	8 (11.9)
Adjuvant chemotherapy (%)	62 (92.5)
Tumor histological grade, well/moderately/poorly/undifferentiated/unknown, *n* (%)	8 (11.9)/44 (65.7)/12 (17.9)/2 (3.0)/1 (1.5)
7th UICC staging, IA/1B/IIA/IIBB/III/IV, *n* (%)	2 (3.0)/1 (1.5)/11 (16.5)/50 (74.5)/3 (4.5)/0 (0)

DP: Distal pancreatectomy; PPPD: Pylorus-preserving pancreatoduodenectomy; SSPPD: Subtotal stomach-preserving pancreatoduodenectomy; TP: total pancreatectomy; UICC: Union for international cancer control

4.1% (bleeding, *n* = 2; pancreatitis, *n* = 1). The pathological adverse event rate was also 4.1% (NTS, *n* = 2; pancreatitis, *n* = 1).

The clinicopathological features of the 2 cases of NTS are described below and summarized in Table 5. Histologically, case 1 was adenocarcinoma and case 2 was acinar cell carcinoma. The tumor was in the head of the pancreas in case 1 and involved the head-to-tail in case 2. Case 1 was treated by pancreatoduodenectomy and case 2 by total pancreatectomy.

Case 1

The patient was a 67-year-old man who underwent pancreatoduodenectomy for PDAC and had developed pancreatitis after EUS-FNB [Figure 1]. Microscopy showed necrotic tissue scattered throughout the pancreatic parenchyma and adenocarcinoma in the muscle layer of the duodenum separate from the main lesion, suggesting NTS. Peritoneal dissemination was detected 1 year after the operation.

Case 2

The patient was a 66-year-old man with acinar cell carcinoma who underwent total pancreatectomy [Figure 2]. Microscopy showed a small isolated tumor in the muscle layer separate from the main lesion and on the puncture route, suggestive of NTS.

DISCUSSION

This is the first report on pathological adverse events associated with EUS-FNB. Surprisingly, EUS-FNB-related NTS was detected in 2.7% of the patients in this series. Considering that serial sections of whole resected specimens are microscopically examined at 5-mm intervals, NTS can be expected to occur more frequently. Our data suggest that an ability to detect NTS microscopically along the EUS-FNB puncture route is important.

Pancreatic surgery itself still has high morbidity and mortality rates. Therefore, preoperative diagnosis of pancreatic lesions using EUS-FNB is needed to avoid unnecessary surgery for mass-forming pancreatic disease, such as chronic pancreatitis and autoimmune pancreatitis. Publication of some case reports of NTS has led to some reluctance to use EUS-FNB for the diagnosis of pancreatic body and tail cancer.[17] However, Beane *et al.* found no difference in the recurrence-free survival or overall survival between patients with adenocarcinoma undergoing distal pancreatectomy who underwent preoperative EUS-FNB and those who did not.[18] Furthermore, El Haji and Al-Haddad found that preoperative EUS-FNB was not associated with longer recurrence-free survival or overall survival.[4]

Table 4. Clinical and histopathological adverse events of EUS-guided fine-needle aspiration

Adverse events	*n* (%)
Clinical adverse events, *n* (%)	
Bleeding	2 (2.7)
Pancreatitis	1 (1.3)
Pathological adverse events, *n* (%)	
Needle tract seeding	2 (2.7)
Pancreatitis	1 (1.3)

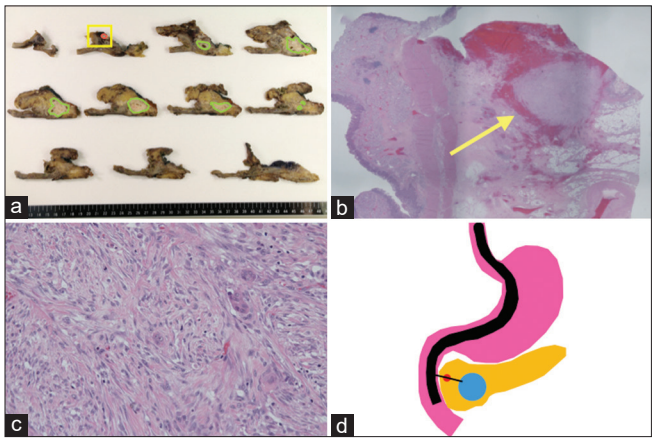

Figure 1. Case 1: (a) Cross-section of the fixed excised specimen. The largest diameter of the tumor was 60 mm and it was localized in the pancreas. (b) Histopathological findings in the resected specimen. Necrotic tissue was scattered in the pancreatic parenchyma (arrow). (c) Adenocarcinoma was located in the muscle layer of the duodenum separate from the primary tumor. (d) Schema showing the location of the puncture route and needle tract seeding (red ball)

Table 5. Clinicopathological characteristics in 2 cases of needle tract seeding

Case	Sex/ age, years	Tumor size (mm)	Tumor site	Puncture route	Needle passes	Needle size (gauge)	Histological grade	7th UICC stage	Type of surgery	Outcomes, R (*n*)	Peritoneal recurrence, *n*
1	M/67	60	H	TD	2	22	Mod	IIB	PPPD	1	1
2	M/66	140	H to T	TG	4	20,22	Acinar	-	TP	0	0

Acinar: Acinar cell carcinoma; H: Head; Mod: Moderately differentiated type; PPPD: Pylorus-preserving pancreatoduodenectomy; T: Tail; TD: Transduodenal; TG: Transgastric; TP: Total pancreatectomy; UICC: Union for international cancer control

Some interesting reports recently discussed the mechanism of metastatic progression based on EUS-FNB for pancreatic cancer. Katanuma *et al.* hypothesized that NTS contributes to distant metastasis by facilitating the spread of tumor cells via the lymphatic vessels.[7] Subsequently, Yamauchi *et al.* noted that this mechanism can be inferred from the fact that metastatic lesions occur mainly in the submucosal layers, which have small blood vessels and contain lymph nodes.[15] In both cases of NTS identified in the present study, tumor cells were located in the muscle layer, which contains blood and lymphatic vessels. As suggested by both Katanuma *et al.* and Yamauchi *et al.*, it is possible these metastases occur as a result of adherence of tumor cells to blood and lymphatic vessels.

Levy *et al.* found that malignant cells were often present in luminal fluid in the gastrointestinal tract following EUS-FNB in patients with pancreatic tumors.[19] They suggested that these tumor cells could have translocated from extraluminal sites into the gastrointestinal tract and intervening tissues.[19] In our study, 11.8% of patients had CT-confirmed peritoneal dissemination during the follow-up period; none of these cases involved NTS but were beyond stage IIA, with tumors extending outside the pancreatic parenchyma. Therefore, it is difficult to associate peritoneal dissemination with EUS-FNB. However, based on the report by Levy *et al.*, it is possible that cancer cells translocate from the puncture route to the peritoneal cavity, leading to peritoneal dissemination.

The details of the 13 previous case reports on NTS are shown in Table 6 and the clinicopathological features of the patients are summarized in Table 7. Stage I or IIA tumors, which are localized within the pancreas, were present in 84.6% of the cases (11/13). Moreover, the main sites of recurrence were in the submucosal layer of the gastric wall, which is separated from the main pancreatic lesion. Therefore, we hypothesize that there are two main mechanisms for disease recurrence as a result of NTS after EUS-FNB: (1) pathological underestimation, in which the tumor is diagnosed as being localized to the pancreas (UICC stage, T1 or T2) but actually extends outside the pancreas, invading the serosa or retropancreatic tissue (UICC stage, T3); and (2) engraftment of core tissue from EUS-FNB into other organs, such as the gastric, duodenal, or intraperitoneal wall on a puncture route. Pathological underestimation of NTS may occur because the

Table 6. Summary of case reports of needle tract seeding

	First author	Year of publication	Age, years/sex	Site	Diagnosis	Stage	Puncture lumen	Needle (gauge)	Passes (*n*)	Time interval (months)	Seeding site	Size (mm)	Outcomes	Layer	Reference
1	Paquin	2005	65/male	Tail	PDAC	T1N0M0	TG	22	5	21	PGW	50	DP	SM	3
2	Ahmed	2011	75/male	Body	PDAC	T2N0M0	TG	-	Multiple	39	PGW	45	CP→ total gastrectomy	Serosa	5
3	Chong	2011	55/female	Tail	PDAC	T2N0M0	TG	22	2	26	PGW	40	DP→ incurable	-	6
4	Katanuma	2012	68/female	Body	PDAC	T2N0M0	TG	22	4	22	PGW	-	DP	SM	7
5	Sakurada	2015	87/female	Body	ASC	T2N0M0	TG	22	-	19	PGW	20	DP→PG	Subserosa	8
6	Minaga	2015	63/female	Body	PDAC	T3N0M0	TG	22	3	8	PGW	12	DP→PG	SM	9
7	Tomonari	2015	78/male	Body	PDAC	T3N0M0	TG	22	2	9	PGW	32	DP→SG	SM	10
8	Naruse	2015	72/female	Body	PDAC	T4N0M1	TG	22	4	10	PGW	16	Died	SM	11
9	Kita	2016	68/female	B-T	PDAC	-	TG	22	2	4	PGW	-	Not reported	SM	12
10	Minaga	2016	72/female	Body	PDAC	T1N0M0	TG	22	3	24	PGW	30	DP→ gastrectomy	SM	13
11	Iida	2016	78/female	Tail	PDAC	T3N0M0	TG	22	3	6	PGW	18	DP→DG→ recurrence	-	14
12	Yamauchi	2016	65/female	Body	PDAC	T3N0M0	TG	22	1	22	PGW	28	DP→PG	SM	15
13	Matsumoto	2018	50/male	Body	PDAC	T3N0M0	TG	21	3	8	PGW	25	DP+PG	-	16

CP: Central pancreatomy; DG: Distal gastrectomy; DP: Distal pancreatectomy; PG: Partial gastrectomy; SG: Subtotal gastrectomy

pathological diagnosis is based on serial sections of a resected specimen at 5-mm intervals, and tumors that are missed could lead to recurrence through direct invasion of the remaining peritoneal or gastric wall after distal pancreatectomy. However, this is not true NTS. In our study, pathological examination revealed 2 cases of engraftment of core tissue from EUS-FNB (2.7% of all cases). Our present observations and the previous case reports on NTS[3,5-16] suggest the possibility that EUS-FNB carries risk of NTS.

Since the publication of reports about NTS after EUS-FNB, several novel methods and devices have been introduced to reduce the number of fine needle aspiration (FNA) punctures required, namely, rapid on-site evaluation and development of novel FNA needles. Mukai *et al.* reported that a large amount of core tissue is needed to establish an accurate diagnosis with fewer FNA passes.[20,21] Although most cases of NTS have occurred after multiple FNA passes, there have been 2 reports of confirmed NTS after a single FNA pass.[22,23] In one of our cases, tumor cells were recognized on the extension of the puncture line. Therefore, we should keep in mind that NTS can occur as a result of puncture itself and is not necessarily a function of the number of punctures, puncture method, or needle size.

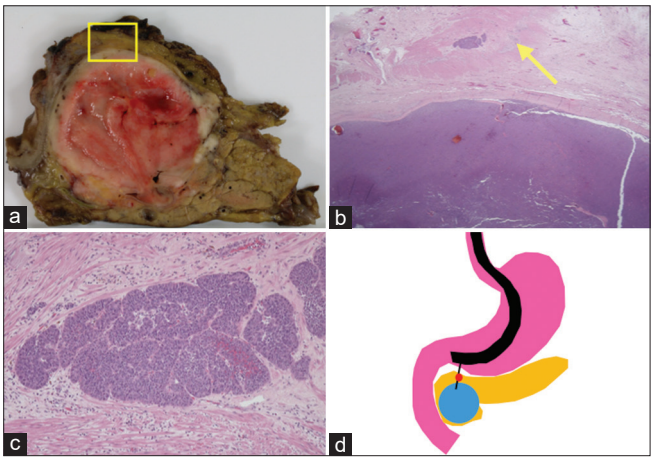

Figure 2. Case 2: (a) Cross-section of the fixed excised specimen. The largest diameter of the tumor was 140 mm. (b) Histopathological findings in the resected specimen. Acinar cell carcinoma was observed in the muscle layer of the stomach at a site distal from the primary tumor (arrow). (c) Magnification of Figure 2b. (d) Schema showing the location of the puncture route and needle tract seeding (red ball)

In terms of risks and benefits, we found that preoperative EUS-FNB had a diagnostic accuracy of 98.6% and a clinical adverse event rate of 4.1%; this rate is similar to the rate of 2.66% in the earlier reports by Huiyun *et al.*[24] Furthermore, each clinical adverse event in this study (2 cases of bleeding and 1 of pancreatitis) was controlled by compression or conservative treatment. Therefore, preoperative EUS-FNB seems to be a safe and effective procedure.

This study has some limitations. First, there were some resected specimens for which we could not confirm the EUS-FNB route because the needles were thin and the routes were unclear when time passed after EUS-FNB. Second, the number of patients might have been too small to estimate the actual frequency of NTS, which is a rare event in EUS-FNB. Third, the follow-up duration may have been too short to observe the incidence or outcome of NTS in that it would be difficult to

Table 7. Clinicopathological features of patients in previous reports

Clinicopathological features	*n* (%)
Patients, *n*	13
Sex, male/female, *n*	4/9
Age (years), mean±SD	68.9±9.8
Tumor site, head/body/tail/body-tail, *n* (%)	0/9 (69.2)/3 (23.1)/1 (7.7)
Cyst, *n* (%)	3 (23.1)
Puncture route, TG/TD, *n* (%)	13 (100)/0
Needle passes, 1/2/3/4/5/multiple/unknown, *n* (%)	1 (7.7)/3 (23.1)/4 (30.8)/2 (15.4)/1 (7.7)/1 (7.7)/1 (7.7)
Needle size, 20G/21G/unknown, *n* (%)	11 (84.6)/1 (7.7)/1 (7.7)
Tumor diagnosis, PDAC/ASC, *n* (%)	12 (92.3)/1 (7.7)
7th UICC staging, IA/IB/IIA/II B/III/IV/unknown, *n* (%)	2 (15.4)/4 (30.8)/5 (38.5)/0/0/1 (7.7)/1 (7.7)
Time of interval, months (median)	16.8
Seeding sites, PGW, *n* (%)	13 (100)
Type of surgery, PD/DP/CP/none, *n* (%)	0/10 (76.9)/1 (7.7)/2 (15.4)
Operation, *n* (%)	11 (84.6)
Additional surgery (%)	8 (63.6)

AS: Adenosquamous carcinoma; CP: Central pancreatomy; DP: Distal pancreatectomy; PD: Pancreatoduodenectomy; PDAC: Pancreatic ductal adenocarcinoma; PGW: Posterior gastric wall; TD: Transduodenal; TG: Transgastric; UICC: Union for international cancer control

distinguish peritoneal tumor seeding caused by FNA from natural disease progression.

CONCLUSIONS

EUS-FNB is useful for preoperative diagnosis of pancreatic tumors. However, the evidence to date suggests that EUS-FNB is not associated with a longer recurrence-free interval or better prognosis. Moreover, our results suggest that we should reconsider use of preoperative EUS-FNB for diagnosis of pancreatic tumors to avoid unnecessary NTS unless the tract is planned to be resected. Minaga *et al.* considered that there could not be any NTS in patients with cancer of the pancreatic head because the site of seeding lesions was included within the area of surgical resection.[17] Furthermore, Hirooka *et al.*[25] reported a case of T1 pancreatic cancer in which NTS after EUS-FNB caused peritoneal dissemination. Therefore, it is unclear whether there is no relationship between EUS-FNB and peritoneal dissemination. Patients who undergo distal pancreatectomy after EUS-FNB should be followed up with diagnostic imaging, such as endoscopy and CT, to detect local recurrence or peritoneal dissemination caused by NTS.

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Conflicts of interest

There are no conflicts of interest.

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