

Peritoneal seeding in intraductal papillary mucinous neoplasm of the pancreas patients who underwent endoscopic ultrasound-guided fine-needle aspiration: The PIPE Study

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Background and study aims: There have been concerns about peritoneal seeding after endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of mucinous pancreatic cystic lesions. The aims of this study were to determine the frequency of postoperative peritoneal seeding in patients with intraductal papillary mucinous neoplasm (IPMN) who had undergone pre-operative EUS-FNA and to compare it with that of patients with IPMN who had surgery with no pre-operative tissue sampling.

Patients and methods: A total of 175 patients who had undergone resection of IPMNs with pre-operative EUS-FNA (EUS-FNA group) were analyzed and compared with 68 patients who had undergone resection with no pre-operative tissue sampling (No Sampling group). Patient characteristics, pathology, and frequency of peritoneal seeding after surgery were analyzed and compared. Peritoneal seeding was diagnosed based on pathology or image findings.

Results: The two groups were comparable with respect to sex, age, follow-up duration, involvement of the pancreatic head, involvement of the main duct, grade of dysplasia, and size of histologically proven branch-duct IPMNs. Four patients (2.3%) with invasive IPMN developed peritoneal seeding in the EUS-FNA group, whereas three (4.4%, two with invasive IPMN and one with high-grade dysplasia) developed peritoneal seeding in the No Sampling group ($P = 0.403$). No peritoneal seeding was noted during surgery in these cases. Except for one patient in the EUS-FNA group, no spillage occurred during resection in these patients.

Conclusions: In this cohort of patients undergoing resection of IPMN, the difference in the frequency of peritoneal seeding in the EUS-FNA group and the No Sampling group was not significant.

Introduction

Endoscopic ultrasound (EUS), with its improved resolution, has been used widely to image the pancreas [1]. It also provides a platform to perform EUS-guided fine-needle aspiration (EUS-FNA). In the evaluation of pancreatic cystic lesions (PCLs), EUS-FNA obtains fluid for cyst fluid analysis such as carcinoembryonic antigen (CEA), cytology, and DNA analysis [2]. The cyst fluid CEA concentration has been reported to be the most accurate marker to differentiate mucinous (i.e. intraductal papillary mucinous neoplasm [IPMN] and mucinous cystic neoplasm) from nonmucinous PCLs [3, 4], whereas cytology has been shown to be the most accurate test for the diagnosis of malignant PCLs [3].

Although EUS-FNA of PCLs carries a low complication rate and is considered to be safe [5], some investigators have expressed concerns over the possibility of peritoneal seeding following EUS-FNA of mucinous PCLs [6]. However, to our knowledge there has been no large scale study evaluating the frequency of peritoneal seeding after EUS-FNA of mucinous PCLs.

The aims of this study were (1) to determine the frequency of postoperative peritoneal seeding in patients with IPMN who had undergone pre-operative EUS-FNA of the lesions, and (2) to compare the frequency with that of IPMN patients who had surgery with no pre-operative tissue sampling (endoscopic or percutaneous). We hypothesized that the frequency of postoperative peritoneal seeding in patients with IPMN who underwent pre-operative EUS-FNA did not be higher than that of patients who did not undergo pre-operative tissue sampling.

* Drs. Brugge and Pitman are co-senior authors of this manuscript.

Patients and methods



Patients

This study was approved by the Partners Human Research Committee Institutional Review Board. A database of patients who underwent EUS-FNA of PCLs and patients who underwent surgical resection of IPMN at Massachusetts General Hospital (MGH) has been maintained by the Gastrointestinal Unit and Department of Surgery, respectively. These databases were reviewed to identify patients who had undergone resection of IPMNs between 1999 and 2010. The study cohort consisted of patients who underwent surgery of IPMNs with pre-operative EUS-FNA and those without any pre-operative endoscopic or percutaneous tissue sampling. Demographic data (sex and age at surgery), post-operative follow-up period, involvement of the head of the pancreas, involvement of the main pancreatic duct (i.e. main-duct type or combined-type IPMN), and surgical histology results were compared. In addition, the size of histologically proven branch-duct IPMNs measured on pre-operative cross-sectional images was compared. For the patients who underwent EUS-FNA, the time between EUS-FNA and surgery was determined; for those who underwent EUS-FNA at MGH, characteristics of FNA (targets of FNA, approaches used, number of needle passes, and size of the needles) were also analyzed. When patients underwent multiple EUS-FNAs before surgery, only the findings of the procedure closest to the surgery were analyzed. All EUS-FNAs were performed prior to the publication of the revised Sendai guidelines in 2012 [6].

Exclusion criteria were one or more of the following: (1) post-operative follow-up duration < 180 days, (2) absence of cross-sectional imaging reports (computed tomography [CT] or magnetic resonance imaging [MRI]) during follow-up, and (3) pre-operative percutaneous or endoscopic retrograde cholangiopancreatography (ERCP)-guided tissue sampling. This was to ensure adequate follow-up data and to provide more homogeneous comparison groups.

EUS-FNA procedure

At MGH, EUS-FNA was performed by three experienced endosonographers using a curvilinear echoendoscope and FNA needle (s) as previously described [3, 4,7]. Doppler imaging was used to identify and avoid the passage of the needle through blood vessels. PCLs in the head/uncinate process of the pancreas were aspi-

rated via a transduodenal approach, whereas the lesions in the body/tail of the pancreas were accessed via a transgastric approach. For prevention of PCL infection, intravenous antibiotics were administered during EUS-FNA; an oral antibiotic was administered for 2–3 days after the procedure. Antibiotics were given to some patients who underwent EUS-FNA of the dilated main pancreatic duct.

Definition of peritoneal seeding

Peritoneal seeding was defined as one or more of the following: (1) development of ascites with malignant cytology, (2) pathologic confirmation of malignancy in peritoneal/omental/mesenteric tumor implants, and (3) cross-sectional image findings indicative of carcinomatosis (enhancing tumor implants on peritoneum/omentum/mesentery, omental cake, peritoneal thickening with abnormal contrast enhancement, and soft tissue stranding with or without ascites) [8–11].

Statistical analysis

All continuous variables were reported as the median (range). For categorical data, the chi-squared test or the Fisher's exact test was performed, as appropriate. For comparison of continuous variables, the Wilcoxon rank-sum test was performed. A 2-sided *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA 12.1 (StataCorp LP, College Station, Texas, USA).

Results



Patient characteristics

Between 1999 and 2010, 328 patients with IPMN underwent surgical resection at MGH. In the majority of cases, the decision to undergo a surgical resection was made based on the 2006 international consensus guidelines [12]. We had been following these parameters (all presumed main-duct type or combined-type IPMN, branch-duct IPMN > 3 cm in diameter, presence of a mass/mural nodule, positive cytology, and/or presence of symptom) for a few years before the guidelines were published. Some patients were referred for resection based on recommendations of the treating gastroenterologists or surgeons. Of these patients, 201 underwent pre-operative EUS-FNA (EUS-FNA group) and 82 had no pre-operative tissue sampling (No Sampling group). A total of

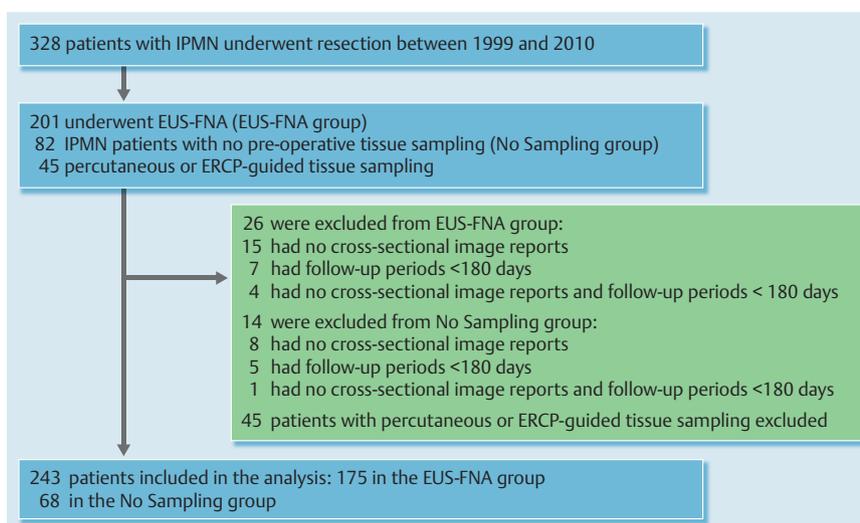


Fig. 1 Study flow chart. IPMN, intraductal papillary mucinous neoplasm; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.

	EUS-FNA Group	No Sampling group	P value
Number of patients, n	175	68	–
Sex, male / female, n	75 / 100	32/36	0.554 ¹
Age at surgery, median (range), years	68 (39–92)	66 (37–89)	0.952 ²
Follow-up period after surgery, median (range), months	56.9 (6.0–163.6)	58.6 (7.6–155.2)	0.206 ²
Pancreatic head involvement, n (%)	102 (58.3)	41 (60.3)	0.775 ¹
Main duct involvement, n (%)	83 (47.4)	37 (54.4)	0.328 ¹
Grade of dysplasia, n (%)			0.385 ¹
Low grade	43 (24.6)	13 (19.1)	
Intermediate grade	64 (36.6)	24 (35.3)	
High grade	36 (20.6)	12 (17.7)	
Invasive	32 (18.3)	19 (27.9)	
Size, n (%) ³			0.113 ¹
≥30 mm	35 (38.5)	16 (55.2)	
<30 mm	56 (61.5)	13 (44.8)	
Peritoneal seeding, n (%) [95%CI]	4 (2.3) [0.05 to 4.5]	3 (4.4) [–0.5 to 9.4]	0.403 ⁴

IPMN, intraductal papillary mucinous neoplasm; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration.

¹ Results of the chi-squared test.

² Results of the Wilcoxon rank-sum test.

³ Size of histologically proven branch-duct IPMNs on cross-sectional images. One patient in the EUS-FNA group and 2 patients in the No Sampling group had no reports of the size and thus were excluded from the analysis.

⁴ Result of the Fisher's exact test.

26 patients from the EUS-FNA group and 14 from the No Sampling group were excluded as they had no postoperative cross-sectional image reports or had follow-up of <180 days. In addition, 45 patients who had undergone percutaneous or ERCP-guided tissue sampling were excluded. As a result, 175 patients in the EUS-FNA group and 68 patients in the No Sampling group were evaluated (● Fig. 1). Of these patients, 227 (162 [92.6%] in the EUS-FNA Group and 65 [95.6%] in the No Sampling group; $P=0.567$, Fisher's exact test) underwent surgical resection based on the parameters of the 2006 international consensus guidelines. In addition, 16 patients (13 [7.4%] in the EUS-FNA group and 3 [4.4%] in the No Sampling group) underwent surgery based on recommendations of the treating gastroenterologists or surgeons; one of these patients had abnormal liver function tests and three had a family history of pancreatic cancer. In the EUS-FNA group ($n=175$), 98 patients underwent EUS-FNA at MGH and 77 at other hospitals. In total, 75 patients were male and 100 were female. The median age at surgery was 68 years (range 39–92 years). Patients were followed up for a median of 56.9 months (range 6.0–163.6 months). The head of the pancreas was involved by IPMN in 102 patients (58.3%). The main pancreatic duct was involved in 83 patients (47.4%). A total of 32 patients had IPMN with an associated invasive carcinoma. The time between EUS-FNA and surgery was obtained for 166 patients, giving a median of 59 days (range 4–810 days).

In the No Sampling group ($n=68$), 32 patients were male and 36 were female. Patients underwent surgery at a median age of 66 years (range 37–89 years). The median postoperative follow-up period was 58.6 months (range 7.6–155.2 months). IPMN involved the head of the pancreas in 41 patients (60.3%). The main pancreatic duct was involved in 37 patients (54.4%). IPMN with an associated invasive carcinoma was diagnosed in 19 patients. Both groups were comparable with respect to sex, age at surgery, postoperative follow-up duration, frequency of pancreatic head involvement/main duct involvement, and grade of dysplasia of the IPMN. In addition, the size of histologically proven branch-duct IPMNs measured on pre-operative cross-sectional images showed no significant difference between the two groups (● Table 1).

Table 1 Characteristics of patients with intraductal papillary mucinous neoplasm who underwent pre-operative endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA group) and those with no pre-operative tissue sampling (No Sampling group).

Details of the EUS-FNA performed at MGH

As stated above, 98 patients underwent EUS-FNA at MGH. The FNA targets were cyst contents in 83 patients, dilated main pancreatic duct in 6, a mass lesion in 5, a mass lesion and dilated main pancreatic duct in 3, and dilated main pancreatic duct and an enlarged lymph node in 1.

In the 83 patients with cyst contents aspirated, 90 distinct PCLs were aspirated. The diameter of the PCLs was reported in 83 lesions; the median diameter measured by EUS was 20.5 mm (range 7–50 mm). A thick wall was observed in 16 PCLs. Septations were present in 50 PCLs. A mass/mural nodule was present in 17 PCLs. In 18 of these patients, dilated main pancreatic duct was demonstrated on EUS; 3 patients underwent additional FNA of the dilated main pancreatic duct.

A transgastric approach was used in 43 patients, a transduodenal approach in 52 patients, and a combined transgastric and transduodenal approach was used in 3 patients. One patient with a PCL at the head of the pancreas was approached via the transgastric route. In 3 patients with diffuse dilation of the main pancreatic duct, the portion of the duct in the body of the pancreas was aspirated via the transgastric route. A median of 1 needle pass (range 1–5 needle passes) was performed. The diameters of the needles used were 22 G in 72, a combination of 19 and 22 Gauge in 7, 25 G in 5, 22 and 25 G in 1, and 20 G (celiac plexus neurolysis needle) in 1; 12 patients had no report on needle gauges.

Frequency of peritoneal seeding

In the EUS-FNA group, postoperative peritoneal seeding was identified in four patients (2.3%). Two of the patients (Patient #1 and #2 in ● Table 2) underwent EUS-FNA at our institution, whereas the other two (Patients #3 and #4 in ● Table 2) were seen at other hospitals. All seven patients who developed postoperative peritoneal seeding had undergone surgical resection based on the 2006 international guidelines. Patient #1 had a 20-mm cystic lesion with an associated mass lesion in the head of the pancreas on EUS. The patient underwent one pre-operative EUS-FNA with two needle passes using a 22-G fine needle. The patient underwent a Whipple procedure. The pathology was branch-duct IPMN with an associated invasive carcinoma with

Table 2 Characteristics of patients with intraductal papillary mucinous neoplasm who developed peritoneal seeding.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Group	EUS-FNA	EUS-FNA	EUS-FNA	EUS-FNA	No Sampling	No Sampling	No Sampling
Sex	Female	Male	Female	Male	Male	Male	Female
Age at surgery, years	64	56	76	61	83	61	75
Location of the tumor	Head	Body	Tail	Head	Tail	Body, tail	Tail
Grade of dysplasia	INV	INV	INV	INV	INV	INV	HGD
Duct type	Branch duct	Combined	Branch duct	Combined	Branch duct	Combined	Combined
Pathologic staging	T3N1M0	T2N0M0	T3N0M0	T3N0M0	T2N0M0	T3N1M0	N/A
Basis of peritoneal seeding diagnosis	Pathology	Imaging	Pathology	Pathology	Imaging	Pathology	Pathology
Approximate time between surgery and identification of peritoneal seeding, months	8.0	17.5	25.0	11.2	21.7	17.5	11.8
History of extrapancreatic malignancy	No	Yes (concurrent transitional cell carcinoma of the bladder treated by cystoscopic resection)	No	No	No	No	Yes (breast cancer 31 years prior to IPMN)
Note		Pancreatic transection margin had been involved by IPMN with intermediate-grade dysplasia	Spillage of cyst contents during operation		Multiple omental nodules with positive uptake on positron emission tomography, development of ascites	Pancreatic transection and retroperitoneal margins involved	

IPMN, intraductal papillary mucinous neoplasm; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; INV, IPMN with an associated invasive carcinoma; HGD, IPMN with high-grade dysplasia; N/A, not applicable.

negative margins. The pathologic staging was T3N1M0. Peritoneal seeding was diagnosed based on FNA of a peritoneal nodule approximately 8 months after surgery. Patient #2 had a hypochoic, 21-mm mass in the body of the pancreas and dilated main pancreatic duct on EUS. The patient had one pre-operative EUS-FNA with three needle passes on the mass using a 22-G and a 25-G fine needle. The patient underwent a distal pancreatectomy with splenectomy. The pathology was combined-type IPMN with an associated invasive carcinoma. The pathologic staging was T2N0M0. The pancreatic transection margin was involved by IPMN with intermediate-grade dysplasia. Peritoneal seeding was diagnosed on image findings in this patient. The patient developed mesenteric soft tissue stranding and multiple omental nodules of up to >10 mm in size.

Patient #3 was reported to have a 6-cm PCL in the tail of the pancreas on EUS performed at another hospital. Spillage of cyst contents occurred during the operation. Surgical pathology was branch-duct IPMN with an associated invasive carcinoma with negative margins. The pathologic staging was T3N0M0. Peritoneal seeding was diagnosed based on FNA of a peritoneal mass approximately 25 months after surgery. Patient #4 had a 3-cm PCL in the head of the pancreas on EUS at another hospital. This patient underwent a Whipple procedure. The pathology was combined-type IPMN with an associated invasive carcinoma. The margins were negative. The pathologic staging was T3N0M0. Peritoneal seeding was diagnosed based on FNA and core biopsy of omental nodule and malignant ascites cytology approximately 11 months after surgery.

In the No Sampling group, postoperative peritoneal seeding was identified in three patients (4.4%). Two patients had IPMNs with an associated invasive carcinoma. One of these patients had pathologic staging of T2N0M0 with negative margins (Patient #5 in [Table 2](#)). Peritoneal seeding was diagnosed on image findings in this patient. The patient developed omental nodules that increased in number over time, and subsequently developed ascites. Some of the omental nodules showed positive uptake on positron emission tomography. The other patient had pathologic staging of T3N1M0 (Patient #6 in [Table 2](#)). The pancreatic transection and retroperitoneal margins were positive in this patient. Peritoneal seeding was diagnosed based on development of ascites with malignant cytology. The pathology of the third patient who developed peritoneal seeding in the No Sampling group (Patient #7 in [Table 2](#)) was a combined-type IPMN with high-grade dysplasia involving 50% of the lesion. There was IPMN with low-grade dysplasia in the main pancreatic duct at the transection margin. Peritoneal seeding was diagnosed based on the development of multiple peritoneal nodules on CT and FNA and core biopsy of a nodule in the surgical bed.

None of these patients had evidence of peritoneal involvement during surgery. Spillage during surgery occurred in only one patient (Patient #3). The approximate time between surgery and identification of peritoneal seeding ranged between 8 and 25 months. Paracenteses were done in Patients #1, #4, #5, and #6, which revealed serous fluid and thus rendering the possibility of pseudomyxoma peritonei less likely. Patients #2 and #7 had a history of extrapancreatic malignancy. Patient #2 had a noninva-

sive transitional cell carcinoma of the bladder diagnosed concurrently with IPMN, which was treated by cystoscopic resection. Patient #7 had been treated for breast cancer 31 years prior to surgery for IPMN. The characteristics of the patients who developed peritoneal seeding are summarized in **Table 2**.

The frequencies of peritoneal seeding in the EUS-FNA group and No Sampling group were 2.3% (95% confidence interval [CI] 0.05% to 4.5%) and 4.4% (95%CI–0.5% to 9.4%), respectively (difference 2.1% [95%CI–3.2% to 7.5%]; $P=0.403$, Fisher's exact test) (**Table 1**).

Discussion

The purpose of this study was to determine the frequency of postoperative peritoneal seeding in patients with IPMN who undergo pre-operative EUS-FNA and to compare it with peritoneal seeding in patients with IPMN who do not undergo pre-operative tissue sampling. The results show that EUS-FNA does not increase the risk of peritoneal seeding compared with patients who do not undergo pre-operative tissue sampling. Furthermore, the frequencies of peritoneal seeding were low (2.3% in the EUS-FNA group and 4.4% in the No Sampling group).

The frequency of peritoneal seeding in the current cohort is in agreement with previously published studies. Review of the literature indicates that postoperative peritoneal seeding may occur in up to 12% of patients with IPMN who undergo surgery [13]. Interestingly, one patient in the current study who had IPMN with high-grade dysplasia developed peritoneal seeding. This patient had not undergone pre-operative EUS-FNA. Peritoneal seeding has been reported in IPMN with high-grade dysplasia [14]. One possible explanation for this is the presence of an invasive component of the tumor that was not detected in initial histological sections. In addition, it is unclear what the risk of residual IPMN in the pancreatic remnant is even if the IPMN is low grade. Recurrences of IPMN do indeed occur and the time to progression to invasive carcinoma remains unknown.

EUS-FNA has been advocated as the method of choice for diagnosis in patients with potentially resectable pancreatic cancer. In one study, EUS-FNA resulted in lower frequency of peritoneal seeding compared with percutaneous FNA in patients with pancreatic cancer. In this study, the frequency of peritoneal carcinomatosis was 2.2% (1/46) in the EUS-FNA group compared with 16.3% (7/43) in the percutaneous FNA group ($P<0.025$) [15]. Needle tract seeding after EUS-FNA is recognized to be extremely low [16]. Since the first report of pancreatic cancer seeding to the gastric wall after EUS-FNA [17], only a few cases of needle tract seeding after EUS-FNA of pancreatic cancers have been reported [18–20]. In all of the cases, the lesions were located in the body/tail of the pancreas and EUS-FNAs were performed via a transgastric approach. When EUS-FNA is performed for a pancreatic head lesion, a transduodenal approach is used, and the site of puncture is included in the surgical resection. However, for tumors of the pancreatic body or tail, a transgastric-transperitoneal approach is used, and the path of the needle is not resected in the subsequent pancreatectomy [21]. A large scale report of gastric or peritoneal recurrence in patients who underwent pre-operative EUS-FNA of pancreatic cancer indicates that 7.7% of the patients who underwent EUS-FNA developed gastric or peritoneal recurrence, whereas 15.4% of the patients who did not undergo EUS-FNA developed recurrence in the stomach or peritoneum ($P=0.21$) [21]. Other cases of potential needle tract seeding after

EUS-FNA include melanoma seeding to the gastric wall after EUS-FNA of a perigastric lymph node metastasis [22] and esophageal seeding after EUS-FNA of metastatic mediastinal lymphadenopathy [23].

The concern over EUS-FNA of mucinous PCLs and peritoneal seeding seems to have been based mostly on anecdotal experiences. Indeed, to the best of our knowledge, there is only one case report of peritoneal seeding after EUS-FNA of IPMN in a letter format in the English language literature [24]. The patient underwent distal pancreatectomy 10 days after the EUS-FNA and tumor cells were identified in the intraoperative peritoneal lavage. The pathology was IPMN with an associated invasive carcinoma. The patient developed peritoneal seeding 20 months after surgery and died approximately 25 months after surgery [24].

The frequency of peritoneal seeding in the EUS-FNA group was low, as was expected. This might be due in part to the relatively low cellularity of the cyst fluid. Another possible explanation might be the relatively lower malignant potential of IPMNs compared with pancreatic ductal adenocarcinoma. Postoperative peritoneal seeding in this group occurred only in the patients with IPMN with an associated invasive carcinoma.

The current study has limitations stemming from the retrospective and single-center nature of the study. First, one may argue that it is difficult to determine the cause of development of postoperative peritoneal seeding. It may be due to the natural history of advanced disease, unnoticed surgical seeding, or in the case of the EUS-FNA group, truly EUS-FNA induced. Regardless of the cause, however, the frequency of peritoneal seeding did not differ significantly between the two groups. Second, cases of EUS-FNA performed at other hospitals were included. This would allow for variation in the EUS-FNA technique. However, this may partly compensate for the single-center nature of the study. Third, one may criticize that some EUS-FNA procedures in this study were done in patients with other high-risk stigmata present. However, EUS-FNAs in this cohort were performed over a long period of time, and recommendations on EUS-FNA of mucinous PCLs have been available only recently [6]. Fourth, one may debate that a retrospective cohort study design might not be the optimal method for this investigation. However, at the design phase of this study, we had expected the frequency of peritoneal seeding to be low in both the EUS-FNA group and the No Sampling group. As the study aim was to determine the frequency of postoperative peritoneal seeding in the EUS-FNA group and to compare this with that in the No Sampling group, we performed a retrospective cohort study. A case-control study or a case series would not have determined the frequency of peritoneal seeding. Considering the low frequency of peritoneal seeding, the numbers of IPMN patients in the two groups are small, possibly raising concerns on the statistical power and reliability of the result. To determine the actual risk of peritoneal seeding associated with EUS-FNA in IPMN patients, a larger patient cohort and a longer follow-up period are required.

To the best of our knowledge, this is the first and the largest study to determine the frequency of peritoneal seeding in patients with IPMN who underwent EUS-FNA. Moreover, the EUS-FNA group was compared with the No Sampling group, adding objectivity to the interpretation of the data. The median postoperative follow-up periods were relatively long for both groups (56.9 months for the EUS-FNA group and 58.6 months for the No Sampling group).

In conclusion, pre-operative EUS-FNA was not associated with an increased frequency of peritoneal seeding in patients with IPMN who underwent surgical resection.

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Institutions

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