ORIGINAL ARTICLE

Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation CME

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Background: EUS-guided FNA is effective for establishing tissue diagnosis in suspected pancreatic cancer. However, data on the frequency of major complications following EUS-FNA are limited.

Objective: To evaluate the frequency of major complications after EUS-FNA of solid pancreatic masses.

Design: Prospective cohort study.

Setting: Tertiary University based referral center for pancreatico-biliary disorder.

Patients: Consecutive patients who underwent EUS-FNA of a solid pancreatic over a 42-month period. All immediate complications were recorded by the endosonographer. Late complications were assessed at 72 hours and at 30-days after the procedure.

Main Outcomes Measurements: Major complications were defined as acute pancreatitis, bleeding, infection, perforation, use of reversal medication, hospitalization or death.

Results: A total of 355 consecutive patients with a solid pancreatic mass underwent EUS FNA. Major complications were encountered in 9 patients (2.54%, 95% CI 1.17-4.76). Acute pancreatitis occurred in 3 of 355 (0.85 %, 95% CI 0.17-2.45); 2 patients were hospitalized, and 1 patient recovered with outpatient analgesics. Three patients were admitted for severe pain after the procedure; all were treated with analgesics and subsequently discharged with no sequela. Two patients (0.56%, 95% CI 0.07-2.02) developed fever and were admitted for intravenous antibiotics; 1 patient recovered with intravenous antibiotics and the other required surgical debridement for necrosis. One patient required the use of reversal medication. Overall, 1.97% (95% CI 0.80-4.02) of the patients were hospitalized for complications (range 1-16 days). None of the patients experienced clinically significant hemorrhage, perforation, or death. No clear predisposing risk factors were identified.

Limitations: Lack of surgical gold standard and referral to a tertiary center.

Conclusions: EUS-FNA of solid pancreatic masses infrequently leads to major complications. Our results can be used by endosonographers to counsel patients before EUS-FNA of solid pancreatic masses. (Gastrointest Endosc 2006;63:622-9.)

EUS-guided FNA (EUS-FNA) has emerged as an effective technique for tissue diagnosis in patients with suspected pancreatic cancer.[1-6] EUS-FNA has replaced ERCP and brush cytology as the endoscopic test of choice for tissue acquisition because of higher success rates and a perception that EUS-FNA is associated with a lower risk of postprocedural complications, mostly pancreatitis. Few investigators, however, have reported their experience with EUS-FNA of solid pancreatic masses and included data on complications.[2,6-9] While some studies carefully analyzed the risk of pancreatitis after EUS-FNA,[6,8] studies that evaluated global risk after EUS-FNA of solid pancreatic masses have not been conducted prospectively. We previously reported on complications after EUS-FNA of solid pancreatic masses and found that the risk of EUS-FNA of pancreatic masses was similar to that of upper endoscopy with most clinically relevant events occurring within a week of the procedure.[2] Moreover, our multicenter U.S. study suggested that a retrospective cohort study may have underestimated the risk of pancreatitis after EUS-FNA of solid pancreatic masses because of reporting

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bias.[10] We, therefore, conducted a prospective evaluation and expanded our series to determine the frequency of major complications encountered after EUS-FNA of solid pancreatic masses. In addition, our prospective data collection enabled us to examine potential risk factors for development of such complications.

Capsule Summary

What is already known on this topic

- EUS-FNA is an effective technique for establishing tissue diagnosis in patients with suspected pancreatic cancer.
- Limited data exist on the major complications associated with EUS-FNA of solid pancreatic masses. Predisposing risk factors are unknown.

What this study adds to our knowledge

- EUS-FNA of solid pancreatic masses uncommonly leads to acute pancreatitis, fever, or admission for significant pain. No predisposing factors are clearly identified.
- These results can be used by endosonographers to counsel patients before EUS-FNA of solid pancreatic masses.

PATIENTS AND METHODS

As we established the EUS program at the University of Alabama at Birmingham (UAB), we conducted a prospective evaluation of EUS-FNA in 355 consecutive procedures with suspected pancreatic cancer. Patients who required a tissue diagnosis or who failed other attempts by ERCP, CT-guided biopsy, and/or US-guided biopsy were included in this study. The institutional review board of UAB approved this study (Protocol X010924009). All patients provided written informed consent to undergo the procedure. Patients were placed in the left lateral decubitus position and were sedated with intravenous (IV) meperidine, midazolam, and/or droperidol according to the judgment of the endoscopist. Standard EUS was performed by using a radial echoendoscope (Olympus GF-UM130, Olympus America Corp, Melville, NY) for evaluating and staging the pancreatic lesion as previously described.[2] In addition, features of chronic pancreatitis were recorded as previously defined.[11] Patients whose pancreas exhibited 4 or more features were considered to have evidence of chronic pancreatitis.[11] Once a solid focal pancreatic lesion was identified, EUS-FNA was performed with a curvilinear echoendoscope (Olympus UC-30P). Solid masses in the head and the uncinate of the pancreas were biopsied via a transduodenal approach, whereas masses in the neck, the body, or the tail of the pancreas were targeted via a transgastric approach. Color Doppler sonography was performed to exclude intervening vascular structures and to choose a vessel-free needle track. All EUS-FNAs were performed with a 22-gauge needle (Echotip; Wilson-Cook Medical Inc, Winston-Salem, NC) inserted through the working channel of the echoendoscope as previously described.[2] No suction was applied during biopsy unless the initial attempt yielded no cellular material ($<5\%$ of the cases). The aspirates then were placed onto glass slides and were prepared as previously described.[12] The smears were immediately reviewed by a cytopathologist on site to ensure specimen adequacy. At least 5 passes were obtained from each target lesion unless the cytology evaluation performed on site confirmed the presence of malignant cells. We used the final cytology reports in our analysis. The cytologic diagnoses were classified into either malignant or benign (including chronic pancreatitis). The cytologic diagnoses then were categorized into the following groups: positive for malignancy; suspicious for malignancy; atypical cells, indeterminate for malignancy; benign/reactive process; or nondiagnostic. Final diagnosis of pancreatic cancer was defined by the following criteria: (1) histologic evidence of pancreatic cancer, (2) initial malignant cytology with a clinical and/or imaging follow-up that was consistent with the diagnosis of pancreatic cancer, such as death from disease or clinical progression. Lesions were considered benign if there was a lack of tumor progression for at least 6 months in conjunction with continued patient well being. The criterion standard for classification of disease included the following: surgical resection, death from pancreatic cancer, and repeat radiologic and/or clinical follow-up.

Complications were defined as any deviation from the clinical course after EUS that was associated with the procedure as observed by the endosonographer, the recovery-room nurses, or reported by the patients.[2,13,14] Excessive bleeding at the FNA site, perforation, hypotension, and the need for reversal medication were carefully documented. Any symptoms reported by the patient during recovery time were carefully assessed and documented by the endoscopist. Patients with abdominal pain were asked to be evaluated by their referring physicians or by the endoscopist, depending on convenience to the patients. For these patients, serum amylase and lipase were initially performed; an abdominal CT was performed if symptoms persisted. An accepted definition of pancreatitis and its severity was used.[15] Acute pancreatitis was defined as upper-abdominal pain associated with nausea or vomiting, and accompanied by at least a 3-fold elevation of serum amylase or lipase. Immediate (intraprocedural and in the recovery area) complications were evaluated in all patients. An experienced GI nurse, not involved in the procedure, called patients 24 to 72 hours after the procedure, as previously described.[2] Serious adverse events were defined as oversedation, requiring the administration of a reversal agent, and those that resulted in a physician or emergency department visits, hospitalization, or death, as previously described.[2,13,14] For the patients who could not be successfully contacted, information was collected from the medical records and

TABLE 1. Patient characteristics by presence or absence of major complication(s)

	No complication (N = 346)	Complication (N = 9)		Total (N = 355)
Patient characteristic	**N (%)**	**N (%)**	***p***	**N (%)**
Age (y)				
Mean (SD)	63.1 (11.8)	64.8 (8.5)	—	63.1 (11.7)
Median	63.5	64.0	0.73*	64.0
Range (min, max)	33, 89	52, 84	—	33, 89
Gender				
Men	219 (63.3)	6 (66.7)	1.00†	225 (63.4)
Women	127 (36.7)	3 (33.3)		130 (36.6)
Race				
White	258 (74.6)	7 (77.8)	1.00†	265 (74.6)
African American	86 (24.8)	2 (22.2)		88 (24.8)
Other‡	2 (0.6)	—		2 (0.6)

SD, Standard deviation; *MIN,* minimum; *MAX,* maximum.
*Mann-Whitney test.
†Fisher two-tailed exact test.
‡Excluded for calculating *p* value.

from clinic follow-up because the majority of our patients are seen for surgical consultation in our pancreaticobiliary center.

Statistical analysis

We analyzed 355 consecutive EUS-FNA procedures. Each procedure was regarded as a separate data point. The procedures were classified according to the presence or the absence of a major complication. Continuous variables were reported as means (with standard deviation) and medians (with range), while categorical variables were reported as frequency with respective percentages (proportions). We compared the two groups with and without complications with regard to subject characteristics, clinical history and presentation, and EUS-FNA features of the mass. Dichotomized variables were compared by using the Fisher exact two-tailed test, and continuous variables were compared by using the Mann-Whitney test. We calculated exact 95% confidence interval (CI) for proportions. Statistical significance was set at 0.05. The analysis was conducted with SAS statistical software (version 9.0; SAS Institute Inc, SAS Campus Drive, Cary, NC).

RESULTS

Baseline characteristics

Baseline characteristics of the study patients are presented in Table 1. Study patients were relatively old (median age, 64.0 years). Approximately 63% of the patients were men. Most of the patients were white (74.6%). We did not find significant differences between the two groups with regard to these patient characteristics.

Abdominal pain (66.5%), loss of weight (78%), jaundice (44.8%), and early satiety (8.2%) were some of the common symptoms at presentation (Table 2). Acute pancreatitis was the mode of presentation in 9.9% (35/355) of patients. Most (81.4%) patients had a CT before EUS. Prior tissue diagnosis was attempted in 148 patients (41.7%), where ERCP was the most common mode of prior investigation. Of the patients with primary adenocarcinoma of the pancreas, 4.4% (11/249) underwent concomitant EUS-FNA and celiac plexus neurolysis. No significant differences were found with regard to clinical history and presentation between those patients with and without a complication.

Complication assessment

Of the 355 procedures performed, major complications occurred in 9 (2.54%: 95% CI[1.17, 4.76]) (Table 3). These complications included pancreatitis (n = 3), severe abdominal pain (n = 3), fever (n = 2), and hypoxia from oversedation (n = 1). Of these 9 patients, 7 were hospitalized. None of the patients encountered clinically significant bleeding at the site of FNA or perforation or died as a result of the procedure. Information about complications was obtained by telephone interviews (54.6%) or clinical follow-up (44.8%); two (0.6%) patients could not be contacted. Of the 194 patients followed by

TABLE 2. Clinical history/presentation of patients by presence or absence of major complication(s)

	No complications (N = 346)	Complications (N = 9)		Total (N = 355)
Clinical feature	**N (%)**	**N (%)**	***p****	**N (%)**
Pain in abdomen				
Yes	231 (66.8)	5 (55.6)	0.49	236 (66.5)
No	115 (33.2)	4 (44.4)		119 (33.5)
Loss of weight				
Yes	270 (78.0)	6 (66.7)		276 (78.0)
No	76 (22.0)	3 (33.3)		78 (22.0)
Obstructive jaundice				
Yes	156 (45.1)	3 (33.3)	0.74	159 (44.8)
No	190 (54.9)	6 (66.7)		196 (55.2)
Early satiety				
Yes	29 (8.4)	—	1.00	29 (8.2)
No	317 (91.6)	9 (100)		326 (91.8)
Presentation with acute pancreatitis				
Yes	33 (9.5)	2 (22.2)	0.22	35 (9.9)
No	313 (90.5)	7 (77.8)		320 (90.1)
Prior tissue diagnosis attempt				
Yes	146 (42.2)	2 (22.2)	0.31	148 (41.7)
No	200 (57.8)	7 (77.8)		207 (58.3)
Prior CT done				
Yes	283 (81.8)	6 (66.7)	0.38	289 (81.4)
No	63 (18.2)	3 (33.3)		66 (18.6)

*Fisher two-tailed exact test.

telephone, 146 (75.3%) were contacted by a nurse, in particular to ask specifically about complications.

Risk factors assessment

To determine factors associated with the development of complications, we compared the groups with and without a complication with regard to clinical presentation, mass characteristics, and technical details of the procedure.

The pancreatic head was the most common location (66.2%) for the mass (Table 4). EUS found changes of chronic pancreatitis (CP) in 29% (103/355) of the patients. The median number of passes was higher for the ''complications'' group (median, 5) compared with the ''no complication'' group (median, 3), but, this difference was not statistically significant ($p = 0.31$). Malignant cytology was obtained in 64.0% (227/355) of the masses on FNA reading, whereas 24.5% (87/355) and 10.1% (36/355) had benign, and suspicious or atypical FNA cytology, respectively. The remaining 5 procedures (1.4%) were inconclusive for a diagnosis (''failed'' or ''inadequate''). Most of the malignant masses were primary adenocarcinoma (249/344, 72.4%), whereas 6.1% (21/344) masses were other types of cancers (neuroendocrine, 13; metastatic renal cell carcinoma, 3; lymphoma, 2; metastatic melanoma, 1; malignant fibrous histiocytoma, 1; metastatic breast cancer, 1). We could not determine the final diagnosis in 11 patients (lost to follow-up, n = 6; indeterminate, n = 5). The criterion standard for classification of final disease status included surgery (n = 97) or clinical follow-up (n = 252). Six patients were lost to follow-up. Median follow-up for all the lesions was 224 days (interquartile range [IQR], 104-384 days). Median follow-up of benign lesions was 385 days (IQR, 261-496 days). There were statistically no significant differences between the two groups (with and without complication)

TABLE 3. Nature and frequency of major complications after EUS-guided FNA of solid pancreatic masses with their corresponding 95% CI

Nature of complication	N (%) (N = 355)	Exact 95% CI
Hospitalization	7 (1.97)	0.80, 4.02
Complications (N = 9)	9 (2.54)	1.17, 4.76
Acute pancreatitis	3 (0.85)	0.17, 2.45
Severe abdominal pain	3 (0.85)	0.17, 2.45
Fever	2 (0.56)	0.07, 2.02
Oversedation-reversal medication	1 (0.28)	0.01, 1.56
Bleeding	0 (0)	0.00, 0.84
Perforation	0 (0)	0.00, 0.84
Death	0 (0)	0.00, 0.84

CI, Confidence interval.

with regard to mass location, size of the lesion, presence of EUS features of CP, initial EUS-FNA results, and type of mass.

Complications management

The detailed management of the patients is shown in Table 5. Of the total cohort, one patient required the use of reversal medication and was discharged from the endoscopy suite without any sequel. Acute pancreatitis occurred in 3 of 355 patients (0.85%: 95% CI[0.17, 2.45]): two patients were hospitalized, and one patient recovered with outpatient analgesics. Two patients (0.56%: 95% CI[0.07, 2.02]) developed fever and were admitted for IV antibiotics: one patient recovered with IV antibiotics, and the other required surgical debridement for necrosis. Three other patients were admitted for severe pain after the procedure, all of whom were treated with analgesics and subsequently were discharged with no sequel. Overall, 1.97%: 95% CI[0.80, 4.02] of the patients were hospitalized for major complications (range 1-16 days). None of the patients experienced clinically significant hemorrhage, perforation, or death.

DISCUSSION

To date, several investigations suggest that EUS-FNA is a highly accurate modality for tissue acquisition in patients with suspected pancreatic cancer.[2,6] Few investigations, however, prospectively evaluated the risk of pancreatitis[6,8] but none provided a global assessment of risk involved after EUS-FNA of solid pancreatic masses. Our prospective investigation suggests that EUS-FNA of solid pancreatic masses infrequently leads to major complications that are directly attributed to the procedure.

Our pancreatitis frequency of 0.85% is similar to what has been reported in the literature for EUS-FNA of the pancreas.[6-9] Our recent multicenter U.S. study suggested that the retrospective cohort study underestimated the risk of pancreatitis after EUS-FNA of solid pancreatic masses.[10] In the largest study to date, the risk of pancreatitis after EUS-FNA of the pancreas reported from expert EUS centers in 4909 patients was 0.29%.[10] Our current study suggests that the risk of pancreatitis is slightly higher (0.85%) but still within acceptable range of risk. EUS-FNA related pancreatitis appears to be lower from that reported by percutaneous FNA of the pancreas, which is closer to 3% (5/184).[16]

Our prospective data collection gave us the opportunity to examine potential risk factors for the development of complications in this large cohort of patients. It is suggested that pancreatitis after EUS-FNA occurs most often in patients with a history of acute recurrent pancreatitis.[7,8] In this investigation, we found that a presentation of acute pancreatitis or features of chronic pancreatitis on EUS were not associated with the development of pancreatitis or any other complications. The radiology literature suggests that patients with either benign lesions or a pseudotumor are more likely to have pancreatitis after FNA.[17,18] In one report of fatal pancreatitis after percutaneous FNA of the pancreas, no cancer or mass was found at the time of autopsy.[17] In addition, surgical pathology revealed that 60% of these patients had a normal pancreas and no evidence of pancreatic carcinoma at surgery. Similarly, death has been reported from pancreatitis after percutaneous FNA. Another study of 100 patients reported a 4% rate of pancreatitis and a mortality rate of 1% after percutaneous US-guided biopsy of the pancreas.[19]

We also investigated whether the size of the pancreatic lesion predicted the occurrence of major complications or pancreatitis. We found no such association between the size of the lesion and the occurrence of a complication. However, when FNA is performed percutaneously, pancreatitis is more likely to occur when lesions are smaller than 3 cm compared with lesions larger than 4.5 cm.[17]

We found that patients with complications were more likely to have undergone more EUS-FNA passes; however, this difference between the two groups did not reach statistical significance. In addition, the size of the needle has been clearly shown to be a predictor of complications when the percutaneous route has been used, with more complications encountered when using higher-gauge needles.[18] In this study, only the same type of a 22-gauge needle was used in all patients, suggesting that the needle type was not a factor contributing to complications.

Fever and infection occurred in two patients. One patient with pancreatic adenocarcinoma had few tiny cystic spaces and developed fever and chills 24 hours after

TABLE 4. Association between pancreatic mass and other EUS-guided FNA characteristics and the presence or absence of major complications

	No complication (N = 346)	Complication (N = 9)		Total (N = 355)
Characteristic	**N (%)**	**N (%)**	***p***	**N (%)**
Mass location				
Head	230 (66.5)	5 (55.6)	0.49*	235 (66.2)
Other	116 (33.5)	4 (44.4)		120 (33.8)
Largest diameter (mm)				
Range	17-36	7-95		7-95
Mean (SD)	27.8 (7.1)	33.7 (11.0)		33.6 (10.9)
Median	28.0	32.5	0.09†	32.0
EUS finding of CP				
Yes	102 (29.5)	1 (11.1)	0.46*	103 (29.0)
No	244 (70.5)	8 (88.9)		252 (71.0)
No. passes‡				
Range	1-12	1-9		1-12
Mean (SD)	3.5 (2.3)	4.2 (2.5)		3.5 (2.3)
Median	3	5	0.31†	3
FNA reading (initial)§				
Benign	85 (24.6)	2 (22.2)	1.00*	87 (24.5)
Malignant	222 (64.2)	5 (55.6)		227 (64.0)
Suspicious/atypical	34 (9.8)	2 (22.2)		36 (10.1)
Inconclusive	5 (1.4)	—		5 (1.4)
Type of masses				
Benign mass/chronic pancreatitis	72 (20.8)	2 (22.2)	0.96*	74 (20.0)
Adenocarcinoma	242 (69.9)	7 (77.8)		249 (69.6)
Other‖	21 (6.1)	—		21 (6.2)
Indeterminate‖	11 (3.2)	—		11 (4.2)

SD, Standard deviation; *CP,* chronic pancreatitis.
*Fishers two-tailed exact test.
†Mann-Whitney test.
‡Failed procedures (n = 3) and unknown passes (n = 1) excluded.
§Malignant and suspicious/atypical categories were combined for calculating *p* value. Inconclusive category is excluded from the analysis.
‖Other and Indeterminate categories are excluded for calculating *p* value.

the procedure. Our current policy is to administer IV antibiotics to patients with solid pancreatic masses with few tiny cystic spaces seen, in the hope to decrease the risk of infection after EUS-FNA. The second patient who developed fever and infection was a patient with acute recurrent pancreatitis and focal area in the tail of the pancreas. Fever developed after EUS-FNA of the pancreas and required surgical debridement. He recovered uneventfully after surgery. In the context of acute pancreatitis, our current practice is either to postpone EUS-FNA for a few weeks until the pancreatitis resolves and consider interval repeat CT to assess the lesion or to administer prophylactic antibiotics before EUS-FNA. Further research is needed to clarify the need for antibiotic use in this setting.

Very few patients in this investigation developed severe abdominal pain (independent of pancreatitis) after EUS-FNA of the pancreas. One patient had chronic pancreatitis,

TABLE 5. Days of hospitalizations, primary diagnosis, and treatment of patients who suffered from a major complication after EUS-guided FNA of solid pancreatic masses

Complication	Hospitalization (d)	Diagnosis	Treatment
Pancreatitis	No	Pancreatic cancer	Outpatient analgesics, clear liquid diet; explored-unresectable from venous invasion
Pancreatitis	Yes (2)	Pancreatic cancer	Surgical exploration and resection
Pancreatitis	Yes (3)	Chronic pancreatitis	Pseudocyst formation
Fever	Yes (3)	Pancreatic cancer	Intravenous antibiotics, no sequel
Fever	Yes (16)	Acute recurrent pancreatitis	Surgical debridement
Severe pain	Yes (5)	Pancreatic cancer/CPN	Pain management
Severe pain	Yes (5)	Calcific pancreatitis	Pain management
Severe pain	Yes (1)	Pancreatic cancer	Pain management
Hypotension	No	Pancreatic cancer	Use of reversal medications

CPN, Celiac plexus neurolysis.

and two others had pancreatic cancer. We typically treat a patient with additional doses of meperidine in the recovery area if the patient complains of postprocedural abdominal pain, and we tend to admit this patient for pain management if the pain does not resolve. Of particular interest are patients who develop pain after dual EUS-FNA and celiac plexus neurolysis. One such patient had severe pain in our study and required IV pain management for 5 days after EUS-FNA. A CT in all these patients revealed no additional intra-abdominal pathology, such as pancreatitis, infection, or bleeding.

Unlike previous investigations,[20] we did not encounter any perforation as a result of EUS and EUS-FNA in this large cohort of patients. In patients with duodenal obstruction due to pancreatic cancer, we resort to biopsy these lesions from a position proximal to the obstruction without a vigorous attempt to bypass the lesion with the echoendoscope.

We have not encountered any clinically important bleeding episodes in patients with EUS-FNA of the pancreas. While exaggerated bleeding can occur in certain patients at the EUS-FNA site, no clinically significant bleeding is usually encountered. Endosonographically apparent bleeding has been previously reported in cystic lesions of the pancreas and has a characteristic appearance.[21,22] Occasionally, it can be clinically important.[22]

This prospective investigation has several strengths. It includes a large number of patients who were carefully followed for acute and long-term complications. Data on potential risk factors were prospectively collected as well.

We note the limitation of this study. While our follow-up was almost complete on all the patients for complications, not all of them were contacted by telephone to specifically inquire about complications. Some information was obtained from clinic follow-up notes that might have not captured all the events. While minor events tend to be underreported, certainly, major events are typically relayed to us by the referring physician or by the patients upon clinical follow-up. In addition, our criterion standard for classifying disease relied on EUS-FNA results, clinical follow-up and surgery. Our methodology is similar to other investigations in the field.[4,6] Furthermore, despite the large number of patients, and because of the fortunately low number of major complication, the lack of association between risk factors and complications could be attributed to a type 2 error in this study.

In summary, EUS-FNA of solid pancreatic masses infrequently leads to acute pancreatitis, fever, or admission for significant pain. Our results can be used by endosonographers to counsel patients before EUS-FNA of solid pancreatic masses.

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