

Repeat endoscopic ultrasound fine needle aspiration after a first negative procedure is useful in pancreatic lesions

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ABSTRACT

Background and Objectives: There is no consensus about the ideal method for diagnosis in patients who have already undergone endoscopic ultrasound fine needle aspiration (EUS-FNA), and the inconclusive material is often obtained. The aim was to evaluate the diagnostic yield of the second EUS-FNA of pancreatic lesions. **Materials and Methods:** A retrospective analysis of prospectively collected data of patients with EUS-FNA of pancreatic lesions is performed. All patients who underwent more than one EUS-FNA for the evaluation of suspected pancreatic cancer over a 7-year period were included in the analysis. **Results:** A total of 296 EUS-FNAs of the pancreas were performed in 257 patients. The diagnostic yield with the first EUS-FNA was 78.6% (202/257). Thirty-nine (13.3%) FNAs were repeated in 34 patients; 17 (50%) patients were women. The mean \pm standard deviation (SD) age was 58.8 ± 16.1 years. The location of the lesions in the pancreatic gland, from which the second biopsies were taken, was head of the pancreas, $n = 28$ (82.4%), body of the pancreas, $n = 3$ (8.8%), and tail, $n = 3$ (8.8%). The mean \pm SD of the size of the lesion was 36.3 ± 14.6 mm. The second EUS-FNA was more likely to be positive for diagnosis in patients with an “atypical” histological result in the first EUS-FNA (odds ratio [OR]: 4.04; 95% confidence interval [CI]: 0.9–18.3), in contrast to patients with a first EUS-FNA reported as “normal” (OR: 0.21; 95% CI: 0.06–0.71). Overall, the diagnostic yield of the second EUS-FNA was 58.8% (20/34) with an increase to 86.3% overall (222/257). **Conclusion:** Repeat EUS-FNA in pancreatic lesions is necessary in patients with a negative first EUS-FNA because it improves the diagnostic yield.

Key words: Endoscopic ultrasound, fine needle aspiration, pancreatic cancer

INTRODUCTION

Endoscopic ultrasound (EUS) has been a useful method for evaluating pancreatobiliary pathology for more than a decade.^[1] The ability to obtain histological samples by EUS-guided fine needle aspiration (FNA)

biopsies has allowed the better care of patients with cystic or solid pancreatic lesions.^[2] Pancreatic tumors present the greatest challenge for diagnosis, with the

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lowest diagnostic values of 76%–90% and a false negative rate of about 15%.^[3,4] There is one report with fine-needle biopsy (FNB) device offering the possibility of obtaining a core sample for histological evaluation in the majority of cases, with an overall sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for diagnosis of malignancy were 90.2%, 100%, 100%, 78.9%, and 92.9%, respectively.^[5] However, this FNB device is not always available.^[6]

However, it is not unusual to find inconclusive pathological results in tissue obtained for diagnosis; factors involved in the diagnostic inaccuracy include the experience of the endosonographer, procedure volume, center, type, size and location of the lesion, the presence of a cytopathologist in the endoscopy room, the number of passes of the needle into the lesion, the use of a stylet and aspiration during the procedure, and the use of different needles to obtain tissue (core) or cell aspirate.^[7,8]

Currently, there is no consensus about the ideal method for diagnosis in patients who have already undergone EUS-FNA, and the inconclusive material is often obtained. Furthermore, there is no information about how many biopsies are acceptable when attempting to find a histological diagnosis. There are a few studies in the literature that provide data about the utility of a second EUS-FNA in pancreatic lesions, with most being case reports and retrospective case series with diagnostic ranges from 63% to 91% in the second EUS-FNA,^[7,9,10] but there is no information about the diagnostic yield of three or more EUS-FNA.

The aim of the present study was to evaluate the utility of the second EUS-FNA in pancreatic lesions.

MATERIALS AND METHODS

We performed a retrospective analysis of prospectively collected data from electronic and paper records of adult patients (older than 18 years) with EUS-FNA for pancreatic lesions. Patients were referred to from January 2006 to December 2012.

Before the procedure, all patients had laboratory tests including prothrombin time and a full blood count. The patients were placed in the left decubitus position and sedated using a combination of midazolam, propofol, and fentanyl by the anesthetist. Patients were continually

monitored using an automated noninvasive blood pressure device, electrocardiogram, and pulse oximetry throughout the procedure. EUS-FNA was performed using a FUJI EG-530UT linear array echoendoscope with an SU-8000 console (Fujifilm Corporation, Minato-Ku, Tokyo, Japan) by two echoendoscopists. All patients were hospitalized and were observed for at least 4 h after the procedure using an automatic monitor for surveillance of possible complications.

Since the majority of these patients are seen for follow-up in our clinic, our physicians requested repeat EUS-FNA since these patients were not candidates for surgical resection. A failed EUS-FNA was defined according to a previous definition:^[9] (i) Failed puncture, (ii) successful puncture but inadequate material, and (iii) cases with successful puncture, where adequate material was obtained but cytology was negative.

All procedures were performed with standard EchoTip Ultra 22-gauge or 19-gauge needles (Cook Medical, Inc., Winston-Salem, NC, USA). In our center, ProCore™ needles (Cook Medical Inc., Limerick, Ireland) were available until May 2012 but because of the small number of patients we decided not to include them in this report. We did no advance planning, but in general, all FNAs via the duodenum were performed using 22-gauge needles, and those via the transgastric route using a 19-gauge or 22-gauge needle according to the physician's preference. Pancreatic masses located in the head or uncinata process was sampled via the transduodenal route and those in the pancreatic body or tail were sampled via the transgastric route. Patients underwent EUS-FNA using the standard technique, as evidence about the fanning technique was not available at the time of inclusion of the patients.^[11]

Endoscopic ultrasound fine needle aspiration technique

First, the transducer was brought into a stable position in front of the targeted lesion. The metal spiral was then introduced into the biopsy channel while ensuring that the needle piston was securely locked and the needle was completely retracted. The spiral was inserted completely, and the handle with the Luer-lock was firmly screwed into the biopsy channel. To ensure that the sheath was protecting the entire length of the working channel, we used the optic of the endoscope. With the stylet retracted but still inside the needle, the biopsy needle was moved forward into the lesion under full real-time ultrasound control. After penetration into

the middle of the lesion, the stylet was completely removed. On reaching the optimal needle position in the middle of the lesion, a 10 mL syringe with a locking device was firmly screwed onto the needle, while pulling on the syringe piston to create low pressure. The syringe piston was locked into this position for permanent suction. The needle was moved to and fro 10–15 times inside the lesion under complete ultrasonic control. With the needle tip still in the lesion, suction was released, and the needle was safely retracted inside the needle sheath and locked in a secure position.

All specimens were recovered, fixed in formalin, and processed for histological and cytological analysis. A single expert pathologist evaluated the tissue samples. The cytological diagnoses of material obtained by EUS-FNA were then categorized as follows: Positive for malignancy, benign/reactive process, or nondiagnostic. For the purpose of this paper, material reported as suspicious for malignancy or atypical cells indeterminate for malignancy were considered negative (failures) in EUS-FNA. The final diagnosis (the gold standard) was based on the results from the surgical specimen, and follow-up (for at least 6 months) in nonoperated cases was achieved via global clinical and radiological assessment.

Complications were defined as any of the following: Excessive bleeding at the FNA site, perforation, hypotension, and the need for reversal medication. 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.

We consider utility of second EUS-FNA as the number of patients with correct diagnosis (malignant or benign lesions).

Statistical analysis

The results were evaluated using descriptive statistics for parametric distribution: Mean and standard deviation (SD), absolute and relative frequencies. Differences between groups were tested using the Chi-square test or Mann–Whitney U-test, according to the variable. A two-tailed $P < 0.05$ was considered statistically significant. To evaluate diagnostic yield, the sensitivity and specificity and positive and negative predictive values were calculated based on the final result of the gold standard. All analyses were conducted using SPSS 20 for Mac (IBM, Chicago, IL, USA).

RESULTS

A total of 2068 EUS were performed during the study period, including 705 EUS-FNAs. A total of 104 procedures were excluded due to incomplete information, 88 biopsies were not accompanied by a histological report, 58 were excluded because the biopsies were performed using conventional forceps and 159 procedures were from a different organ than pancreas.

A total of 296 EUS-FNAs of the pancreas were performed in 257 patients. One hundred and thirty-five (52.5%) patients were women. The mean \pm SD age was 59.5 ± 13.8 years. The diagnostic yield with the first EUS-FNA was 78.6% (202/257).

Patients with two or more endoscopic ultrasound fine needle aspiration

Thirty-nine (13.3%) FNAs were repeated in 34 patients; 17 (50%) patients were women. The mean \pm SD age was 58.8 ± 16.1 years. The location of the lesions in the pancreatic gland, from which the second biopsies were taken, was: Head of the pancreas $n = 28$ (82.4%), body of the pancreas $n = 3$ (8.8%), and tail $n = 3$ (8.8%). The mean \pm SD of the size of the lesion was 36.3 ± 14.6 mm. The indication for the EUS-FNA in all patients but one was a pancreatic mass. Histological results in the first EUS-FNA are shown in Table 1. The median duration between the two EUS-FNA procedures was 6 (3–290) days. Overall, the diagnostic yield of the second EUS-FNA was 58.8% (20/34) with an increase to 86.3% overall (222/257). Three patients underwent a third EUS-FNA, and the overall performance increased to 87.1% ($2/3 = 66.6\%$; 224/257). A fourth EUS-FNA was performed in only one patient, and the diagnosis was achieved with this procedure, giving a final overall diagnostic yield of 87.5%. Differences between patients

Table 1. Histological diagnosis of first endoscopic ultrasound fine needle aspiration in patients with a repeated endoscopic ultrasound fine needle aspiration

First EUS-FNA result	n (%)
Normal pancreatic tissue	12 (35.3)
Fibrin/necrotic tissue	9 (26.5)
Inadequate/insufficient material for diagnosis	4 (11.7)
Inflammatory tissue	5 (14.7)
Atypical	3 (8.8)
Eosinophilic amorphous material	1 (2)

EUS-FNA: Endoscopic ultrasound fine needle aspiration

with and without diagnosis after the second EUS-FNA are shown in Table 2. The median number of passes performed in these patients was 3.^[2-4]

The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for diagnosis of malignancy of the second EUS FNA were 61.9%, 30%, 65%, 27.3%, and 51.6%, respectively.

Patients without histological diagnosis by endoscopic ultrasound fine needle aspiration

In 11/34 (32.3%) patients, no diagnosis was achieved by EUS-FNA at any time; seven (63.6%) patients were women. The mean \pm SD age was 53 ± 19.8 years. Of these 11 patients, a third EUS-FNA was performed in only one patient. Eight patients underwent surgery with histological report of neuroendocrine tumor in three patients, IPMN in two patients, adenocarcinoma in two patients, and pseudotumoral chronic pancreatitis in one patient. Three patients were lost at follow-up.

Finally, 21/34 patients had malignant lesions, 10/34 had a benign lesion, and in 3/34, we did not reach a definitive diagnosis [Table 3]. In 8/34 patients, the definitive diagnosis was achieved with surgery.

When we analyzed the final results of the second EUS-FNA, an “atypical/inflammation” diagnosis in the first EUS-FNA was more likely to give a positive yield in the second EUS-FNA (OR: 4.04; 95% confidence interval [CI]: 0.9–18.3), in contrast to patients with a first EUS-FNA reported as “normal” (OR: 0.21; 95% CI: 0.06–0.71).

None of the patients who underwent repeat EUS-FNA experienced pancreatitis or major complications.

DISCUSSION

According to our results, repeat EUS-FNA in pancreatic lesions is necessary in patients with a negative first EUS-FNA because it improves the diagnostic yield.

When a negative initial cytology exists, there are several options including clinical observation and follow-up with serial imaging, surgical exploration without a definitive tissue diagnosis and repeating the EUS-FNA. According to our results, the third option is a good alternative in such patients. Previously

Table 2. Differences between patients with and without histological diagnosis on second endoscopic ultrasound fine needle aspiration

Characteristic	Patients with second EUS-FNA positive $n=20$ n (%)	Patients with second EUS-FNA negative $n=14$ n (%)	<i>P</i>
Age, years	62.1 \pm 13.8	54.5 \pm 18.5	0.22
Female	8 (40)	9 (64)	0.16
Size of lesion, mm	40 (20-70)	32 (10-50)	0.17
Head pancreas	17 (85)	11 (78.5)	0.62
Days between the two EUS-FNA	8 (3-290)	3 (3-124)	0.06
Atypical/inflammation in first EUS-FNA	6 (30)	2 (14)	0.10
Normal tissue in first EUS-FNA	6 (30)	6 (43)	0.44

EUS-FNA: Endoscopic ultrasound fine needle aspiration

Table 3. First cytopathology and final diagnosis of patients with two or more procedures

EUS-FNA cytology on the first sample	Final diagnosis			Total
	Benign	Malignant	Indeterminate/unknown	
Normal tissue	4	5	3	12
Necrosis/fibrin	1	8	0	9
Inadequate/insufficient	2	2	0	4
Inflammatory tissue	1	4	0	5
Atypical	1	2	0	3
Eosinophilic amorphous material	1	0	0	1
Total	10	21	3	34

EUS-FNA: Endoscopic ultrasound fine needle aspiration

published results support our data.^[9,10,12,13] In the paper of Nicaud *et al.*,^[9] final diagnosis was achieved in 17/28 patients with a sensibility of 35% and 100% of specificity; Eloubeidi *et al.*^[10] achieved the final diagnosis in 20/24 patients. In the paper of Ainsworth *et al.*^[12] reported utility of second EUS procedure and not necessarily with second EUS-FNA. In other interesting paper, results of repeated EUS-FNA at a tertiary referral center following a failed first EUS-FNAs performed in the community hospitals is shown with a yield of second EUS-FNAs of 63%.^[13] Our results represent a good sample size comparable with these previous data with similar results, and important differences with previous data without histology data, besides our second procedure was performed for the same physicians avoiding bias related with the operator.

In some cases, alternative diagnostic tools could be chosen to achieve a tissue diagnosis such as bile duct brushing with endoscopic retrograde cholangiopancreatography

(ERCP), computed tomography (CT)-guided biopsy, or tissue samples obtained by the laparoscopic approach. However, ERCP with brushing is associated with low diagnostic yield and postprocedural complications such as pancreatitis, and CT-guided biopsy bears the risk of seeding. Surgical approaches are more invasive and costs must be considered. It is evident that after a negative second EUS-FNA, we have to consider very carefully whether a new biopsy is really necessary and how possible it is that this third (or fourth) EUS-FNA could give us the histological diagnosis. Because of the low number of patients undergoing three or more EUS-FNA in our study, it is difficult to investigate predictive factors of diagnostic yield in this setting. In our series, the decision to perform more than two EUS-FNA was directly associated with the endoscopist's criteria, which include many subjective components.

We are conscious that EUS-FNA has some limitations and that there are some patients in whom it is inappropriate. In our center, when the clinical and imaging suspicion is high, our practice is to recommend surgical exploration despite a negative EUS-FNA. The cohort in this study consisted of patients who were deemed initially to be unresectable by either EUS or CT scan because in patients with a resectable lesion, our current practice is direct surgery, without any EUS-FNA. Another limitation is that not all patients had a 2nd biopsy in case of noncontributive or negative biopsy, and we have some not included all patients. Unfortunately this is a retrospective study.

Previous data about the utility of repeated EUS-FNA at a tertiary referral center following a failed first EUS-FNAs performed in community hospitals demonstrated a yield of second EUS-FNAs of 63% when performed by experts.^[13] It should be noted that the yield reported in that study was very similar to our results when the same group of physicians did the second EUS-FNA. This study did not include patients who underwent failed EUS-FNA or “missed” diagnosis by other referring physicians from the community. Limitations of this study include its retrospective nature; however, our data represent a good number of cases of repeated EUS-FNA in pancreatic lesions and include results about third and additional EUS-FNA.

CONCLUSION

Repeat EUS-FNA in pancreatic lesions is necessary in patients with a negative first EUS-FNA because it improves diagnostic yield.

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Conflicts of interest

There are no conflicts of interest.

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