

## EUS-guided FNA diagnostic yield of malignancy in solid pancreatic masses: a benchmark for quality performance measurement

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**Background:** The diagnostic yield of EUS-guided FNA (EUS-FNA) of solid pancreatic masses is a potential benchmark for EUS-FNA quality, because the majority of EUS-FNA of solid pancreatic masses should be diagnostic for malignancy.

**Objectives:** To determine the cytologic diagnostic rate of malignancy in EUS-FNA of solid pancreatic masses and to determine if variability exists among endoscopists and centers.

**Design:** Multicenter retrospective study.

**Patients:** EUS centers provided cytology reports for all EUS-FNAs of solid, noncystic,  $\geq 10$ -mm-diameter, solid pancreatic masses during a 1-year period.

**Main Outcome Measurement:** Cytology diagnostic of pancreatic malignancy.

**Results:** A total of 1075 patients underwent EUS-FNA at 21 centers (81% academic) with 41 endoscopists. The median number of EUS-FNA of solid pancreatic masses performed during the year per center was 46 (range, 4-177) and per endoscopist was 19 (range, 1-97). The mean mass dimensions were 32  $\times$  27 mm, with 73% located in the head. The mean number of passes was 3.5. Of the centers, 90% used immediate cytologic evaluation. The overall diagnostic rate of malignancy was 71%, 95% confidence interval 0.69%-0.74%, with 5% suspicious for malignancy, 6% atypical cells, and 18% negative for malignancy. The median diagnostic rate per center was 78% (range, 39%-93%; 1st quartile, 61%) and per endoscopist was 75% (range, 0%-100%; 1st quartile, 52%).

**Limitations:** Retrospective study, participation bias, and varying chronic pancreatitis prevalence.

**Conclusions:** (1) EUS-FNA cytology was diagnostic of malignancy in 71% of solid pancreatic masses and (2) endoscopists with a final cytologic diagnosis rate of malignancy for EUS-FNA of solid masses that was less than 52% were in the lowest quartile and should evaluate reasons for their low yield. (Gastrointest Endosc 2007;66:277-82.)

EUS-guided FNA (EUS-FNA) has become widely accepted as an effective modality for obtaining a tissue diagnosis of pancreatic masses. The most common indication for pancreatic EUS-FNA is to biopsy a mass lesion that

is suspicious for malignancy. EUS-FNA is generally not recommended or performed to diagnose chronic pancreatitis. The sensitivity of EUS-FNA for diagnosing pancreatic cancer is 80% to 90%.<sup>1-7</sup> Because most pancreatic masses that undergo EUS-FNA have a very high pretest probability of being malignant and because EUS-FNA is very sensitive for diagnosing pancreatic cancer, most pancreatic masses that undergo EUS-FNA biopsy should have cytologic findings of malignancy.

Quality performance in endoscopy is becoming an important issue for patient care.<sup>8</sup> There currently is no accepted method for quality performance indicators in EUS, mostly because cancer staging accuracy cannot be verified without surgical resection and FNA yields of some sites (such as mediastinal lymph nodes) vary greatly based on pretest probabilities.<sup>9,10</sup> The overall diagnostic yield for cytologic malignancy with EUS-FNA of solid pancreatic masses seems, potentially, an ideal method of trying to compare or evaluate endoscopic performance. This is because of the high pretest probability of cancer in a solid, noncystic pancreatic mass, and the high reported sensitivity of EUS-FNA for these lesions. There are many variables associated with increased cytologic yield from EUS-FNA, such as the prevalence of chronic pancreatitis, endosonographer skill, needle characteristics, ability to puncture the lesion, number of passes performed, sample preparation, immediate cytologic evaluation, and pathologic interpretation. However, knowing the overall expected diagnostic rate for EUS-FNA of solid pancreatic masses would allow individuals or institutions to compare their results with their peers and to determine if their yield is similar. As EUS-FNA becomes more widely available in a variety of practice settings, the question of quality performance will be more important, and an objective measure would be helpful.

The aim of this study was to determine the cytologic diagnostic rate of malignancy in EUS-FNA of solid pancreatic masses and to determine if variability exists among centers and endoscopists. These findings could lead to proposed benchmarks for performance of EUS-FNA.

## PATIENTS AND METHODS

### Study design

This was a retrospective multicenter study. This study was approved by the human research protections program (HRPP) at the University of California, San Diego, as the coordinating site, as well as by the local HRPP committees of each participating institution.

### Participating EUS centers

Members of the American Society for Gastrointestinal Endoscopy (ASGE)-sponsored Endoscopic Ultrasound Special Interest Group were notified about the study in May 2005 by e-mail and at the annual meeting of the group. This is a group of approximately 400 physicians who are members of the ASGE and who have identified themselves as having an interest in EUS. The majority of the endosonographers in the United States belong to this group. Those individuals who expressed interest were sent additional information regarding the study design. Each center designated a single investigator to coordinate data collection at that site. Once a center had obtained HRPP approval from its institution, the

### Capsule Summary

#### What is already known on this topic

- In the evaluation of pancreatic masses, EUS-guided FNA is sensitive for diagnosing pancreatic cancer.

#### What this study adds to our knowledge

- In a multicenter retrospective study of 1075 patients who underwent EUS-guided FNA of solid pancreatic masses, the overall diagnostic rate of malignancy was 71%, the median rate per center was 78%, and the median rate per endoscopist was 75%.

investigator could collect deidentified data and submit it to the central data registry.

### Case identification

The participants at each center were asked to retrospectively review their endoscopy and/or pathology databases to identify all pancreatic EUS-FNA cytology biopsy specimens obtained during a 1-year time period, from July 1, 2004, to June 30, 2005. All cases were performed as part of routine patient care.

### Data collection

Coinvestigators were asked to submit the following data for each case: patient age, patient sex, location of lesion, short- and long-axis dimension of lesion (mm), number of FNA passes, exact wording of final cytology report, and deidentified endoscopist (ie, A, B, or C) who performed each case. Demographic information obtained about the center where the EUS was performed included type of practice (university program, private practice, or large multispecialty practice) and whether immediate cytologic evaluation was generally used. The demographic data obtained about the endosonographers included whether they had received "4th year training in advanced endoscopy or EUS" and an estimated total lifetime number of EUS cases performed (0-500, 500-1000, >1000).

### Inclusion and exclusion criteria

EUS procedures between July 1, 2004, and June 30, 2005, were reviewed. Only cases of solid pancreatic masses with a short-axis diameter of at least 10 mm were included. Cytology results were required for each case. The definition of a solid pancreatic mass was a solid, noncystic lesion for which the endoscopy report listed both the short- and long-axis dimensions in millimeters. The reason for this was that most pancreatic cancers have defined margins, whereas chronic and autoimmune pancreatitis may not have distinct dimensions. The reason for choosing a short-axis diameter of at least 10 mm was to increase the likelihood of a pancreatic cancer and to avoid the possibility of FNA of subtle nodularity in chronic

pancreatitis or diminutive neuroendocrine tumors, which may have lower diagnostic yields. Patients were excluded if a nonpancreatic site (ie, liver lesion or lymph node) EUS-FNA was also performed during the same session as the pancreatic-mass FNA, from concern that the in-room cytologic evaluation results of a possible metastatic lesion might have influenced the endoscopist's effort to obtain diagnostic material from the primary pancreatic mass. The location of the mass was required to be recorded and was characterized as head or body/tail. Masses described as being in the genu, the neck, or the uncinata were categorized as pancreatic-head lesions.

### Categorization of cytology results for cases

Participants at centers were asked to provide the exact wording from the cytology report for the patient. The results of these reports were then categorized as "positive for malignancy," "suspicious for malignancy," "atypia," or "negative for malignancy." Malignancy was defined as any malignancy (ie, "adenocarcinoma," "neuroendocrine tumor," "metastatic"). "Positive for malignancy" required cytology wording such as "diagnostic for malignancy," "diagnostic of malignancy," "compatible with carcinoma," "consistent with adenocarcinoma," "positive for malignant cells," "malignant cells present," or specifying the exact tumor type. "Suspicious for malignancy" required the wording "suspicious for malignancy" or "suggestive of malignancy." "Atypical" included the phrasing "atypical cells" or "atypical/inconclusive." "Negative for malignancy" required wording that included "benign," "non-diagnostic material," "inconclusive for malignancy," or "benign inflammatory changes" (either nonspecific, or consistent with autoimmune pancreatitis or chronic pancreatitis).

### Data entry and statistical analysis

Deidentified data were entered into computer spreadsheets. The response variable was "positive" diagnostic cytology. All other cytologic findings were considered "not positive for malignancy" (negative, atypia, suspicious). The positive diagnostic rate was estimated from the total population. A  $\chi^2$  analysis was performed for categorical covariates based on the binary response (positive/not positive). Summary statistics and univariate logistic regression were used for continuous variables. A multivariate logistic regression model was fitted with fixed effects for significant covariates and random effects for the center and the endoscopist. A *P* value less than .05 was considered significant.

## RESULTS

A total of 1075 patients were enrolled from 21 centers. Twenty centers were from the United States, and 1 center was from Brazil. Self-classified academic centers comprised

**TABLE 1. Overall final cytologic diagnoses for 1075 patients who underwent EUS-FNA of solid pancreatic masses**

Cytologic diagnosis	Yield, %
Positive for malignancy	71, 95% CI 0.69-0.74
Suspicious for malignancy	5
Atypia	6
Negative for malignancy	18

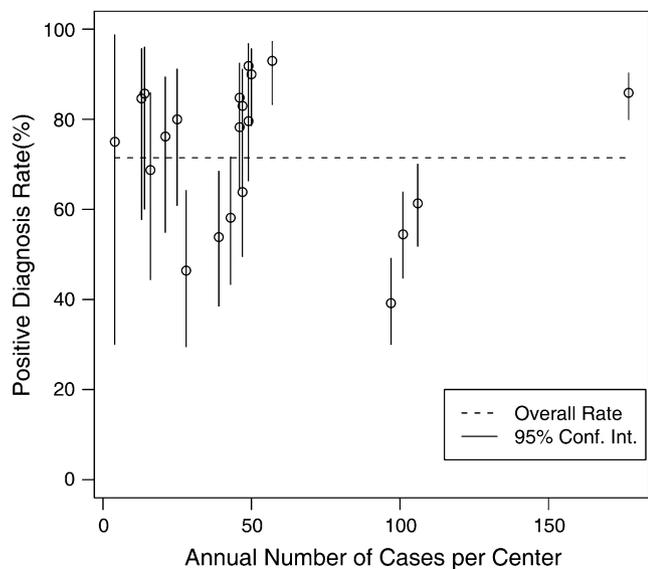
81% of the centers. EUS was performed by 41 endoscopists, of whom 56% had 4th year advanced endoscopy training and 63% had performed > 1000 lifetime EUS procedures.

The median number of solid pancreatic mass EUS-FNA cases performed during the year per center was 46 (range, 4-177) and per endoscopist was 19 (range, 1-97). The mean mass dimensions were 32 × 27 mm, with 73% located in the head. The mean (standard deviation [SD]) number of passes was 3.5 ± 1.9 (range, 1-13). Immediate cytologic evaluation during the procedure was used at 90% of the centers. The mean (SD) age of the patients was 66.1 ± 12.4 years (range, 16-92 years). Men comprised 53% of the patients.

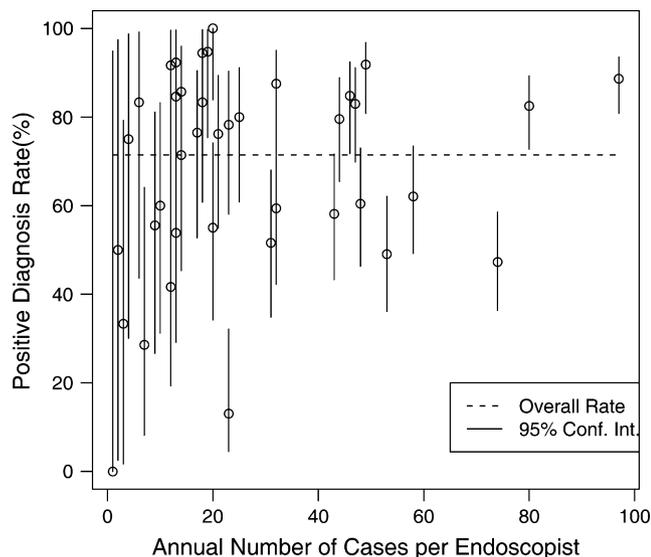
The overall diagnostic rate of malignancy was 71%, 95% confidence interval (CI) 0.69-0.74). The rates for other cytologic diagnoses are shown in Table 1. The median diagnostic rate per center was 78% (range, 39%-93%; 1st quartile, 61%; 3rd quartile, 85%). The positive diagnostic rate for malignancy in patients based on the number of cases performed in the study year by center is shown in Figure 1. The univariate logistic regression results of a positive EUS diagnostic yield by number of cases performed per center revealed no significant difference (*P* = .605).

The median diagnostic rate per endoscopist was 75% (range, 0%-100%; 1st quartile, 52%; 3rd quartile, 85%). The univariate logistic regression results of the positive EUS diagnostic yield by number of cases performed per endoscopist revealed no significant difference (*P* = .093). The positive diagnostic rate for malignancy in patients based on the number of cases performed in the study year by the endoscopist is shown in Figure 2. Box and whisker plots of the diagnostic rates per center and per endoscopist are shown in Figure 3.

The multivariate analysis of variables associated with a positive diagnostic rate for malignancy is shown in Table 2. Factors associated with an increased odds ratio for a positive diagnostic yield for malignancy on multivariate analysis were older patient age, female patient sex, and larger short-axis diameter. Factors associated with a decreased odds ratio for a positive diagnostic yield of malignancy on multivariate analysis were a mass located in the pancreatic head and an increasing number of FNA passes.



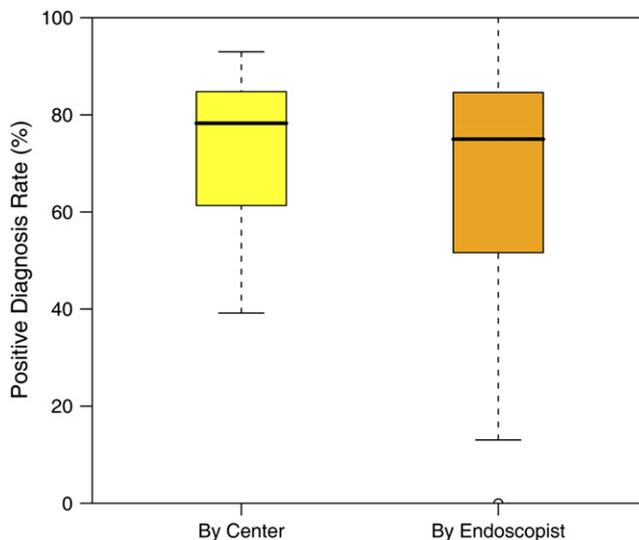
**Figure 1.** Positive diagnostic rate of EUS-FNA of solid pancreatic masses by annual number of solid pancreatic mass EUS-FNA cases performed at each center during the 1-year study period. The range was 39% to 93%, and the 1st quartile was 61%.



**Figure 2.** Positive diagnostic rate of EUS-FNA of solid pancreatic masses by annual number of solid pancreatic mass EUS-FNA cases performed by individual endoscopists in the 1-year study period. The range was 0% to 100%, and the 1st quartile was 52%.

**DISCUSSION**

This multicenter retrospective study found a wide variation in the diagnostic rate of malignancy with EUS-FNA of solid pancreatic masses with a high pretest probability for malignancy. Although the overall diagnostic rate of malignancy was 71%, 95% CI 69%-74%, for EUS-FNA of solid pancreatic masses, the diagnostic range among endosonographers was 0%-100%. The lowest quartile of



**Figure 3.** Box and whisker plot of positive malignancy diagnostic rate of pancreatic EUS-FNA by center and endoscopist. Note that the *solid line* represents the median of the distribution of diagnostic yields. The top of the box represents the 3rd quartile, and the bottom of the box represents the 1st quartile. For each center, the median was 78% (interquartile range, 61%-85%), and, for the endoscopists, the median was 75% (interquartile range, 52%-85%).

**TABLE 2. Multivariate analysis of variables significantly associated with a positive diagnostic yield for malignancy of EUS-FNA of solid pancreatic masses**

Variable	Odds ratio	P value
Age	1.029	<.001
Female sex	1.469	.01
Mass location in pancreatic head	0.616	.006
Short-axis diameter of mass	1.042	<.001
No. FNA passes into mass	0.803	<.001

diagnostic rate among endosonographers was below 52%, which represents a marked decrease in performance rate compared with other endosonographers in the study.

The reason for differences in diagnostic rates cannot be accurately determined from this retrospective study. Multivariate analysis showed a higher diagnostic rate of malignancy in older, female patients, with a larger mass size. It is possible that these differences in diagnostic rates reflect a higher prevalence of chronic pancreatitis in younger male patients. Besides differences in the prevalence of chronic pancreatitis in the patients who underwent EUS, other potential factors that could be related to a positive diagnostic yield, including endoscopist skill; technical factors, such as needle size, ability to puncture the lesion, number of passes, who prepares cytology slides, and pathologist expertise; and willingness to diagnosis malignancy. The reason that fewer passes were associated with a greater

diagnostic yield is also likely to reflect that, in cases of pancreatic cancer, only a few passes may be needed to diagnosis malignancy when using immediate cytologic evaluation, but if there is no malignancy detected, then more passes will be performed until the cytologist and the endosonographer are certain that there is no malignancy (as might happen in the case of focal chronic pancreatitis).

In this study, 11% of the 1075 pancreatic biopsy specimens had a final cytologic diagnosis of “suspicious for malignancy” or “atypical cells.” Given the retrospective study design, it is not possible to know how many of these were in patients with true malignancy. Lower rates of “positive for diagnostic yield” were associated with higher rates of “suspicious” or “atypical” cytology. This suggests that, in some centers the pathologists’ willingness to commit to a “positive” or “negative” diagnosis, rather than “suspicious” or “atypical” cells, could directly impact the diagnostic yield. In addition, it is possible that some biopsy specimens that were considered “suspicious” or “atypical” by 1 pathologist may have been interpreted as “positive for malignancy” by another pathologist. Centers with lower than expected diagnostic rates of malignancy of EUS-FNA of solid pancreatic masses might evaluate their cytologic diagnostic rates of suspicious for malignancy or atypia to help determine if possibly their pathologists were less likely than others to definitively diagnose malignancy in a pancreatic mass cytology sample.

The main limitations of this study were the retrospective nature and the inability to have a true criterion standard for whether a patient had pancreatic cancer. In addition, there can be pathologist variability in the diagnosis of “positive for malignancy.” There may also be variation in what different endosonographers consider to be a “mass” versus “chronic pancreatitis.”

There may also have been participation bias in that there was a low participation rate of approximately 10% (41 of approximately 400 EUS Special Interest Group members). It is possible that only centers where the participants felt they had acceptable yields may have volunteered to participate, whereas those with perceived low diagnostic yield rates might not have participated. The low participation rate may also reflect that some effort was needed to obtain these data in terms of obtaining local institutional review board approval and then reviewing endoscopy/pathology reports and submitting them. This is often easier to do in a training program, where there are trainees or research nurses who can help with the study, which would result in additional participation bias toward academic programs.

There was no difference in diagnostic yield between endosonographers who performed low versus high volumes of procedures. In fact, some of the lowest yield endoscopists performed some of the highest number of procedures. It is possible that endoscopists who performed fewer EUS-FNA procedures may tend to biopsy only the lesions most suspicious for pancreatic cancer (ie, pancreatic head mass

with obstructive jaundice), which could raise their diagnostic yield, whereas pancreatic referral centers may biopsy more subtle lesions or lesions associated with chronic pancreatitis, which would lower their diagnostic yield. It is also important to appreciate that endoscopists who performed only a few pancreatic mass EUS-FNA per year might have a wider range of positive diagnostic yields compared with endoscopists who performed higher case volumes, based on greater statistical variance with small numbers of cases. Endoscopists in this study performed a median of 19 per year (1.6 per month), which suggests that perhaps approximately this number should be used before evaluating an endoscopist’s experience.

This study was not designed to determine diagnostic accuracy or operating characteristics of pancreatic EUS-FNA, nor was it designed to specifically identify the exact reasons to explain differences in diagnostic yields. To do this would require a prospective study that would include attempts at final diagnosis based on subsequent surgical pathology or clinical follow-up. A future prospective study could look at other issues, such as clinical presentation (ie, obstructive jaundice), pathologist variability in interpretation, impact of different needle types, and complication rates.

This study showed that a benchmark for EUS-FNA could be obtained by evaluating malignant diagnosis rates of solid pancreatic masses. As predicted, a high proportion of these biopsy specimens (71%) were positive for malignancy. In addition, the wide range of diagnostic yield among endosonographers and EUS centers suggested that benchmarking might identify significant outliers.

The ideal benchmark for pancreatic EUS-FNA performance would be the actual sensitivity and specificity of diagnosing malignancy, but these require the criterion standard of either surgical pathology or long-term follow-up, which would be more difficult or impossible data to collect. The use of diagnostic yield is easy data to collect, because it only requires the final cytologic diagnosis from pancreatic FNA and may also serve as a surrogate marker of diagnostic accuracy.

Care must be taken with interpreting benchmarking data, because patient mix can severely skew the results (eg, high prevalence of chronic pancreatitis, difficult to sedate patients, training programs, inexperienced pathologists). However, by selecting a very low threshold (ie, the lowest quartile), only the most severe outliers are identified. Individual endosonographers with an overall yield of malignancy less than 50% for pancreatic masses should evaluate factors that might contribute to this low rate.

Benchmarking is increasingly being considered for a variety of GI endoscopic procedures.<sup>11</sup> For colonoscopy, variables evaluated have included cecal intubation and adenoma detection rates. It has also been proposed that endoscopists who perform ERCP keep a “report card” of their success rate for a variety of ERCP maneuvers, eg, successful cannulation, stone removal.<sup>12</sup> The malignant diagnostic rate of EUS-FNA of solid pancreatic masses could

also be easily considered along with these other endoscopic benchmarks.

In summary, the diagnostic rate of EUS-FNA of solid pancreatic masses is a simple way to benchmark EUS-FNA performance. The overall diagnostic yield of EUS-FNA in a variety of settings was 71%. Endosonographers who had diagnostic rates less than 50% were in the lowest quartile, and should assess possible reasons for performance below others who performed the same procedure. Future prospective studies should ideally be performed to validate these findings, to compare with the criterion standard sensitivity and specificity, and to determine which variables are associated with lower diagnostic yields.

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## DISCLOSURE

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