# Role of serial EUS-guided FNA on pancreatic cystic neoplasms: a retrospective analysis of repeat carcinoembryonic antigen measurements CME

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**Background and Aims:** Pancreatic cystic neoplasms (PCNs) often need interval surveillance, including repeat EUS, but the role of repeat FNA with fluid analysis is poorly defined. The aim of this analysis is to evaluate the potential clinical significance of serial carcinoembryonic antigen (CEA) measurements by EUS-guided FNA (EUS-FNA) in the surveillance for PCNs.

**Patients:** Patients who underwent EUS-FNA for PCNs were studied retrospectively. EUS-FNA findings were compared between index and prior procedures among patients who underwent repeat EUS-FNA.

**Results:** A total of 400 patients with PCNs underwent EUS-FNA. Eighty-seven of those patients had prior EUS-FNA with cyst fluid analysis. Patients with repeat FNA were significantly more likely to have multiple cysts (57% vs 41%; $P = .008$), multilocular cysts (75% vs 62%; $P = .042$), connection to pancreatic duct (33% vs 18%; $P = .005$), and higher initial CEA levels (94.8 vs 25.6 ng/mL; $P = .003$) compared with patients who had only a single FNA. A comparison of prior and index FNAs did not show significant differences in EUS or cyst fluid analysis findings. After log transformation, the association between CEA level at prior and index FNA was moderate ($R^2 = 0.626$; $P < .001$), but cystic fluid CEA classification with a cutoff value of 192 ng/mL changed in 17 patients (20%), without significant changes in EUS findings.

**Conclusions:** Repeat surveillance EUS-FNA resulted in stable CEA levels in the majority of patients, with spurious fluctuations of CEA in approximately 20% of patients. These data call into question any clinical significance attributed to an isolated interval rise in CEA level, especially in light of a stable EUS examination. (Gastrointest Endosc 2016;84:780-4.)

*(footnotes appear on last page of article)*

We increasingly encounter asymptomatic pancreatic cystic neoplasms (PCNs) in clinical practice because of the increase in opportunities of abdominal imaging such as US or CT as well as the improvement in imaging modalities.[1] Given the wide range of diagnoses from benign to malignant, the accurate diagnosis of PCN is essential, albeit challenging, for treatment decisions.[2,3]

Cytology and cyst-fluid analysis are performed routinely in EUS-guided FNA (EUS-FNA) for PCN.[4,5] Specificity of cytology in the diagnosis of malignant PCNs is high, but its sensitivity is low. Meanwhile, carcinoembryonic antigen (CEA) levels in the cyst fluid are useful to differentiate mucinous versus nonmucinous cysts, but they are not useful for the diagnosis of malignant PCNs.[6,7] Although various molecular markers have been reported,[8] they are not yet readily available for clinical use, and cyst fluid CEA measurement remains the mainstay for evaluation of PCNs. Given the malignant potential of PCNs such as side-branch intraductal papillary mucinous neoplasms (IPMNs), many patients with PCN need continued surveillance. The revised Sendai consensus guideline[9] recommends EUS and magnetic resonance imaging (MRI) as the procedures for surveillance; however, little is known about the role of repeat EUS-FNA during surveillance of PCNs. We, therefore, conducted this retrospective analysis of EUS-FNA for PCNs to evaluate the potential clinical significance of serial CEA measurements by EUS-FNA in patients under surveillance for PCNs.

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## PATIENTS AND METHODS

### Patients

Consecutive patients with clinically suspected PCNs who underwent EUS-FNA with cyst fluid analysis (index FNA) between June 2009 and May 2012 at the H.H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, were included in the analysis. Medical records including age, sex, EUS-FNA findings, cyst fluid analysis, and cytology results were retrospectively reviewed. Cyst characteristics (cyst number, location, diameter, macrocystic versus microcystic, multilocular versus unilocular, the presence of connection to the pancreatic duct, mural nodule) on EUS, and FNA procedure details (needle size, the amount of obtained cyst fluid) were retrieved from EUS reports. Data from previous EUS-FNA (prior FNA), if any, also were retrieved. This study was approved by the local Institutional Review Board.

### EUS-FNA procedure

After careful EUS examination, the cyst was punctured by using a 19-, 22-, or 25-gauge FNA needle, and cyst fluid was aspirated with suction. A 22-gauge needle was used primarily for EUS-FNA for PCNs, but if the fluid was too viscous to come through the smaller needle, a 19-gauge needle was used. A 25-gauge needle was used only in cases with a risk of bleeding because of cysts located adjacent to a vessel. The cyst fluid was sent for fluid analysis (CEA and amylase) and cytology. Cyst fluid CEA measurement was performed in a 1-step sandwich immunoassay on Immulite 2000 XPi (Siemens Medical Solutions USA Inc, Malvern, Pa). Cyst fluid CEA was categorized by using a cut-off value of 192 ng/mL. When the amount of the aspirated cystic fluid was small, the fluid was preferentially sent for fluid analysis with dilution by normal saline solution, if necessary.[10] A prophylactic oral quinolone was routinely administered for 5 days after the procedure.

### Statistical analyses

EUS and EUS-FNA results of index and prior EUS-FNAs were compared among patients who underwent repeated EUS-FNAs for PCNs. The Pearson correlation coefficient was used to assess the correlation between cyst fluid CEA levels of prior and index EUS-FNAs. Cyst fluid CEA category ($\geq$192 vs <192 ng/mL) was compared between index and prior EUS-FNAs by using the McNemar test.

Continuous variables are presented as the mean and standard deviation (SD) or the median and range. Statistical comparisons were performed with a chi-square test or the Fisher exact test for categorical variables and the *t* test or the Wilcoxon rank-sum test for continuous variables. A *P* value < .05 in a 2-tailed test was considered a statistically significant difference. JMP software version 10.0 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

## RESULTS

### Patients

A total of 400 patients with PCNs underwent EUS-FNA between June 2009 and May 2012, and among these 400 patients, 87 patients had prior EUS-FNA with cyst fluid analysis with a median interval of 8.7 months (range 0.8-91.7 months). These patients underwent repeat EUS-FNA for various reasons as clinically dictated, including CEA values inconsistent with gross fluid characteristics, unusual EUS features, and patient or physician preferences.

Patient characteristics and FNA results in patients with repeat FNAs (n = 87) compared with those with 1-time FNA (n = 313) are shown in Table 1. Patients with repeat FNA were more likely to have multiple cysts (57% vs 41%; $P = .008$), multilocular cysts (75% vs 62%; $P = .042$), connection to a pancreatic duct (33% vs 18%; $P = .005$), and higher cyst fluid CEA levels (94.8 vs 25.6 ng/mL; $P = .003$).

### EUS-FNA results in 87 patients with repeat FNAs

A comparison of index and prior EUS-FNA results in 87 patients with repeat FNA is shown in Table 2. There were no significant differences in EUS and EUS-FNA findings between index and prior EUS procedures. The median cyst fluid CEA was 94.8 ng/mL at index FNA and 118 ng/mL at prior FNA. Cyst fluid CEA levels decreased 18.1% at median (range 1241% decrease to 100% increase) from prior FNA. Although cyst fluid CEA levels at index and prior EUS-FNAs were well correlated with each other after log transformation ($R^2 = 0.626$; $P < .001$), the CEA category with a cutoff value of 192 ng/mL changed in 17 patients (20%). Cyst fluid CEA changed from low to high in 6 cases (7%) and high to low in 11 cases (6%). Details of these 17 discordant cases are shown in Table 3.

After repeat EUS-FNA, only 3 patients underwent surgical resection, although EUS findings with CEA category did not change between 2 EUS-FNA procedures. Surgery was performed at the discretion of patients, and the pathologic diagnoses of these patients were 1 IPMN with concomitant pancreatic intraepithelial neoplasia (PanIN) and 2 PanIN.

### Serial cyst fluid CEA change in patients undergoing 3 or more EUS-FNAs

Among 87 patients with repeat EUS-FNAs, 14 patients underwent 3 or more EUS-FNAs for PCNs; 3 EUS-FNAs in 11 patients, 4 EUS-FNAs in 1, and 5 EUS-FNAs in 2. Serial CEA change is shown in Figure 1. Cyst fluid CEA levels showed considerable fluctuations over time. CEA category was not consistent in 7 patients (50%), although EUS findings did not change considerably.

## DISCUSSION

In our retrospective analysis of EUS-FNA in the surveillance of PCNs, cyst fluid CEA levels did not change