COMIRB Protocol

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Protocol #: 18-1854

Project Title: Evaluation of pancreatic cystic lesions via EUS-guided fine needle aspiration with and without micro forceps biopsies: A randomized controlled study

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I. Hypothesis: Evaluation of pancreatic cystic lesions using endoscopic ultrasound with fine needle aspiration (EUS-FNA) of cyst fluid and microforceps biopsies (EUS-MFB) has greater diagnostic yield and equivalent safety profile compared to EUS with fine needle aspiration (EUS-FNA) alone.

Specific Aims: To prospectively compare the efficacy and safety of EUS evaluation of pancreatic cystic lesions with 1) EUS-FNA plus MFB versus 2) EUS-FNA alone, in a randomized controlled study.

II. Background and Significance:

Pancreatic cystic lesions (PCLs) are a common incidental finding in cross sectional imaging (up to 27% on CT scan and 41% on MRI[1]) and pose a management challenge to physicians. According to society guidelines,[2–4] PCLs with specific features should prompt additional workup with endoscopic ultrasound (EUS) for cyst characterization as well as cyst sampling. This can help determine if the cyst is mucinous or non-mucinous which has implications for its malignant potential. Cyst fluid has traditionally been sampled using EUS with fine needle aspiration (EUS-FNA) and sent for fluid analysis and cytology. However, despite use of a cyst fluid carcinoembryonic antigen (CEA) level cutoff[5] of 192 ng/mL and cytology, accuracy of diagnosis for PCLs is poor. As the spectrum ranges from benign to high risk for neoplasm, precise diagnosis is critical.

More recently, the adjunctive use of the Moray® through the needle microforceps biopsy (EUS-MFB) has shown promise for diagnosis of PCLs.[6] This technology utilizes a microforceps through a 19-guage

needle to biopsy the cyst wall for histology, in addition to collecting cyst fluid for CEA level and cytology. Only a few small retrospective reports have been published regarding the use of MFB.

D. Innovation:

Pancreatic cysts continue to pose a management dilemma for practicing clinicians, especially with the increased use of radiologic imaging modalities identifying incidental pancreatic cystic lesions with higher frequency. This leads to patient anxiety and increased costs due to radiologic surveillance and even surgery. The results of this study will hopefully help increase diagnostic yield by obtaining a histopathologic diagnosis of these PCLs, and potentially affect practice patterns of gastroenterologists and the endoscopic community, specifically those physicians who perform EUS in these patients. Furthermore, the results will help determine whether there is reason to continue this line of research to obtain a definite histologic tissue diagnosis of PCLs.

III. Preliminary Studies/Progress Report:

We recently published our retrospective series of 27 patients using EUS-MFB for evaluation of PCLs and reported technical success of 100% and obtained a pathological diagnosis in 24 of 27 cases (yield 88.9%) with MFB. In 7 patients (26%), microforceps biopsy results drastically changed the diagnosis, providing diagnoses otherwise not suggested by cytology or cyst fluid CEA levels. However, cytology provided a diagnosis of mucinous cyst in 4 cases (14.8%) not detected by microforceps biopsies. No adverse events were noted.

Other small retrospective studies have shown that cyst fluid analysis via FNA is comparable to MFB for distinguishing mucinous from non-mucinous cysts, but MFB is better at diagnosing the specific cyst subtype.[8,9] However, prospective data on the use and safety of MFB for PCLs is lacking.

IV. Research Methods

The study will be performed at 3 participating sites:
(1) University of Colorado Hospital-Anschutz Medical Campus (UCH-AMC), Aurora, CO (Primary site)
(2) Mt. Sinai Medical Center, New York, NY
(3) University of California, Irvine, CA.
The study will be conducted after obtaining approval from the Institutional Review Board at all sites.

A. Outcome Measure(s):

Primary Outcomes:

A. Compare the efficacy and safety of EUS-FNA plus MFB, with EUS-FNA alone for evaluation of PCLs

   Definitions:
   A. Efficacy will be defined as technical and clinical success in performing MFB during EUS evaluation of PCLs.
   (1) Technical success will be defined as the ability to puncture the cyst with the FNA needle under EUS guidance, advance the micro forceps into the cyst to perform cyst biopsies and obtain a visible tissue fragment.
   (2) Clinical success will be defined as the ability to obtain a pathologic tissue diagnosis of the PCL with MFB. Based on prior experience, expected diagnoses include pseudocyst, serous cystadenoma, mucinous cyst (mucinous cystic neoplasm, intra-ductal papillary mucinous neoplasm), adenocarcinoma, and neuroendocrine tumor, to name a few.

B. Compare safety of EUS-FNA plus MFB with that of EUS-FNA by recording adverse events per published ASGE criteria (10).

Secondary Outcomes:

A. Technical ease in performing FNA and MFB:
   (1) Ease of passage of FNA needle
   (2) Ease of passage of Micro Forceps
   (3) Ease of EUS visualization of Micro Forceps

   Technical ease will be scored on a predetermined 5-point Likert scale (1 = best, 5 = worst)

B. Time taken for FNA and time for MFB

B. Description of Population to be Enrolled:

Inclusion criteria:

- Adult patients >18 years old
- Cysts > 20 mm in size deemed appropriate for FNA by the endoscopist, based on clinical presentation, radiologic imaging features, associated solid mass or nodules, and patient anxiety about the diagnosis

Exclusion criteria:

- Age <18 years
- Inability to provide informed consent
- Thrombocytopenia (Platelets < 50,000) or coagulopathy (INR > 1.8)

- Pregnancy
- Post-surgical anatomy where the cyst is not accessible for FNA
- EUS findings suggesting that cyst FNA would be unsafe (e.g. intervening blood vessels)
- EUS appearance suggesting FNA is not indicated (e.g. cyst smaller than prior radiologic imaging, cyst not seen, EUS suggestive of serous cystadenoma)

C. Study Design and Research Methods

Patients will be provided the necessary information regarding the study and consent will be obtained either in person and/or electronically through medical records depending on specific site IRB approval guidelines. Patients will be randomized to intervention 1) EUS-FNA plus MFB or 2) EUS-FNA alone

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Patients will be enrolled in this study when evaluated in GI clinics, hospital wards, and endoscopy suites. Consent for the study will be obtained either in person, by the interventional endoscopist who will be performing the procedure or by the research assistant/ study coordinator or electronically through medical records depending on specific site IRB approval guidelines. All UCH interventional endoscopists who perform EUS will participate in the study. All participating investigators are experienced interventional endoscopists proficient in EUS. Initial evaluation of patients will include collection of data on demographics, history, physical examination and pertinent radiologic, laboratory, and endoscopic data, and prior management/therapies. Details of previous endoscopic and surgical evaluation along with histopathology data will be documented, as needed for clinical care.

After obtaining informed consent, subjects will undergo EUS per clinical protocol. All procedure-related clinical decisions and interventions will be dictated by the performing physician as he or she sees fit. Once the pancreatic cystic lesion is seen and assessed by EUS, randomization will be performed after determination by the endoscopist and research coordinator that the patient meets inclusion criteria and does not have exclusion criteria.

A pancreatic cyst with high risk stigmata (presence of dilated main pancreatic duct > 10 mm, mural nodule or associated solid mass) would be referred for surgical resection based on patient's clinical status, irrespective of cyst fluid analysis/cyto/pathology. Cysts without high risk stigmata are followed with radiologic surveillance imaging in 1-3 years

Procedure description:
Prophylactic antibiotics (Ampicillin-Sulbactam 3 g or Ciprofloxacin 500 mg intravenous) will be administered to all patients prior to needle puncture of the cyst, and for 3-5 days post procedure (Amoxicillin-Clavulanate or Ciprofloxacin orally) as per routine standard of care. A detailed endosonographic examination of the cyst will be performed using a curvilinear array echoendoscope (Olympus America, Center Valley, PA) as per routine clinical care. Careful evaluation will be performed for cyst location, size, presence of mural nodule, associated solid mass, and communication with the main pancreatic duct. Patients will then be randomized by a computer-generated algorithm to EUS-FNA plus MFB (group 1) or EUS-FNA alone (group 2).). Histological diagnosis is considered a gold standard and a positive MFB diagnosis is considered a true diagnosis. Please note that currently we have been performing EUS-FNA and MFB for pancreatic cysts as part of routine clinical care and this is NOT considered experimental. This procedure does not have negative implications for insurance coverage, patient charges, and hence will not affect our budget. We will perform the procedure for patient care irrespective of the study.

(1) EUS-MFB plus FNA group:
The cyst will be punctured using a 19-G EUS-FNA needle with a stylet. A transgastric approach will be used for PCLs located in body/tail region, and a transduodenal approach for PCLs in the head/neck region, or as determined by the endoscopist. The stylet will be removed and the wall of the cyst biopsied using the micro forceps passed through the 19 G needle under direct EUS visualization. A minimum of 4 cyst wall biopsies will be obtained to procure at least 4 visible tissue fragments. Cyst fluid will be aspirated and sent for CEA and cytology.

(2) EUS-FNA alone group:
The cyst will be punctured using an EUS-FNA needle with a stylet. A transgastric approach will be used for PCLs located in body/tail region, and a transduodenal approach for PCLs in the head/neck region, or as determined by the endoscopist. The stylet will be removed, and cyst fluid will be aspirated and sent for CEA, and cytology.

UCH cytopathologists and pathologists experienced in pancreatic cytology and pathology will evaluate all cytology and micro forceps biopsy specimens per standard clinical care. Clinical follow-up will be obtained as per routine clinical care.

Use of fine needle aspiration as well as micro forceps biopsy for pancreatic cysts is safe with low rates of adverse events. Therefore, the risk to the patient is minimal. Additionally, accurate diagnosis is critical, as pancreatic cysts range from benign to malignant. Thus, comparing two interventions to evaluate cystic lesions to determine the optimal modality for diagnosis is justified.

Data collection will be carried out by the study team under the direction of the principal investigator. A REDCap database will be used to store clinical data information for subjects who consent to participate. This will serve as a clinical data repository for subject data. Clinical data will be extracted by the investigators or PRA from medical chart review. Access to the REDCap database will be granted by the study team, sometimes in limited fashion (e.g. no access to identifiers), to research staff and to co-investigators when needed. The final responsibility for the completeness and accuracy of all study data will belong to the principal investigator.

The study team will reach out to the subject at two different points post procedure. 1) Up to 72 hours post-procedure to collect data on the first 24 hours and 2) At day 30 to collect data AE data from the previous 30 days. Adverse events will be recorded per published ASGE criteria (10). The PI will continuously review local AEs and a safety officer not directly participating in the endoscopic procedures will review adverse events every 6 months. The PI will review serious device related events within 48 hours of the lead site becoming aware of the event. No serious adverse events were seen in our initial study (7) and in the study by Basar et al (9). Potential adverse events after these procedures include bleeding, perforation, infection, pancreatitis, and sedation-related complications, to name a few. Based on prior experience (7, 9) we do not expect a high rate of adverse events. Hence, we do not anticipate the need for an interim analysis.

E. Potential Scientific Problems: N/A

F. Data Analysis Plan:

The primary outcome of the study is to compare the diagnostic yield of the efficacy and safety of EUS-FNA plus EUS-MFB, with EUS-FNA alone for evaluation of PCLs.

Descriptive statistics will be used to summarize the data. Continuous variables will be expressed as mean $\pm$ standard deviation and categorical variables will be mentioned in percentages. T-test for continuous variables and Fisher's exact test or chi-square test for categorical variables will be used as appropriate.

Sample size calculation was performed as follows: to power the study to detect a 20% difference in efficacy would require enrollment of 76 patients in each group. However, after accounting for screen failures, technical failures in performing FNA/MFB based on actual findings during EUS where FNA/MFB would not be possible, patient drop out and loss to follow-up, we estimate 25% more patients would need to be included i.e.102 patients would be needed in each group to get 76 patients in each arm who would actually get FNA/MFB. Statistical

analysis will be independently performed by intention to treat analysis by the University of Colorado Center for Innovative Design and Analysis, not by the PI

G. Summarize Knowledge to be Gained:

Most of the current data on evaluation of PCLs emphasizes the limitations in cyst sampling techniques and technologies. We are still far from being able to accurately diagnose many of these lesions. We have recently published results showing the safety and efficacy of the microforceps biopsy in a retrospective cohort, and much of the other data on MFB comes from case reports and small retrospective case series. There has never been a head to head trial comparing these two interventions. Additionally, there is no “standard” intervention and approach to PCLs is largely influenced by practice patterns among physicians as well as equipment availability. This is a prospective randomized controlled study that will help answer the question on which approach lends itself to more technical success and higher diagnostic yield while monitoring safety profile.

H. References:

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