Cover letter

Study title:
EUS-guided FNA with rapid on-site evaluation (ROSE) of cytopathology vs. EUS-guided FNB alone in the diagnosis of pancreatic solid lesions: a randomized controlled trial

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EUS-guided FNA with rapid on-site evaluation (ROSE) of cytopathology vs. EUS-guided FNB alone in the diagnosis of pancreatic solid lesions: a randomized controlled trial

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Background:

EUS-guided tissue acquisition of pancreatic masses is the main modality for the diagnosis of pancreatic solid tumors including adenocarcinoma and neuroendocrine tumor. Traditionally, this is done through sampling with fine needle aspiration (FNA); however, this approach has led to variable diagnostic yield with approximately 20% of the samples being non-diagnostic[1-3] needing repeat procedures. Several tertiary centers worldwide have adopted rapid on-site evaluation (ROSE) of cytopathology, where a cytopathologist is at the bedside of the procedure and looking at each samples in real-time to give feedback to the endoscopists in terms of adequacy and preliminary diagnosis of their EUS-guided FNA. ROSE has been shown to increase the diagnostic yield by 10 to 15%[1 4]. Although currently unavailable at most Canadian sites, hospitals have been contemplating the implementation of ROSE in hopes of improving care for patients with pancreatic cancer and to prevent the need for repeat procedures and its associated costs and potential adverse events. Recently, however, novel core biopsy needles have been developed for fine needle biopsy (FNB) and histological assessment[5]. These needles allow for the acquisition of core samples with intact tissue architecture enabling immunohistochemical staining thereby enhancing the diagnostic yield. Although some studies suggest that FNB alone may be just as effective as FNA with ROSE, there are no comparative outcomes trials. As such, the goal of our study is to compare EUS-FNB with core needle sampling alone vs. EUS-FNA with ROSE in pancreatic solid lesions. If shown to be equivalent, FNB could potentially obviate the need for ROSE and be implemented in a more readily and affordable fashion across Canada.

Objectives:

Aim: To compare the diagnostic accuracy of EUS-FNB alone vs. EUS-FNA with ROSE in patients with solid pancreatic masses suspected to be of malignant origin.

Hypothesis: EUS-FNB is non-inferior to EUS-FNA with ROSE in the diagnostic accuracy for solid pancreatic masses while being associated with fewer needle passes and shorter procedure time.

Primary outcomes

• Diagnostic accuracy defined as (true positive + true negative)/all samples
• Final diagnosis will be based on the following criteria
A) Final diagnosis of malignancy (one of the following):

- histological evidence of malignancy on the corresponding subsequent surgical specimen
- presence of an unresectable lesion during subsequent surgery
- malignant cytology/pathology on EUS-sampling followed by documented loco-regional progression/development of metastases on follow-up axial imaging.

B) Final diagnosis of benign pancreatic mass (one of the following):

- surgical pathology or exploration showing the absence of malignancy

- follow-up imaging at > 6 months reporting stability of the pancreatic lesion
- cytological or histopathological diagnosis of benign disease with an appropriate clinical course of disease for minimum of 6 months

Secondary Outcomes

- Diagnostic characteristics: sensitivity, specificity, positive and negative predictive value
- Specimen adequacy: defined as the proportion of samples in which a final histopathological diagnosis could be made
- Median number of needle passes, procedural time
- Rate of procedure-related adverse events with severity graded as per the ASGE lexicon[6]
- Cost-effectiveness

Methods:

EUS procedure :
Procedures are performed with a linear echoendoscope under conscious sedation. EUS-FNB is performed with a 22 gauge Core-needle. Tissue sampling technique is standardized between the endoscopists. Two passes are performed using the core needle. The biopsied samples are then expressed using a stylet into a jar filled with 10% formalin. A third pass is allowed if, on macroscopic inspection of the acquired sample, the specimen is deemed insufficient by the endoscopist. EUS-FNA with ROSE is performed with a 22 gauge FNA needle. The sampled specimen is expressed into a glass slide with a stylet; then using another glass slide the sample is spread out to make smears on two slides. Each pair of slides is then numbered according to their respective needle passes. One slide is air dried and stained with modified Giemsa stain for ROSE, while the other slide is fixed in 95% ethanol and later coated with with Pananicolaou stain.

This is a multi-center, randomized, single blinded, non-inferiority, trial comparing EUS-FNB alone to EUS-FNA with ROSE in the diagnosis of solid pancreatic masses. Following consent, patients are randomized, at the time of the procedure, to undergo either EUS-FNB alone or EUS-FNA with ROSE. The randomization sequence will be generated by a computerized randomization scheme using a block size of 10 stratified according to the endoscopist.

Inclusion Criteria:

1. Age > 18 years
2. Patients referred for EUS evaluation of a definite solid pancreatic mass noted on CT/MRI/EUS, in which malignancy is suspected with no previous histological diagnosis

Exclusion Criteria: 1.

1. Age < 18 years, pregnant patients
2. Uncorrectable coagulopathy PT>50% of control, PTT>50 sec, or INR>1.5 and/or uncorrectable thrombocytopenia platelet count<50, 000109/L.

Feasibility: The primary analysis is a noninferiority comparison of EUS-FNB vs. EUS-FNA with ROSE in terms of diagnostic accuracy, which, according to the most recent literature, is approximately 90% for both modalities. The margin of noninferiority is set at 10% in accordance with the USFDA recommendations. To achieve a statistical power of 80% with a two-sided type I error of 5%, a total of 224 patients (112 per group) is needed. Assuming a 5% dropout rate, a final sample size of 236 (118 per group) is estimated. The study is anticipated to take 2 years to complete.

Analysis: An intention-to-treat analysis will be carried out. The noninferiority hypothesis for the primary outcome will be assessed using the Z-test with a 95% two-sided confidence interval of the difference in the diagnostic accuracy and the margin of noninferiority. Interim analysis is planned after 50% of the cohort is recruited. If a > 20% difference in sensitivity is found between both methods then the study will be terminated early. Exploratory imaging and patient predictors of a diagnostic sampling is carried out using standard multivariable logistic regression analysis.

Cost-effectiveness:
A decision tree will be created for the two possible sampling approaches. Probability assumptions will be extracted from the RCT. Costs will be determined from the RAMQ. Third-party costs related to the procedure and downstream management costs will be determined based on the RCT resource utilization data. Deterministic and probabilistic sensitivity analyses will be undertaken.

Patient follow-up:
Patients will be contacted by telephone interview at 48-72 hours post procedure to ensure that no adverse events have occurred. All other follow-up will be standard of care and at the discretion of the treating physician.

Anticipated results:
We anticipate that the results will show that EUS-FNB alone will be non-inferior to EUS-FNA with ROSE in the diagnostic accuracy of solid pancreatic masses. We also expect that both modalities will have similar diagnostic characteristics such as sensitivity, specificity, and positive and negative predictive value. Finally, the use of EUS-FNB will likely be associated with fewer needle passes, shorter procedure time, and be more cost-effective.

If our data is consistent with the anticipated results then it would have a large impact on improving diagnostic yield of EUS tissue acquisition in pancreatic mass and potentially obviate the need for on-site cytopathology at a time where centers across Canada are contemplating the addition of this effective but expensive and resource intensive modality.

MULTICENTER GUIDELINES

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that REB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of REB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written
- Submitting data to the Coordinating Center.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

ANTICIPATED RISKS

We do not anticipate major risk or discomfort beyond that associated with the conventional procedure. Both EUS-FNA with ROSE and FNB alone are part of standard or care. The following are conventional risks associated with EUS-FNA or FNB.

1) Perforation: Only physicians specially trained in EUS will be performing these procedures. The exact risk is minimal (<1%).
2) Infection: It is not standard practice to give antibiotics to all patients prophylactically for either percutaneous liver biopsy or EUS-FNA of non-cystic lesions. Therefore, no subjects will receive antibiotics prophylactically for EUS sampling except those patients at risk for infective endocarditis according to American Heart Association guidelines.
3) Bleeding: The exact risk is minimal (1 in 5,000 chance). Doppler examination will be performed under EUS guidance prior to biopsy to ensure that the needle does not traverse a blood vessel. As a precautionary measure,

furthermore, all patients will have PTT, PT/INR, hemoglobin, and platelet count checked prior to the procedure. Those below acceptable standards will not be offered inclusion into the study. Frequent vital signs will be measured and recorded. If vital signs are abnormal and prolonged, a repeat CBC and possibly CT scan will be performed after procedure to ensure the absence of internal or external hemorrhage. These measures should ensure any clinically significant hemorrhage is detected and treated in a timely manner.
4) Pancreatitis (risk: 1%): Will be detected by the presence of pain with or without nausea and vomiting after pancreatic biopsy. If present, the patient will be hospitalized, kept NPO, and receive IV hydration.

a. Steps taken to minimize the risks.
Adherence to the standard of practice of EUS-guided tissue sampling at the McGill University Health Center as outlined above

b. Financial risks to the participants.
None.

ADVERSE EVENT REPORTING

Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a procedure done, whether or not considered causally related to the procedure. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during the procedure or any time after the procedure, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Coordinating Center

The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the REB promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by

the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)

Participating Sites

Participating sites are responsible for reporting adverse events to their REB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events must be reported to the Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within three (3) working days of the participating site Principal Investigator's learning of the event.

Adverse events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

All SAEs must be collected whether or not they are considered causally related to the investigational procedure. Investigators and other site personnel are responsible for reporting all casually related SAEs to their REB and the coordinating center.

1. Klapman JB, Logrono R, Dye CE, et al. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol 2003;**98**(6):1289-94.
2. Gress FG, Hawes RH, Savides TJ, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc 1997;**45**(3):243-50.
3. Chang KJ, Katz KD, Durbin TE, et al. Endoscopic ultrasound-guided fine-needle aspiration. Gastrointest Endosc 1994;**40**(6):694-9.
4. Kulesza P, Eltoum IA. Endoscopic ultrasound-guided fine-needle aspiration: sampling, pitfalls, and quality management. Clin Gastroenterol Hepatol 2007;**5**(11):1248-54.

5. Kandel P, Tranesh G, Nassar A, et al. EUS-guided fine needle biopsy sampling using a novel fork-tip needle: a case-control study. Gastrointest Endosc 2016;**84**(6):1034-39.
6. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;**71**(3):446-54.