DETAILED PROTOCOL

Title:

Prospective comparison of a novel 22-gauge core biopsy needle with reverse bevel design to a standard endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) needle for diagnosis of solid pancreatic mass lesions

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Location:

The University of Texas MD Anderson Cancer Center

1. Objectives

The ability to obtain an adequate specimen during endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) is dependent on a variety of factors. New needle technology has been developed which potentially improves diagnostic yield and reduces the number of needle passes required. The latest ultrasound needle, has a reverse bevel design with the potential to obtain a core specimen in a 22-gauge size needle that may provide a better cytologic specimen than the most commonly used straight hollow-core standard (22-gauge and 25-gauge) FNA needles. A histologic specimen may also be provided which is not otherwise possible to obtain using current FNA needles of this size.

Primary Aim:

- To compare the performance of a novel 22-gauge core biopsy needle with reverse bevel design to straight hollow-core standard EUS guided FNA needles for cytologic diagnosis of solid pancreatic lesions.

Secondary Aims:

- To evaluate the performance of a novel 22-gauge core biopsy needle with reverse bevel design to obtain an adequate specimen for histologic diagnosis
- To identify potential pancreatic lesions that are best suited for sampling with this needle

2. Background

Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) is an effective technique to diagnose a variety of different lesions within or adjacent to the gastrointestinal tract including the pancreas.[1-3] A cytologic specimen is provided with the most commonly used straight hollow-core 22-gauge or 25-gauge standard EUS guided FNA needle and an immediate diagnosis can be made in the majority of cases. The procedure is relatively safe and minimally invasive compared to

alternative methods.[4, 5] The ability to obtain adequate sampling with minimal number of passes and trauma to surrounding tissue is desirable.

The ability to obtain an adequate specimen has been shown to be dependent on a variety of factors i.e.: nature of lesion (i.e. pathology, tumor differentiation, presence of inflammation/necrosis, size, location), type and size of needle, number of passes taken, experience of endoscopist and cytopathologist, as well as the presence of immediate on-site cytologic evaluation, etc.[6-12]

Standard EUS guided FNA needles used in clinical practice today are straight hollow core needles with a forward bevel design. The most commonly used size is either a 22- or 25-gauge needle; both have comparable results and may for the most part be used interchangeably.[7, 9, 12] In our practice, the number of passes needed to obtain adequate cytologic sampling of solid pancreatic lesions in an estimated 90% of cases is approximately four with immediate on-site cytologic evaluation.

Some lesions are difficult to adequately sample by EUS guided FNA, particularly in the pancreas. Additional passes may be required before a diagnosis is made and in some instances (<5%) cytologic findings alone may be insufficient. Larger cytologic yield or tissue histology for additional tests may be needed. Dedicated large core 19-gauge EUS needles or Tru-cut biopsy needles are currently available which have ability to obtain a larger cytological or pathological specimen when needed. However these larger needles have limitations and the potential for increased risks of complications which restricts their use.[13-18] A major limitation of the larger 19-gauge needle devices is the technical difficulty of performing FNA with these less flexible needles when the tip of the endoscope is sharply deflected or in a tortuous position; this is a frequent problem for lesions located in the pancreatic head, the most common site of pancreatic adenocarcinoma. Smaller lesions (ie. less than

2cm) are also less suited to sampling with larger needles. Cytologic analysis will in most cases allow for immediate assessment to determine adequate sampling for diagnosis during EUS. Histologic tissue analysis does not lend itself to immediate assessment. However tissue specimens may allow for more detailed analysis versus cytologic specimens. On-site cytology for immediate assessment in not universally available and is resource intensive but may prevent patients from undergoing repeat procedures for nondiagnostic exams and unnecessary additional passes.

A new EUS needle is commercially available – EchoTip® Procore™ High Definition Ultrasound Biopsy Needle from Cook Medical. This needle is a single use, disposable needle available in 22-gauge size which was approved for use by the FDA on February 14, 2011. The novel reverse bevel design allows collection of a core sample which may be submitted for cytologic and histologic analysis unlike standard FNA needles which provide a cytologic specimen only. Procore™ acts by shearing material from the target lesion during retrograde movement of the needle. A core trap at the tip of the needle receives the tissue sample while the reverse bevel enables collection of the core sample. The tip of the needle has the same ultrasound visibility as current needles. The mechanism to use the needle is similar to current practice with only minor adjustments of technique which are standardized as per manufacturer recommendation. The needle may increase sampling yields and improve both accuracy and collection of core biopsies. The potential ability to take fewer needle passes may improve efficiency and safety of the procedure. The capacity to obtain a core specimen may provide tissue for additional histologic evaluation such as immunohistochemical and genetic biomarker studies.

3. Patient Eligibility

3.1 Inclusion Criteria:

3.1.1 Patient age 18 years and older.

3.1.2 All patients referred for EUS FNA of endoscopically accessible solid pancreatic lesions

3.2 Exclusion Criteria:

3.2.1 Unable to obtain informed consent.

3.2.2 Unable to tolerate the procedure.

3.2.3 Women with known pregnancy at time

3.2.4 Patient age less than 18 years of age

3.2.5 Bleeding diathesis

3.2.6 Cystic pancreatic lesions

3.2.7 Lesion not accessible by EUS guided FNA

4. Subject Enrollment:

4.2.1 All consecutive patients referred for EUS FNA of solid pancreatic lesions

Procedures for Obtaining Consent:

Written consent to participate in the study will be obtained by the principal investigator or co-investigators prior to the procedure. This consent will be in addition to the standard procedure consent for *esophagogastroduodenoscopy* with EUS FNA.

Source of Subjects and Recruitment Methods:

Subjects for this study will be recruited from those patients referred for diagnostic EUS FNA of solid pancreatic lesions by a physician responsible for their care (i.e. gastroenterologists, oncologists, general internists, and surgeons) to the principal investigator or co-investigator / collaborators as per standard practice.

5. Study Procedures

Data to be Collected, Study Visits and Parameters Measured.

Demographic data:

Demographic related data will be collected from the subject, medical records and the referring physician. This includes age, gender, co-morbid illnesses, type of cancer, tumor location, presence of metastases, method of diagnosis, therapy to date, laboratory results, relevant imaging studies and reports.

Procedural data:

Procedural related data will also be recorded from procedure report such as lesion location, lesion size, echogenic features of lesion, number of FNA passes performed, site of FNA (i.e. transduodenal or transgastric), type and sequence of needle used, use of stylet, use of suction, cytologic and histologic diagnosis.

Immediate outcomes:

Immediate outcomes to be assessed are adequacy of specimen obtained for cytologic and histologic diagnosis. Adequacy of the specimen will be determined by review of cellular/tissue material obtained by a cytologist/pathologist for each needle pass that is taken. See appendix E & F for representative analysis. Any procedure-related complications related to the FNA will be recorded.

Medications:

Subjects will not receive or be exposed to any additional medications as a result of participation in this study. Subjects will receive sedation for endoscopic procedures as this is standard practice and as would be administered regardless of participation in the study. Patient will have an intravenous line placed for administration of sedation prior to the procedure as is standard practice. Anesthesia will sedate and monitor all patients referred for EUS FNA procedures in accordance with our endoscopy unit practice. The duration of the procedure and length of sedation period is not expected to be any longer than would otherwise be required. The patient will sign a separate consent for sedation.

Devices (see device package inserts):

The 22-gauge core biopsy needle with reverse bevel design (EchoTip® Procore™) will be compared prospectively to the standard straight hollow-core 22-gauge or 25-gauge FNA needle already used in our clinical practice for the diagnosis of solid pancreatic lesions. The needles to be used in this study are FDA-approved, commercially available and currently in use at MDACC.

EUS FNA 22/25-gauge Needle	EUS FNA 22-gauge Needle
Straight Hollow-Core Needle	Reverse Bevel Design
Collect only Cells	Collect Cells and Tissue

Interventions:

Patients who are referred for EUS guided FNA and who consent to participate will have their examination performed using two different needles. As part of the study two passes will be performed with the standard 22-gauge or 25-gauge straight hollow core needle and two passes will be

performed using the 22-gauge EchoTip® Procore™ needle. All passes will be taken from a single lesion and from the same endoscopic location. All passes will be numbered. Both passes taken with the standard needle will be sent for immediate cytologic evaluation as is standard. One of the 22-gauge EchoTip® Procore™ passes will be sent for immediate cytologic evaluation and one pass will be sent for histology. Additional non-study passes will be obtained if necessary (after immediate cytologic evaluation of the three initial passes) using needle of endoscopist's choice. If adequate sampling is believed to have been obtained in fewer than 4 total passes as confirmed by immediate cytologic assessment then no additional passes need be performed at the discretion of the endoscopist and analysis will be performed with existing data. All other elements of the exam will be otherwise unchanged. The endoscopist performing the procedure will alternate the sequence of EUS needles used in any given patient. In addition we will alternate which Procore™ pass is sent for histology and cytology. The primary intervention will be which needle is used and in which sequence. The reason for alternating sequence is to eliminate any confounding variable associated with sequence such as increased bloody aspirate or possible variability in cytologic yield related to increased number of passes. The study does not involve an increased or excessive number of passes or other additional interventions beyond what would be current standard practice. This procedure will be explained to subjects at time of consent.

Cytopathologic Evaluation:

The specimens are to be assessed independently by members of the MDACC cytology/pathology department who will be blinded to the needle sequence and type of needle used. For the purposes of the study cytopathologic results will be recorded from the slides of each of the numbered individual passes taken. Reports for immediate assessment purposes will be based on the 3 passes sent to cytology and any additional passes required outside the study including the cellblock made from wash of all needle passes. The cytological specimen quality will be graded on cellularity and other features

comparable to the assessment in our earlier study by Lee et al. (10) (see Appendix E & F). The single Procore™ sample sent to histology will be processed like any other endoscopic biopsy specimen (immediate assessment not possible as with cytology due to processing requirements) and the final pathology report will be used for comparison purposes to the cytological specimen results.

Study Duration:

The expected duration of the study is approximately 2 years from the commencement of subject enrollment. Subject enrollment is expected to be up to one year. All subjects will be followed until surgery, death, or at least six months until last subject enrolled.

6. Biostatistical Analysis

Study design

The primary objective of the study is to assess if the 22-gauge EchoTip® Procore™ needle has a better diagnostic performance compared to standard 22-gauge and 25-gauge straight hollow core needles (both 22-gauge and 25-gauge needles are used interchangeably). The primary endpoint is whether or not the needle pass result provides diagnostic material (yes vs. no). For each patient, both needles will be used to sample the same lesion. Two needle passes will be performed with each needle type. The average number of needle passes needed to obtain a diagnostic specimen of solid lesions in the pancreas is four using the standard 22-gauge or 25-gauge straight hollow core needle in our practice (although the number of passes can be variable in any given lesion for a variety of reasons). All needle passes will be numbered and evaluated individually. For the two passes taken from the straight hollow-core standard-needle, the specimens are to be assessed by cytology for immediate review. For the two passes taken with the EchoTip® Procore™ needle, one pass will be submitted to cytology for immediate review and one pass for pathology (immediate review not

possible). Any additional passes will not be included in the study. The need for additional passes will be determined based on the three passes (two straight hollow-core standard FNA needle and one EchoTip® Procore™ needle) sent for immediate cytologic assessment during the procedure as is routine at our center. Immediate assessment is not possible for the one pass submitted for histologic analysis with the EchoTip® Procore™. Each needle pass submitted for review will be rated individually by the cytologist/pathologist (see appendix E & F for cytopathology rating sheet as applicable). A final analysis will be performed on the diagnostic results from each needle pass. For the purpose of the study, if the passes are adequate to be diagnostic, the result will be considered "yes". If the passes are inadequate, the result will be considered "no". Equal number of biopsies will be taken for each needle sequence.

Power and Sample Size:

The two standard straight hollow-core FNA passes are assumed to be diagnostic in 65% of patients. The two Procore™ needle passes are assumed to be diagnostic in 85% of patients. Assuming a discordant proportion of 30%, a sample size of 60 patients will be needed to achieve 80% at a 5% significance level.

For the comparison, McNemar's test will be used for the sample size justification. Our null and alternative hypotheses are:

H0: $P_a - P_b = 0$ vs. Ha: $P_a - P_b \neq 0$

Where P_a and P_b are the diagnostic proportions for the 22-gauge EchoTip® Procore™ needle and standard 22-gauge or 25-gauge straight hollow core needle respectively.

Table 1 displays in the scenario the sample sizes needed to achieve about 80% power with a two-sided significance level of 0.05 for different scenarios with different assumptions for proportion discordant.

Sample size	**Difference in positive** proportions	**Proportion Discordant**	**power**
60	0.2	0.3	0.8

In this study, we assume that the 22-gauge EchoTip® Procore™ needle will have a higher diagnostic yield (85%) than a standard straight hollow-core FNA needle after two passes (65%). A sample size of 60 patients will achieve about 80% power at a 5% significance level using a two-sided inequivalence test of correlated proportions when it is assumed that there is 20% difference regarding biopsy result (positive vs. negative) and the discordant proportion is 30%.

Statistical Analysis:

Data analysis will be performed using SAS as appropriate. Intent-to-treat data will be used for primary analysis. Demographic and disease characteristics of the patients at registration will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Biopsy result (diagnostic proportion) from each needle type will be presented with 95% confidence intervals. McNemar test will be used to compare diagnostic ability (yes vs. no) between the two pass information obtained from the standard straight hollow-core needle (22-gauge or 25-gauge) and the one pass information obtained from the 22-gauge EchoTip® Procore™ needle. In addition, McNemar test will be used to compare diagnostic ability (yes vs. no) between either of the two pass information obtained from the standard straight hollow-core needle (22-gauge or 25-gauge) and the one pass information obtained from the 22-gauge EchoTip® Procore™ needle.

Demographics and Other Characteristics:

Summary statistics for patients' demographics and other characteristics will be presented descriptively.

Primary Endpoint:

Comparison of a diagnostic cytopathology specimen provided from FNA of a solid pancreatic lesion using the two different needles as determined by a cytologists who will be blinded to needle type and sequence.

Secondary Endpoint:

Assessment of adequate specimen for histologic diagnosis with Procore™ needle of a solid pancreatic lesion. Comparison of cytological diagnosis from both needle types with histological assessment of Procore™ needle specimen.

7. Risks and Discomforts

There is not expected to be any increased risk with use of either needle above and beyond what is standard for the procedure. Both needles used in the study are already FDA approved, commercially available and used in clinical practice, including here at MD Anderson. Both needles are similar in size. There is no increased number of passes performed as part of this study. In addition it would not be possible to determine any specific procedure related complication to use of one needle verses the other in the setting of this study. We will keep track of the overall frequency of adverse events that are standard to the procedure.

There will not be any additional laboratory studies, radiologic studies, interventions or exposure to medications or radiation. There will be no additional cost to the patient for use of a second needle. Specimens will be sent for cytological and histological evaluation as is standard.

There is an inherent risk of accidental disclosure of confidential information when gathering research data from a protected source, such as medical records. To minimize the risk to subjects, access to data will be restricted to study personnel only and all study personnel agree to and have signed the HSD Confidentiality Agreement. All data will be coded with a unique study code and the master list linking the subjects to the study code will be kept in a separate, secured location. The master list will be kept long enough to complete data analysis, at which time the link will be destroyed. Creation of this link is necessary in the event re-evaluation or clarification of data is required. The master list will be electronically stored on secure University of Texas servers with restricted and traceable user authorizations, accessible only to study personnel and further restricted via password protection.

8. Potential Benefits

Patients enrolled in this study will receive the standard of care. There will be no direct individual benefit.

9. Monitoring and Quality Assurance

Independent Monitoring of Source Data:

The specimens are to be assessed independently by members of MDACC cytology/pathology department who will be blinded to the needle sequence and type of needle used. The results data will be monitored for completeness periodically by the principal investigator. The protocol will be monitored by the MDACC Data and Safety Monitoring Board (DSMB).

Adverse Event Reporting:

We will follow the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0/U.S., Department of Health and Human Services. Adverse events will be reported to the Human Research Committee as follows. Serious adverse events including death, life-threatening experience, an event requiring hospitalization, an event requiring an intervention will be reported within 24 hours, followed by a full written report within 1 week. Mild to moderate adverse events that are unexpected and may be related to the study will be reported in writing within 2 weeks to the Human Research Committee. Mild to moderate adverse events that are unexpected but not related to the study will be reported to the Human Research Committee in the periodic review. Expected adverse events that are not serious will be reported to the Human Research Committee in the periodic review. A written periodic review will be submitted to the Human Research Committee for continuing review annually.

Instructions are given to each patient post procedure to call if having any problem (i.e. pain, bleeding, fever, or other problems) prior to discharge from endoscopy unit per standard protocol. All adverse events (including but not limited to aspiration, adverse reaction sedation, bleeding, perforation, pancreatitis, infection, missed lesion) will be reviewed by the principal investigator.

External Support:

No external funding is forthcoming.

10. References:

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Appendix E

Cytopathology Rating

Criteria	Scale	Rating
Clot	0	No Significant Obscuring Blood
	1+	= < 25% of tumor obscured by blood/blood clot
	2+	= < 25% to < 75% of tumor obscured by blood/blood clot
	3+	= < 75% or more of tumor obscured by blood/blood clot
Cellularity	1+	Minimal
	2+	Mild
	3+	Moderate
	4+	Abundant
Diagnostic	Yes	
	No	

Appendix F.

Histology Rating

Criteria	Scale	Rating
Diagnostic	Yes	
	No	