A randomized noninferiority trial comparing the diagnostic yield of the 25G ProCore needle to the standard 25G needle in suspicious pancreatic lesions

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ABSTRACT

Background and Objectives: The aim of the study was to perform the first randomized trial comparing the diagnostic yield, bloodiness, and cellularity of the 25G standard needle (25S) and the 25G ProCore™ needle (25P). **Materials and Methods:** All patients referred to the tertiary care referral center for EUS guided fine-needle aspiration (EUS-FNA) of suspicious solid pancreatic lesions were eligible. EUS-FNA was performed in each lesion with both 25S and 25P needles (the choice of the first needle was randomized), using a multipass sampling pattern, without stylet or suction. Rapid on-site evaluation was used when possible. Pap-stained slides were read by a single experienced cytopathologist, blinded to the needle type. **Results:** One hundred and forty-three patients were recruited. Samples were positive for cancer in 122/143 (85.3%) with the 25S needle *versus* 126/143 (88.1%) with the 25P needle, negative in 17/143 (11.9%) with the 25S needle *versus* 13/143 (9.1%) with the 25P needle, and suspicious in 4/143 (2.8%) with each needle. There was no difference in any outcome based on the type of the first needle. No carryover effect was detected ($P = 0.214$; NS). Cumulative logistic regression analyses showed no associations between the type of needle and diagnostic yield for cancer, cellularity, or bloodiness. The difference in the yield for cancer was 2.9% (−4.2; 10.1%); with the confidence interval upper within the predetermined noninferiority margin of 15%. **Conclusion:** The 25S needle is noninferior to the 25P needle for diagnosing cancer in suspicious pancreatic lesions.

Key words: 25G ProCore™, EUS-guided fine needle aspiration, mass, pancreas

INTRODUCTION

EUS provides excellent imaging resolution of the gastrointestinal wall and the surrounding organs.

EUS-FNA allows the acquisition of material for cytological diagnosis of different lesions.[1,2] It provides

Access this article online

Quick Response Code:

Website:
www.eusjournal.com

DOI:
10.4103/eus.eus_69_20

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adequate cytological specimens for interpretation in 80%–95% of the patients; in these cases, sensitivity and specificity are typically of 90% and 100%, respectively.[3-5] However, one drawback is that cytological specimens may be difficult to interpret for inexperienced pathologists. Furthermore, while cellblock processing of cytological aspirates allows special staining for certain tumor markers, it does not provide information on tissue architecture. Moreover, when cytology is negative for cancer, one cannot conclude whether it is a true negative or a false negative since it cannot provide sufficient information to diagnose benign conditions such as chronic pancreatitis.

Therefore, there has been ongoing interest in developing EUS sampling needles that can provide tissue core biopsies that permit true histological evaluation. By slightly modifying the traditional EUS-FNA needle, the EchoTip ProCore™ (Cook Medical, Salem, NC, USA) was developed in the hope of obtaining core samples. It has a small notch (a reverse bevel) near its tip that would theoretically provide core samples. However, studies to date with the 22G ProCore have shown no significant ability to obtain core samples better than standard 22G needle[6-8] although it may reduce the number of passes needed to obtain a cytological diagnosis.[8,10] Therefore, the ProCore needle may not be a core needle but a more effective cytology needle.

One noncomparative study showed that the 25G ProCore needle is a good cytology needle (single-pass sensitivity for cancer 92%) but a poor core needle that provided cores in only 32% of cases.[11-13] Kamata *et al.* performed the first randomized trial comparing the 25G ProCore needle to the standard 25G needle.[14] They showed improved cellularity with the 25G ProCore design.

This is the first randomized trial comparing the yield of the 25G Procore to the standard 25G needle, "using and aggressive, multi-pass sampling technique, with no stylet and no suction". We hypothesized that this aggressive sampling technique would overcome any previously reported benefits reported regarding the reduced number of passes required to obtain a diagnosis or sample cellularity.

MATERIALS AND METHODS

Design
This noninferiority crossover controlled trial comparing the 25G ProCore needle with the standard 25G needle

for EUS-FNA was undertaken at the Department of Gastroenterology of Centre Hospitalier de l'Université de Montréal (CHUM) in Montreal, Canada. Patients ≥18 years old presenting with suspicious solid pancreas lesions in whom EUS-FNA was considered clinically indicated and safe and who signed informed consent were recruited from June 2014 to June 2018. Exclusion criteria were age <18 years old, patients with suspected diagnosis of lymphoma, gastrointestinal stromal tumor, or sarcoidosis; patients with significant coagulopathy (INR >1.5, platelets <50,000/mm^3, ongoing use of anticoagulants, and use of clopidogrel within 7 days of EUS); patients with cystic lesions; and inability or refusal to sign the informed consent. This study was approved by our institutional review board (Clinical Trials Registration Number: NCT02048124), and all patients provided informed consent.

Outcomes
The primary outcome was the diagnostic yield for cancer, defined as the number of participants with a positive diagnosis for pancreatic cancer based on the final pathological evaluation of EUS-FNA samples. Secondary outcomes were bloodiness, cellularity, and the incidence and severity of immediate complications.

EUS–FNA technique
All EUS examinations were performed under conscious sedation (midazolam, fentanyl), by one of two experienced endosonographers (>10,000 EUS procedures each), according to the standard procedures at the CHUM, using the Pentax curvilinear array echoendoscope (Pentax America, Melville, NY, USA). During the procedure, if a suspicious pancreatic lesion was identified, and all inclusion criteria were met, the patient was enrolled and a randomization envelope was opened.

EUS-FNA was obtained with both the standard 25G needle and the 25G ProCore needles in each lesion. The randomization settled the order in which the needles were used (the standard 25G needle then 25G ProCore *vs*. 25G ProCore then the standard 25G needle). EUS-FNA passes were performed without stylet and with no suction. One "needle pass" was defined as five strokes in four different areas of the lesion (20 strokes total). The needle was fully withdrawn and reinserted to sample a different part of the target. The material was expelled onto slides using an air-filled syringe for cytological analysis. Ease of

puncture was scored qualitatively as poor (1), good (2), or excellent (3). Immediate complications were assessed and recorded by nurses and/or physicians during the procedure as well as after the procedure in the recovery room for at least 60 min before discharge.

Cytological analyses

Samples from all needle passes were stained using a standard Papanicolaou stain and analyzed by an experienced cytopathologist who was blinded to the needle type. Specimens were assessed for cellularity (score 1 "poor;" score 2 "good;" and score 3 "excellent"),[12] bloodiness (score 1 "minimal;" score 2 "moderate;" and score 3 "significant"), and the presence or absence of malignancy ("positive"/"negative"/"suspicious"/inconclusive).

Data collection

Clinical data were collected prospectively and saved in a secure database regarding cellularity, bloodiness, cytological diagnosis, final diagnosis, and immediate complications. Moreover, in addition to patient demographics, the following variables were collected: lesion size and technical and procedure variables (number of needle passes, needle visibility, ease of fanning, and actuation).

Sample size calculations

The sample size was calculated based on prespecified noninferiority margins, considering the crossover design. We were assuming the diagnostic yield for cancer to be 85%–95% for the 25G ProCore needle with a noninferiority margin of 15%. A sample size of 112 patients was needed for $\alpha = 0.05$ and $\beta = 0.2$.

Statistical analysis

Descriptive analysis was carried out using mean ± standard deviation for continuous variables and using proportions and 95% confidence intervals (CIs) for categorical variables. For analysis of the crossover effect, a 95% CI was calculated with a method for paired data (McNemar test). Generalized linear mixed models (GLMMs) were used, incorporating repeated designs with discrete outcomes. The logit link function was used, as the outcome (diagnostic yield, cellularity, and bloodiness) was ordinal. These regression models are also known as ordered logistic regression with random effects or as cumulative logistic regression. At the end of this noninferiority randomized controlled trial, a 95% CI for the difference of proportion of diagnosis yield between the two needles was calculated with a method for paired

data (McNemar test). For this test, the suspicious group was considered as negative. The upper bound of this CI was compared to the prespecified noninferiority margin of 15%. All analyses were performed using the Statistical Package for the Social Sciences (SPSS v15.0) statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

In this study, 143 patients with suspicious pancreatic lesions were recruited. EUS-FNA was performed in each lesion with both needles. Table 1 summarizes patient and lesion characteristics. The characteristics (sex and age) of our study population is similar to those of the population with pancreatic cancer because our hospital is a tertiary reference center for EUS, receiving patients from many other regional hospitals.

Table 2 summarizes the results regarding primary and secondary outcomes. There was no statistically significant difference in any outcome, and the results were not influenced by the order of needle use.

A carryover effect is defined as an effect of secondary intervention that can be influenced by an effect of the first intervention. No carryover effect was detected ($P = 0.214$; NS) [Table 3]. Cumulative regression analyses showed no associations between the type of needle and the cancer diagnosis yield (odds ratio [OR]: 1.61; 95% CI: 0.66; 3.90), cellularity (OR: 1.29; 95% CI: 0.79; 1.59), or bloodiness (OR: 1.68; 95% CI: 0.84; 3.37).

The mean and median number of passes required to achieve a diagnosis was for the standard 25G needle *vs* 25G Procore 2.1 *vs* 1.9 (p:0.9; NS) and 2.4 *vs* 2.6 (p:0.6; NS), respectively.

The difference in proportion was 2.9%, 95% CI (−4.2; 10.1%) where the upper bound of the CI was less than the prespecified noninferiority margin of 15% [Figure 1].

Table 1. Patient and lesion characteristics

	n (%)
Sex (male)	81 (56)
Age (years), mean±SD	68±2.1
Lesion size (mm), mean±SD	15.2±6.2
Location of pancreas lesion	
Head	74 (51.7)
Nonhead	68 (47.5)

SD: Standard deviation

Table 2. Comparison of outcomes

	25S	25P	OR (95% CI)	P
25P first				
67	143	143		
25S first				
76				
Diagnostic yield				
Positive	122	126	1.61 (0.6-3.9)	0.8 (NS)
Suspicious	4	4		
Negative	17	13		
Cellularity				
Poor	35	24	1.29 (0.8-1.6)	0.2 (NS)
Good	56	78		
Excellent	50	39		
Bloodiness				
Minimal	41	36	1.68 (0.8-3.4)	0.7 (NS)
Moderate	88	89		
High	9	12		
Fanning				
Good	117	117		
Moderate	12	14		
Poor	13	8		
Actuation				
Good	123	122		
Moderate	18	15		
Poor	1	2		
Visibility				
Good	134	133		
Moderate	5	4		
Number of pass				
Mean	1.7	1.9		0.9 (NS)
Median	1.8	1.6		

25P: 25G Procore Needle; 25S: Standard 25G Needle; CI: Confidence interval; NS: Not significant; OR: Odds ratio

Table 3. Test for crossover effect

	Concordance	Discordance	OR (95% CI)	P
25S-25P	71	5	0.217 (0.004-2)	0.2
25P-25S	66	1		

25P: 25G Procore Needle; 25S: Standard 25G Needle; CI: Confidence interval; OR: Odds ratio

No complications were noted.

DISCUSSION

The utility of EUS-FNA for cancer diagnosis is increasingly recognized.[7-10] Potential alternatives such as transabdominal ultrasound, computed tomography, and magnetic resonance imaging are often limited by the suboptimal yield of aspiration or interposition of intervening organs. EUS-FNA is safe with no significant immediate and late complications, and it presents an excellent yield for the diagnosis of pancreatic cancer.[8-12] Sensitivity and specificity are typically of 90% and 100%, respectively.[3-5] By slightly modifying
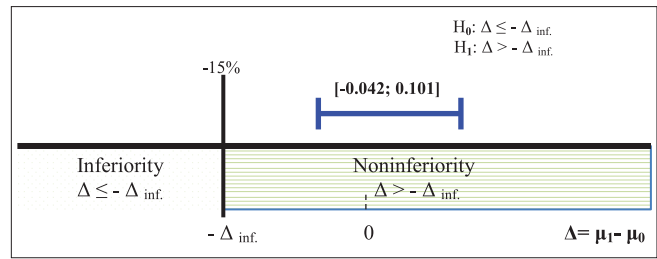

Figure 1. 95% Confidence interval of the difference between diagnosis yield of two needles ($\Delta = \mu_1 - \mu_0$) and the noninferiority margin (Δ_{inf})

the traditional EUS-FNA needle, a new needle, the EchoTip ProCore® (Cook Medical, Salem, NC, USA), was developed in the hope of obtaining core samples and increasing diagnostic yield.

This is the first randomized trial comparing the yield of the 25G Procore to the standard 25G needle, "using and aggressive, multi-pass sampling technique, with no stylet and no suction". We hypothesized that this aggressive sampling technique would overcome any previously reported benefits reported regarding the reduced number of passes required to obtain a diagnosis or sample cellularity.

The study design is also somewhat unusual since we used a noninferiority design to ensure an adequate sample size. We hypothesized that, when combined with our aggressive sampling technique, the ProCore design would offer no significant advantage for acquiring specimens for cytology. The ProCore model is generally more expensive than that standard model. Therefore, as it shows no clear clinical benefit, its greater cost is unjustified.

Regression analyses showed no associations between diagnosis yield of cancer and the type of needle, nor for cellularity or bloodiness. Rapid on-site evaluation (ROSE) was done in almost all cases. Our study supported the utility of the ROSE by limiting the number of passes and decreasing the number of inadequate samples.[3,4,15,16]

We could show no statistically significant difference for any outcome. We see no reason to suspect any systemic bias that could influence our results, and the sequence of needle use had no effect.

We conclude that, when combined with an aggressive approach, no stylet, and no suction sampling technique, the standard 25G needle is noninferior compared to the 25G ProCore needle for the diagnosis of cancer in suspicious pancreatic lesions in terms of all outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Crowe DR, Eloubeidi MA, Chhieng DC, *et al*. Fine-needle aspiration biopsy of hepatic lesions: Computerized tomographic-guided versus endoscopic ultrasound-guided FNA. *Cancer* 2006;108:180-5.
2. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. *Gastrointest Endosc* 1999;50:357-61.
3. Eloubeidi MA, Chen VK, Eltoum IA, *et al*. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: Diagnostic accuracy and acute and 30-day complications. *Am J Gastroenterol* 2003;98:2663-8.
4. Savides TJ, Donohue M, Hunt G, *et al*. EUS-guided FNA diagnostic yield of malignancy in solid pancreatic masses: A benchmark for quality performance measurement. *Gastrointest Endosc* 2007;66:277-82.
5. Williams DB, Sahai AV, Aabakken L, *et al*. Endoscopic ultrasound guided fine needle aspiration biopsy: A large single centre experience. *Gut* 1999;44:720-6.
6. Vanbiervliet G, Napoléon B, Saint Paul MC, *et al*. Core needle versus standard needle for endoscopic ultrasound-guided biopsy of solid pancreatic masses: A randomized crossover study. *Endoscopy* 2014;46:1063-70.
7. Wang KX, Ben QW, Jin ZD, *et al*. Assessment of morbidity and mortality associated with EUS-guided FNA: A systematic review. *Gastrointest Endosc* 2011;73:283-90.
8. Gimeno-García AZ, Elwassief A, Paquin SC, *et al*. Randomized controlled trial comparing stylet-free endoscopic ultrasound-guided fine-needle aspiration with 22-G and 25-G needles. *Dig Endosc* 2014;26:467-73.
9. Lee YN, Moon JH, Kim HK, *et al*. Core biopsy needle versus standard aspiration needle for endoscopic ultrasound-guided sampling of solid pancreatic masses: A randomized parallel-group study. *Endoscopy* 2014;46:1056-62.
10. Yusuf TE, Ho S, Pavey DA, *et al*. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: A multicenter experience. *Endoscopy* 2009;41:445-8.
11. Iwashita T, Nakal Y, Samarasena JB, *et al*. High single-pass diagnostic yield of a new 25-gauge core biopsy needle for EUS-guided FNA biopsy in solid pancreatic lesions. *Gastrointest Endosc* 2013;77:909-15.
12. Siddiqui UD, Rossi F, Rosenthal LS, *et al*. EUS-guided FNA of solid pancreatic masses: A prospective, randomized trial comparing 22-gauge and 25-gauge needles. Gastrointest Endosc 2009;70:1093-7.
13. Conway J, Kundu S, Mishra G, *et al*. Is there a difference in diagnostic yield between 22g and 25g needles in endoscopic ultrasound fine needle aspiration (EUS-FNA) of solid lesions? Gastrointest Endosc 2009;69:S248.
14. Kamata K, Kitano M, Yasukawa S, *et al*. Histologic diagnosis of pancreatic masses using 25-gauge endoscopic ultrasound needles with and without a core trap: A multicenter randomized trial. Endoscopy 2016;48:632-8.
15. Jenssen C, Dietrich CF. Endoscopic ultrasound-guided fine-needle aspiration biopsy and trucut biopsy in gastroenterology An overview. *Best Pract Res Clin Gastroenterol* 2009;23:743-59.
16. Paquin SC, Gariépy G, Lepanto L, *et al*. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. *Gastrointest Endosc* 2005;61:610-1.