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ORIGINAL ARTICLE

Suction versus slow-pull for endoscopic ultrasound-guided fine-needle aspiration of pancreatic tumors: a prospective randomized trial

Spencer Cheng[1], Vitor O. Brunaldi[1], Mauricio K. Minata[1], Danielle A. Chacon[2], Eduardo B. da Silveira[3], Diogo TH. de Moura[1], Marcos EL. dos Santos[1], Sergio E. Matuguma[1], Dalton M. Chaves[1], Raony F. França[4], Alfredo L. Jacomo[5] & Everson LA. Artifon[5]

[1]Gastrointestinal Endoscopy Unit, Gastroenterology Department, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, [2]Pathology Unit, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Insite Digestive Health, San Jose, CA, USA, [4]University of São Paulo Medical School, and [5]General Surgery Department, University of São Paulo Medical School, São Paulo, SP, Brazil

Abstract

Background: Suction (S) is commonly used to improve cell acquisition during endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Slow-pull (SP) sampling is another technique that might procure good quality specimens with less bloodiness. We aimed to determine if SP improves the diagnostic yield of EUS-FNA of pancreatic masses.

Methods: Patients with pancreatic solid masses were randomized to four needle passes with both techniques in an alternate fashion. Sensitivity, specificity, positive, and negative predictive values were calculated. Cellularity and bloodiness of cytological samples were assessed and compared according to the technique.

Results: Sensitivity, specificity, and accuracy of suction *vs.* SP were 95.2% *vs.* 92.3%; 100% *vs.* 100; 95.7% *vs.* 93%, respectively. As to the association of methods, they were 95.6, 100 and 96%, respectively. Positive predictive values for S and SP were 100%. There was no difference in diagnostic yield between S and SP (p = 0.344). Cellularity of samples obtained with SP and Suction were equivalent in both smear evaluation (p = 0.119) and cell-block (0.980). Bloodiness of SP and suction techniques were similar as well.

Conclusions: S and SP techniques provide equivalent sensitivity, specificity, and accuracy. Association of methods seems to improve diagnostic yield. Suction does not increase the bloodiness of samples compared to slow-pull.

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Correspondence

Vitor Ottoboni Brunaldi, Gastrointestinal Endoscopy Unit, Gastroenterology Department, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Dr. Enéas de Carvalho Aguiar Av. 155, 6th floor, São Paulo, 05403-900, Brazil. E-mail: vitor.brunaldi@usp.br

Introduction

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the preferred method to obtain histological diagnosis of solid pancreatic masses. Previous studies suggest the sensitivity and specificity of EUS-FNA range between 83-93% and 83–98% and the positive and negative predictive value between 96-100% and 19–84%, respectively.[1–5]

The diagnostic yield of EUS-FNA is influenced by a number of factors including but not limited to the characteristics of the lesion, experience of the endosonographer, type of needle, biopsy technique, and presence of onsite cytopathologist.[6–9] Nonetheless, a fraction of patients has no histopathological diagnosis despite multiple FNA passes. Therefore, there is a need to improve the yield of this technique which is essential for the management of patients with pancreatic neoplasia.

Bhutani *et al.* firstly described the suction technique during EUS-FNA.[10] It is known to increase tissue contact against the cutting edge of the needle as it moves through the lesion, ultimately leading to a greater cell detachment.[11] Slow-pull (SP) was first described by Chen *et al.* in 2011.[12] It consists of a gradual removal of the needle stylet during the *to and fro* movements of the needle. Previous reports suggest this method to be associated

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with diagnostic yield similar to conventional techniques but less blood and clot aspiration.[13] To date, few randomized trials compared suction and SP techniques and literature is controversial. Moreover, there is little data concerning cellularity and bloodiness of EUS-FNA of pancreatic masses as well as few studies assessing the role of smear in this context.

In the current study, the primary aim was to test the null hypothesis that there is no significant difference between slow pull and suction techniques versus the alternative hypothesis that there is a difference between methods. The slow pull technique may: (i) Improve the diagnostic yield of EUS-FNA of solid pancreatic masses; (ii) reduce the blood contamination and increase the specimen cellularity obtained during EUS-FNA. The secondary aim was to assess if smear is similar to cell-block in providing adequate cytological samples in terms of cellularity and bloodiness.

Methods

Study design

This study was a prospective randomized controlled trial conducted at a tertiary referral center (Hospital das Clínicas da Universidade de São Paulo, São Paulo, Brazil). The trial was approved by the Institutional Review Board and registered at ClinicalTrials.gov (NCT03111368). All patients provided informed consent for participation in the study.

Participants

Eligible participants were adults aged 18 or older with the diagnosis of a solid pancreatic mass by an imaging study abdominal ultrasound, CT scan or magnetic resonance, without a prior biopsy. Exclusion criteria were pregnancy, sepsis, cystic lesions, intractable coagulopathy (international normalized ratio > 1.5) or thrombocytopenia (platelets < 50,000), and refusal to participate in the study.

Procedure

We performed EUS-FNA under conscious sedation or general anesthesia in the left lateral decubitus position using a linear array echoendoscope (Fujinon EG 530UT or EG530UT2 – Fujifilm Co., Tokyo, Japan) for all examinations. First, a diagnostic study was carried out. The endoscopist interrogated and measured the lesion, assessed for vascular invasion, lymph nodes or metastasis. Subsequently, the protocol for FNA was initiated. We employed two brands of 22-gauge FNA needles: either the Expect Slimline (Boston Scientific, Marlborough, Massachusetts, USA) or the Sonotip (Medi-Globe GmbH, Rosenheim, Germany). The same needle was utilized for sampling of the lesion in both strategies, suction and slow-pull. Each patient underwent 4 needle passes with both techniques in an alternate fashion. The patients were randomized to determine the order of puncture technique. The procedures were performed by five experienced endoscopists (SC, SEM, MELS, DMC, ELAA).

After locating the best position for puncture, the needle was introduced into the working channel of the scope, sharpened by withdrawing the stylet 2 mm, and then advanced into the lesion. Suction technique was performed removing the stylet completely and applying a 10 cc syringe negative pressure. After the sample was collected, the syringe was closed and needle retracted and removed from the scope. For the slow-pull technique, we gradually and continuously removed the stylet during the *to and fro* movements. For each pass we performed 20 *to and fro* movements into different areas of the lesion in a fanning fashion.[14] To extract the procured material from the needle, we reintroduced the stylet after each puncture. Then, we removed it again completely and flushed the needle with saline in order to decrease cell contamination from one puncture technique to the other.

Randomization

We generated a computer-based randomization using the online software Research Randomizer with 1:1 ratio (www.randomizer.org). An independent researcher not involved in this trial created the randomization list and sealed sequential opaque envelopes with the random allocation sequence. The list was completely generated before the first enrollment.

The patients were allocated in two groups to determine the order of the puncture technique (Group A: Suction, SP, Suction, SP or Group B: SP, Suction, SP, Suction). The order of the puncture strictly followed the alternate fashion: in Group A first puncture was Suction, second was SP, third was Suction and fourth was SP; in Group B the first was SP, second was Suction, third was SP and fourth was Suction.

During procedures of eligible patients, an independent researcher (DTHM) opened the sealed envelope in the exam room immediately after the operator obtained an optimal position for puncture. Both patient and cytologist were blinded to the allocation.

Histopathological assessment

One expert cytologist (DAC) reviewed all samples and was blinded to the allocation. Rapid onsite cytology evaluation was not available. The samples obtained with each technique were separated in two groups. We made a total of four smears for each group, two of which were stained with Papanicolaou method and the other two with panoptic stain. The remaining specimens were fixed in formalin solution, embedded in paraffin, sectioned, and stained using hematoxylin and eosin (H&E) for histological interpretation.

In a posterior retrospective analysis, we retrieved all available samples to assess cellularity and bloodiness according to the technique of tissue acquisition. Then, we graded the cellularity and bloodiness of the cytological samples using a standardized semi-quantitative classification. Cellularity was defined as the presence of intact diagnostic cells and was graded as follows: 0 (absence or <10% of cell groups); 1+ (≥10–50% of cell

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groups); 2+ (≥50–70% of cell groups); and 3+ (≥70–90% of cell groups). Bloodiness was defined as the presence of red blood cells and clots interfering in the cytological analysis and was graded as follows: 1+ (red blood cells ≥10–50%); 2+ (red blood cells ≥50–70%) and 3+ (red blood cells ≥70–90%). Figs. 1,2 illustrates this semi-quantitative classification.

Follow-up

Adverse events were recorded from immediately after the procedure up to 4 weeks. Patients were instructed to return to our unit in case of any unexpected symptom. Early adverse events were defined as those within 48 h, and late adverse events from 48 h to 4 weeks after the procedure. We assessed for adverse events during hospitalization, and/or with phone calls up to 30 days after the procedure (for outpatients or after discharge).

In case of an initial inconclusive cytological diagnosis, we performed a second attempt of EUS-FNA outside the current study. The gold standard for comparison was the surgical histology for patients with resectable lesions. The final diagnosis for malignancy in patients not referred to surgery was the cytopathology, considering clinical outcome and/or imaging deterioration after 6-month follow-up. Final diagnosis negative for malignancy was considered in case of negative cytopathology with consistent clinical outcomes and imaging at 6 months follow-up.

Outcomes

The primary endpoint was the proportion of conclusive diagnosis achieved by each technique, SP EUS-FNA and Suction EUS-FNA. The secondary endpoints were the quality of the specimen assessed through the aforementioned semi-quantitative scale regarding the quantity of diagnostic cells and blood in each group.

Statistical analysis

To detected a difference of more than 25% in diagnostic accuracy between suction and slow-pull, with a two-sided 5% significance level and a power of 80% and a 90% confidence interval, a sample size of 44 patients in each arm was determined to a binary outcome equivalence trial. Considering a 10% dropout rate, a total of 50 patients were submitted to both techniques resulting in two groups: 50 Suction EUS-FNA and 50 SP EUS-FNA.

Continuous variables were presented as medians and means. Categorical data were expressed with frequencies and proportions. Fisher's exact test was used to assess the correlation between diagnostic accuracy of each technique. We employed the McNemar and Student's t-Test to verify the marginal correlation between the test accuracy and order of puncture. For cellularity and blood contamination analyses, we used the Wilcoxon signed-rank test and Spearman correlation. A p-value of 0.05 indicated statistical significance and 95% confidence interval was considered.

Factors with $p < 0.15$ in the univariate analysis were considered to be potential risk factors for pancreatic neoplasm and were further analyzed in a multiple logistic regression model. The backward selection procedure was used for model selection. Variables with $p < 0.05$ were considered statistically significant. The sensitivity, specificity, PPV, negative predictive value, and overall accuracy were calculated using the standard definitions.

Results

Between May 2015 to June 2016, 957 patients were referred to our unit for EUS evaluation, of which 695 were excluded at the time of EUS (biliary stones investigation or non-pancreatic lesions). Among the remaining 262 patients with pancreatic lesions, 50 presented with cystic lesions, 10 had previous pancreatic surgery and 1 had very poor clinical condition and was not suitable for EUS-FNA. Of 201 patients that presented with solid pancreatic mass, 151 met at least one of the exclusion criteria. Finally, fifty patients fulfilled eligibility criteria and were randomized for one of the two groups. Fig. 3 details the enrollment and randomization process.

The mean age was 63.9 ± 10.4 years and most patients were male (29/50). Seventy percent (35/50) of the lesions were located in the head of the pancreas and most were larger than 4 cm^2 (42/50). Tables 1 and 2 outlines all demographic data. Both groups were statistically similar for all characteristics.

Suction provided 44 (88%) true positive diagnoses while slow-pull technique presented 40 (80%), with no statistical difference

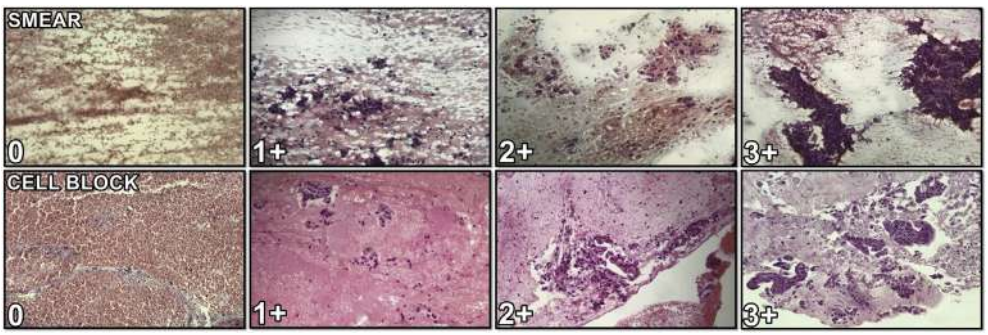

Figure 1 Semi-quantitative grading for cellularity

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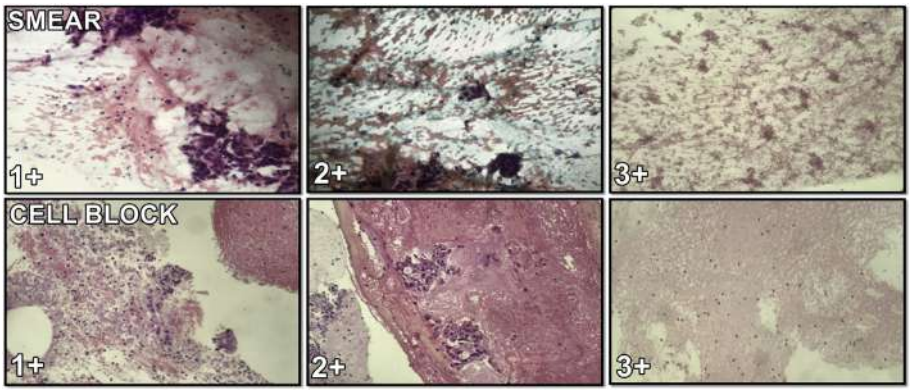

Figure 2 Semi-quantitative grading for bloodiness

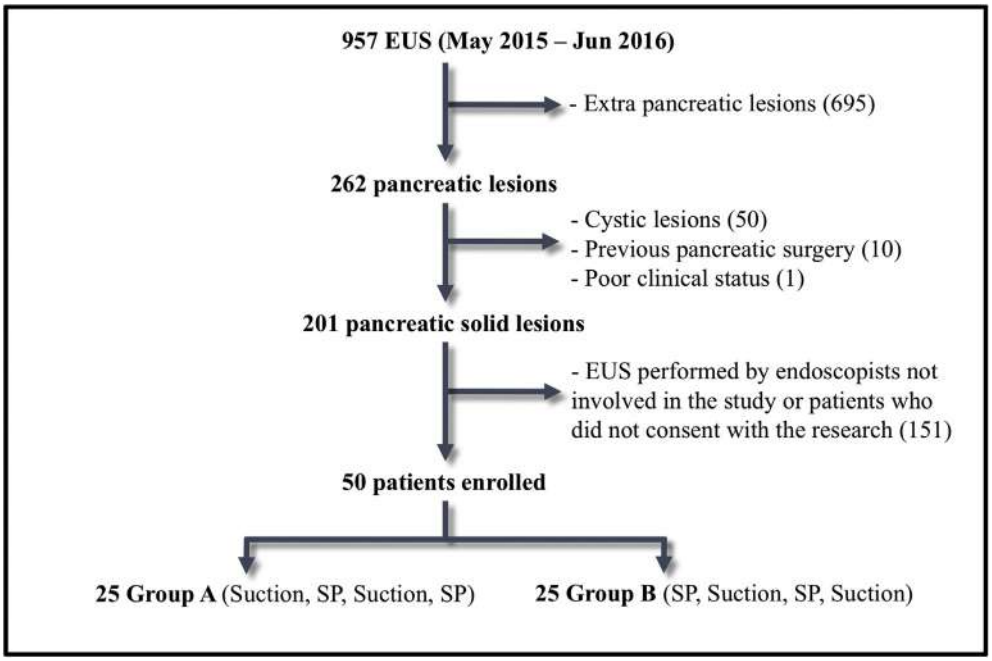

Figure 3 Enrollment and randomization flowchart

(p = 0.344). The combination of techniques provided 47 (94%) conclusive diagnoses, which was significantly higher than slow-pull alone (94% x 80%, p = 0.016). In the univariate analysis, size greater than 4 cm^2 positively correlated with higher positivity rate for both methods (p = 0.044 and p = 0.041) while the location in the head of the pancreas favored positive diagnosis for suction only (p = 0.048). The kind of technique employed firstly and the brand of the needle had no impact on positivity rates. The duration of the procedure was similar for both methods (Group A = 5.37min *vs* B = 5.02min, p = 0.27). Accuracy, sensitivity, and specificity were extremely high and similar for all groups. We could not calculate negative predictive values since there was no true negative case. The area under the ROC curve for SP, Suction and combination of methods were 0.662, 0.864 and 0.888, respectively (Fig. 4). Other diagnostic data is outlined in Table 3.

Slow-pull EUS-FNA was inconclusive in seven patients but suction EUS-FNA provided positive cytology for adenocarcinoma. Three patients in the Suction group were inconclusive for malignancy but Slow-pull EUS-FNA adequately diagnosed pancreatic adenocarcinoma. Both techniques were inconclusive for a single patient, who was referred to another EUS-FNA using a standard 22G needle with both techniques. The lesion seemed to have a significant fibrotic component precluding adequate sampling. EUS-FNA of a local lymph node was consistent with neuroendocrine carcinoma. Other two patients were diagnosed with chronic pancreatitis, one of them underwent a later EUS-FNA using a standard 22G needle with Suction technique and was found to have pancreatic adenocarcinoma. The other patient was ultimately diagnosed with mucinous neoplasia after sample review (Fig. 5).

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Table 1 Baseline demographics of patients enrolled in the study

Characteristics	Description (N = 50)
Age (years), mean ± SD	63,9 ± 10,4
Gender, n (%)	
Female	21 (42)
Male	29 (58)
Needle Brand, n (%)	
EXPECT 22	34 (68)
SONOTIP 22	16 (32)
Location, n (%)	
Body	14 (28)
Head	35 (70)
Uncinate	1 (2)
Size of lesion (cm^2), n (%)	
≤ 4	8 (16)
> 4	42 (84)
Histology, n (%)	
Adenocarcinoma	43 (86%)
Mucinous neoplasia	2 (4%)
Melanoma	1 (2%)
Neuroendocrine neoplasia	1 (2%)
Chronic pancreatitis	2 (4%)
Inconclusive	1 (2%)

Table 2 Patients' characteristics according to allocation group

Characteristics	Groups		*p*
	A-Suction first (N = 25)	B-Slow-pull first (N = 25)	
Age (years), mean ± SD	65,6 ± 9,4	62,2 ± 11,1	0,239[a]
Gender, n (%)			0,774[b]
Female	11 (44)	10 (40)	
Male	14 (56)	15 (60)	
EUS Needle Brand, n (%)			0,225[b]
EXPECT 22	19 (76)	15 (60)	
SONOTIP 22	6 (24)	10 (40)	
Location, n (%)			0,065[c]
Body	10 (40,0)	4 (16)	
Head	14 (56,0)	21 (84)	
Uncinate	1 (4,0)	0 (0)	
Size of the lesion (cm^2), n (%)			0,702[d]
≤ 4	3 (12)	5 (20)	
> 4	22 (88)	20 (80)	

[a] Student's t-test.
[b] Chi-square test.
[c] Likelihood-ratio test.
[d] Fisher's exact test.

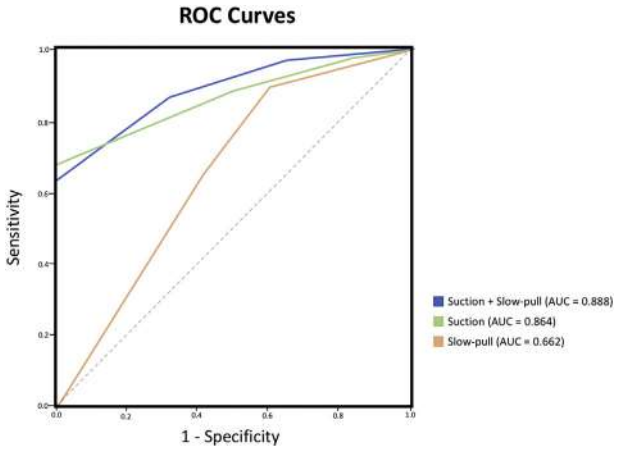

Figure 4 ROC curves for slow-pull FNA, suction FNA, and association of methods

Cytological samples from 44 patients were posteriorly available to compare the yield of cell-block and smear. The semi-quantitative analysis showed equivalent cellularity in both cell-block and smear, regardless of the technique employed (SP or Suction). Bloodiness was also similar for suction and SP (Table 4). Cellularity scores inversely correlated with bloodiness ($p < 0.05$).

Two patients presented early adverse events (4%). The first had rigors without fever and the second complained of mild abdominal pain. Both received intravenous medications and were discharged hours later asymptomatic. No patient required hospitalization after the EUS-FNA. There was no mortality related to the procedure and no late adverse events were reported for 31 patients. We were unable to contact nineteen patients.

During follow-up of patients diagnosed with adenocarcinoma, only one patient underwent Whipple's procedure but deceased few months after surgery. The surgical pathology confirmed the result of the previous EUS-FNA cytology. The remainder were treated with systemic chemotherapy but died within follow-up.

Discussion

EUS-FNA is well-established as the gold standard method for sampling pancreatic masses. However, a number of patients do not have the tissue diagnosis despite multiple FNA attempts, which may have a significant impact on the treatment options and outcomes. A number of factors are known to alter the yield of the FNA procedure including but not limited to size of the lesion, localization, presence of fibrotic tissue or necrosis, peri-tumoral inflammation, and vascularization. Our results confirmed the effect of the first two factors. Our demographics were also in accordance with literature data.[15–17]

The type of needle has also been reported to affect the FNA performance. Recently, fine-needle biopsies with specific needles have been employed with great enthusiasm. However, most studies report similar accuracy with the only advantage of

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Table 3 Diagnostic profile of slow-pull, suction and combination of techniques

Technique	Accuracy	Sensitivity	Specificity	PPV
	CI (95%)	CI (95%)	CI (95%)	CI (95%)
Suction	95,7 (89,8; 100)	95,2 (83,8; 99,4)	100 (39,8; 100)	100 (91,2; 100)
Slow-pull	93 (85,4; 100)	92,3 (79,1; 98,4)	100 (39,8; 100)	100 (90,3; 100)
Combination	96 (90,5; 100)	95,6 (84,9; 99,5)	100 (39,8; 100)	100 (91,8; 100)

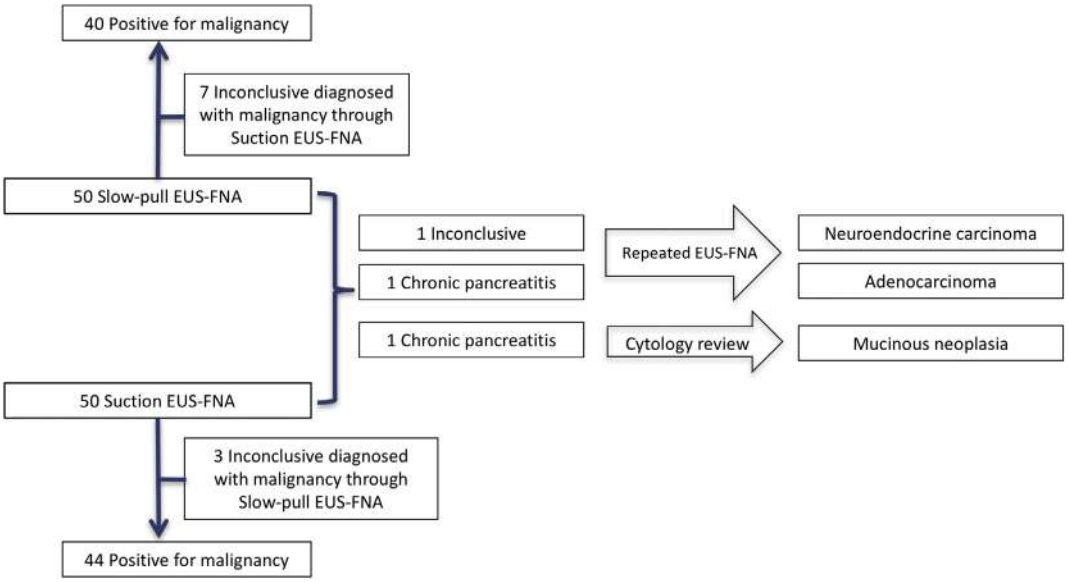

Figure 5 Flowchart of EUS-FNA cytopathological results

Table 4 Semi-quantitative comparison between cell-block and smear

Outcome	Cytological assessment		*p*	Outcome	Cytological assessment		*p*
	Smear	Cell-block			Smear	Cell-block	
Suction - Cellularity			*0.963*[a]	Suction - Bloodiness			*0.403*[a]
None	11 (25)	8 (18.2)		None	0 (0)	3 (6.8)	
1+	9 (20.5)	17 (38.6)		1+	13 (29.5)	10 (22.7)	
2+	13 (29.5)	6 (13.6)		2+	9 (20.5)	12 (27.3)	
3+	11 (25)	13 (29.5)		3+	22 (50)	19 (43.2)	
SP - Cellularity			*0.098*[a]	SP - Bloodiness			*0.313*[a]
None	18 (40.9)	10 (22.7)		None	0 (0)	1 (2.3)	
1+	11 (25)	14 (31.8)		1+	14 (31.8)	13 (29.5)	
2+	4 (9.1)	6 (13.6)		2+	6 (13.6)	12 (27.3)	
3+	11 (25)	14 (31.8)		3+	24 (54.5)	18 (40.9)	
p	*0.119*	*0.980*		*p*	0.805	0.708	

[a] Wilcoxon test for paired samples.

reducing the number of punctures.[18–20] Purposively, we opted to employ the standard needle which is currently more available worldwide.

Our study demonstrated good test performance characteristics of both suction and slow-pull techniques, comparable to previous reports. The combination of both techniques provided an even higher sensitivity, specificity and accuracy than any of the strategies alone. Moreover, the result of our ROC curve analysis also supported that the association of methods holds the best diagnostic yield. While this finding might be due to a

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higher number of passes, it may also suggest that a combination of both techniques is the preferred method of sampling pancreatic masses. The optimal number of passes to properly diagnose pancreatic masses ranges widely in the literature.[21–24] However, robust data support two passes as adequate for masses larger than 15 mm,[22] which correspond to the majority of our sample.

It remains unclear if suction is superior to SP. Alizadeh *et al.*[25] and Lee *et al.*[26] showed opposite results: the first found equivalence of SP and suction while the latter revealed superiority of suction. Interestingly, however, Lee *et al.* presented accuracy and sensitivity rates much inferior than other similar studies, including ours. This could have probably accounted for the relative superiority of the suction technique in his trial.

Our study also attempts to assess the quality of the FNA sampling through cellularity and bloodiness evaluation. Previous studies have addressed similar topics. Wen J *et al.* assessed cellular adequacy of FNA samples of small solid renal tumors.[27] Othman MO *et al.* evaluated cellularity yield from 3 different EUS needles for pancreatic and extrapancreatic masses[28] while Wani S *et al.* compared cellularity and bloodiness between punctures with and without stylet.[29] However, to our knowledge, this is the first study in the literature addressing both bloodiness and cellularity FNA in pancreatic solid lesions. Of note, we demonstrated similarity between methods despite the rationale of augmented trauma leading to bleeding and higher bloodiness of samples from suction technique.

This study is not free of limitations. First, the expertise of our endoscopist and cytologist might impair generalization. Also, the experience of our cytologist may have a major impact on the diagnostic yield. The sample size might have accounted for an inability to demonstrate a real difference between techniques. We tried to address such issue by performing both methods for each patient, which ultimately doubled our sample size. Another limitation of this study was the absence of true negative cases. We may explain such finding by working in a tertiary referral center where most of patients present with advanced illnesses but no previous diagnosis from primary and secondary healthcare system. Finally, the cytological assessment is subjective and interobserver agreement was not evaluated since we have only one cytologist in our unit.

Conclusion

Both slow-pull and suction EUS-FNA techniques are safe and have equivalent test performance characteristics. Association of methods seems to improve diagnostic yield. Bloodiness is equivalent despite of the technique of tissue acquisition, and inversely correlates with cellularity. Both cell-block and smear may provide with adequate material for cytological evaluation.

Declarations

All work has been carried out in accordance with the Declaration of Helsinki. Written consent was obtained from all participants in this trial.

Conflict of interest

None.

Funding

None.

Specific author contributions

- Spencer Cheng: conception and design; drafting of the article; critical revision of the article for important intellectual content.
- Vitor Brunaldi: drafting of the article; critical revision of the article for important intellectual content.
- Mauricio Minata: drafting of the article, analysis and interpretation of data.
- Danielle Chacon: conception and design; critical revision of the article for important intellectual content.
- Eduardo da Silveira: analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article.
- Diogo de Moura: conception and design.
- Marcos dos Santos: conception and design.
- Sergio Matuguma: conception and design.
- Dalton Chaves: conception and design.
- Raony França: conception and design, drafting the article.
- Alfredo Jacomo: drafting the article and critical revision of the manuscript.
- Everson Artifon: conception and design, final approval of the article.

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