—Original Article—

Comparison of specimen quality among the standard suction, slow-pull, and wet suction techniques for EUS-FNA: A multicenter, prospective, randomized controlled trial

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ABSTRACT

Background and Objectives: Standard suction technique (SST), slow-pull technique (SPT), and wet suction technique (WEST) of EUS-FNA are designed to improve the diagnostic yields of solid and solid-cystic lesions. We conducted a multicenter, prospective, randomized crossover trial to compare SST, SPT, and WEST on specimen quality and diagnostic accuracy using a 22G needle. **Methods:** Patients with solid or solid-cystic lesions referred for EUS-FNA at four tertiary hospitals from December 2017 to August 2019 were considered eligible. All lesions were sampled using a 22G needle by the three techniques performed consecutively in a randomized order. The primary outcome was quality of the specimen acquired by each technique regarding blood contamination, tissue integrity and cellularity for diagnosis, graded on a predefined scale. The secondary outcomes were the diagnostic yield of EUS-FNA and the incidence of adverse events. ClinicalTrial.gov registration number: NCT03567863. **Results:** A total of 300 patients (mean age, 60.6 years, 188 men) were enrolled. WEST was superior (mean score 4.02 ± 1.51) over SST (3.67 ± 1.57, $P = 0.018$), but comparable to SPT (3.83 ± 1.55, $P = 0.370$) in overall specimen quality evaluation. WEST produced better tissue integrity (1.42 ± 0.74) and higher cellularity (1.32 ± 0.80) than SST and SPT. SPT (1.43 ± 0.69)

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was superior to SST (1.27 ± 0.72, $P = 0.004$) and WEST (1.28 ± 0.71, $P = 0.006$) in avoiding blood contamination. WEST achieved a diagnostic accuracy of 74.7%, higher than SST (64.4%, $P = 0.007$) and SPT (65.0%, $P = 0.012$). One bleeding event occurred with a pancreatic lesion. **Conclusions:** WEST was comparable to SPT and superior to SST in the overall quality of the specimen and achieved highest diagnostic yield.

Key words: EUS-FNA, pancreatic mass, specimen quality, wet suction

INTRODUCTION

EUS-FNA has become the most effective and valuable modality for the diagnosis of a variety of solid and solid-cystic lesions.[1] Although the adoption of EUS-fine needle biopsy (EUS-FNB) is becoming popular in western countries in the last decade,[2-7] in most countries, EUS-FNA remains to be one of the main ways of obtaining specimens for diagnosing various abdominal, pelvic, and mediastinal lesions due to its widespread availability and low cost. The reported accuracy and diagnostic yield of EUS-FNA have varied significantly in the literature.[8-11]

In recent years, in addition to the standard suction technique (SST), new techniques of EUS-FNA have been developed, including the slow-pull technique (SPT) and the wet suction technique (WEST). SST was designed to increase the quantity of the aspirated tissue by using negative pressure during EUS-FNA. However, negative pressure increases not only the amount of tissue acquired but also the amount of blood contamination and disruption of tissue integrity.[12] SPT, in comparison, uses minimal negative pressure to siphon the tissue, and thus in theory avoids excessive blood contamination.[13,14] Both SPT and SST have been well studied.[8,13-19] WEST, on the other hand, is still a novel and promising method with limited knowledge of its effectiveness.[20,21] The technique involves flushing the EUS-FNA needle with a saline solution to replace the column of air within the lumen of the needle before aspiration. The saline solution column keeps the needle from getting clogged while avoiding the inherent inconvenience of a metal stylet.[12] While WEST has showed potential, relevant studies were limited, and the sample sizes were too small to confirm its true clinical value.[12,17,20] To date, there has been no study comparing head-to-head the three techniques.

Therefore, we conducted this study to compare the three techniques in a prospective, randomized crossover trial. Our study aimed to examine the effects of SST, SPT, and WEST on specimen quality and diagnostic accuracy in solid and solid-cystic lesions using a 22G needle to find the best technique.

METHODS

Study design and oversight

This multicenter, prospective, randomized crossover trial was conducted in four tertiary care hospitals in China, including Zhongshan Hospital (Fudan University, Shanghai), Huashan Hospital (Fudan University, Shanghai), Qilu Hospital (Shandong University, Jinan) and Renmin Hospital of Wuhan University (Wuhan University, Wuhan) from December 2017 to August 2019. The study was carried out in accordance with the Helsinki Declaration and was approved by the institutional review boards at all participating centers. All patients provided written informed consent before enrollment. The study was registered in the ClinicalTrial.gov database (NCT03567863). The trial steering committee designed the study and supervised the fidelity of the study protocol. The trial coordinating center managed the data collection and biostatistical analysis. All authors had full access to the study data and approved the final manuscript.

Patients

All patients who were referred to the endoscopy center for EUS-FNA in all four hospitals during the study period were screened. Patients were eligible for enrollment if they are at least l8 years old and had at least one imaging study (computed tomography [CT], magnetic resonance imaging, or positron emission tomography-CT) confirming the presence of and adequately characterizing a solid or solid-cystic lesion in the mediastinum, abdomen, or pelvis. The exclusion criteria were pregnancy, sepsis, cystic lesions, coagulopathy (international normalized ratio >1.5) or thrombocytopenia (platelets <50,000/mm^3), and refusal to participate in the study.

Randomization

Randomization, stratified according to the hospital, was done using a computer-generated sequence. The

randomization assignments establishing the order of the three techniques were placed in sealed envelopes and opened during the procedure when the patient matched the inclusion criteria. All three techniques were used on each patient. For Group A, the order was SST-SPT-WEST, and for Group B, Group C, Group D, Group E, Group F, the orders were SST-WEST-SPT, WEST-SST-SPT, WEST-SPT-SST, SPT-SST-WEST, SPT-WEST-SST, respectively. The sequence was assigned regardless of lesion location or characteristics (solid/solid-cystic). The endosonographers were aware of the study-group assignments, but the patients, study coordinators, and pathologists were blinded.

Intervention

Equipment

The endosonographers performed the procedures using a Fujifilm linear echoendoscope (EG-580UT; Fujifilm, Tokyo, Japan) with a SU9000 (Fujifilm, Tokyo, Japan) ultrasonic processor or an Olympus linear echoendoscope (GF-UCT 260, GF-UCT 240; Olympus, Tokyo, Japan) with an EU-ME2 (Olympus, Tokyo, Japan) ultrasound processor based on availability in each center. The procedures were performed using a 22G needle (EchoTip Ultra HD; Cook Endoscopy, Winston-Salem, NC).

EUS-FNA procedures

All procedures were performed by one of the four experienced endosonographers at each center (Z.Y., J.C., Z.N., C.J.). Each had experience of over 1000 EUS-FNA procedures. All patients received monitored anesthesia care with propofol. The EUS exam was performed before FNA in each case to locate the lesion. Once targeting the lesion, a total of 3 needle passes were performed according to the randomization sequence. Macroscopic on-site evaluation (MOSE)[22] was used to assess on-site specimen adequacy. Each specimen was examined by MOSE no matter which technique it was to determine whether extra passes were needed. Additional passes were added if the endosonographer considered all three specimens inadequate.

For the SST, after the needle was advanced into the lesion, the stylet was removed, and a 10-mL syringe was attached in a "locked" position to the needle with maximal suction. Once the lesion was punctured, suction was applied. The slow-pull technique (SPT) required the assisting nurse to withdraw the stylet slowly and continuously throughout the FNA process once the needle was advanced into the lesion. For the wet suction technique (WEST), the stylet was removed before the puncture. The needle was then flushed with 5-mL saline solution to replace the column of air. A 10 mL syringe with maximal suction was applied after the needle punctured into the lesion.

With each technique, every pass required approximately 20-30 back and forth movements of the needle. Upon the completion of specimen collection, the suction was turned off, and the needle was withdrawn.

All samples were sent to a designated pathologist at each center, who had no information of the technique with which the specimens were collected.

Histopathological assessment

All aspirate specimens were reviewed and graded by an experienced pathologist (who had experience of over 500 EUS-FNA diagnoses) at each center. Each slide of the aspirate specimen was graded in three aspects: (1) blood contamination (0 = blood clots present, 1 = red blood cells contaminated and 2 = free of blood); (2) tissue integrity (0 = no architecturally intact tissue present, 1 = 1-2 architecturally intact tissue present, 2 = ≥3 architecturally intact tissue present); (3) cellularity (0 = <10/high power field [HPF], 1 = <50/HPF, 2 =>50/HPF). The grading system was modified from a previously validated scale,[12,23] aiming for a comprehensive evaluation of the quality of the specimen. All three scores were added for a final score [Table 1 and Figure 1].

Study outcomes

The primary outcome was defined as the recorded quality of the specimens obtained by EUS-FNA with each aspiration technique. The specimen quality was assessed based on the grading system determined by blood contamination, tissue integrity, and cellularity, as mentioned above. The secondary outcomes included the diagnostic accuracy of each EUS-FNA technique and the incidence of an adverse event. The diagnostic accuracy was defined as the proportion of correct

Table 1. Scoring system for specimen assessment

Score	0	1	2
Blood contamination	blood clots present	red blood cells contaminated	free of blood
Tissue integrity	0	1-2	≥3
Cellularity	<10/HPF	<50/HPF	>50/HPF

HPF: high power field

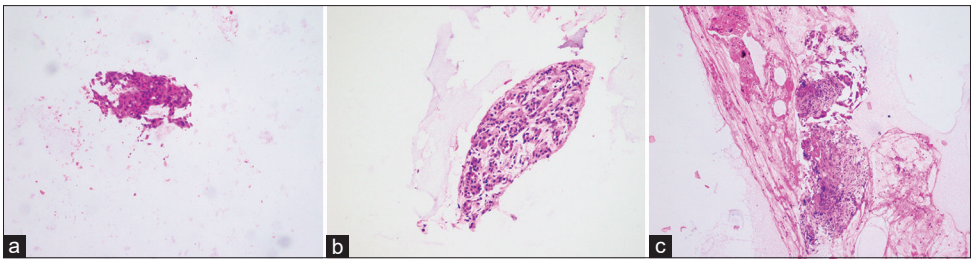

Figure 1. Pathology sections from a patient diagnosed with pancreatic adenocarcinoma. (a) Standard suction technique. Heterocysts are evident with little blood in the background. Blood contamination: 2; Tissue integrity: 0; Cellularity: 2; Final score: 4. (b) Slow-pull technique. Only atrophic pancreatic tissue is evident with little blood in the background. Blood contamination: 2; Tissue integrity: 1; Cellularity: 2; Final score: 5. (c) Wet suction technique. Clusters of heterocysts are evident with red blood cells in the background, and the stromal reaction is noticeable. Blood contamination: 1; Tissue integrity: 2; Cellularity: 2; Final score: 5

diagnoses based on histologic diagnosis obtained by EUS-FNA or surgical resection, or confirmation of disease by clinical follow-up of 12 months.

Follow-up was scheduled in the outpatient clinic for all patients on weeks 1, 12, 24, and months 12 to confirm the diagnostic yield of the EUS-FNA results. The gold standard of malignancy was: (1) surgical pathology showing malignancy when available; (2) if surgical pathology was not available, a positive EUS-FNA result or a characteristic clinical course indicative of malignancy was considered positive; (3) if surgery was not performed, a negative EUS-FNA result and no disease progression on clinical follow-up was considered negative.

Statistical analysis

Based on prior publications,[12] we hypothesized that the WEST was superior to SST and SPT. A sample size of 285 participants gave us an 80% power at a significance level (alpha) of 0.05 to detect a mean of paired differences of 0.1 with an estimated standard deviation of 0.6 with respect to the grading system. The sample size was expanded to 300 to compensate for possible sample loss. Intention-to-treat analysis was performed for patients who had at least one pass.

All categorical variables were described as counts and percentages, whereas the continuous variables were expressed as mean ± standard deviation. Quantitative descriptive analyses were computed for all variables as appropriate. Frequencies or means were calculated for demographic and clinical characteristics and compared between technique groups. To compare specimen quality, which was quantified by the grading system, a two-way analysis of variance followed by a two-tailed paired t-test was used. A two-tailed *P* value of <0.05 was considered statistically significant. Bonferroni's correction was applied to adjust for multiple testing. All analyses were performed with SPSS version 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between December 2017 to August 2019, a total of 300 patients underwent randomization, 52 in Group A, 53 in Group B, 55 in Group C, 38 in Group D, 51 in Group E, and 51 in Group F. Two patients (1 in Group C, 1 in Group E) dropped out of the trial due to presence of a vessel in the puncture path [Figure 2]. The baseline patient demographic and clinical characteristics are listed in Table 2. The six groups (A-F) were well matched in terms of baseline characteristics in the intention-to-treat population [Supplement Table 1]. Of the remaining 298 patients, 145 patients were from Zhongshan Hospital, 41 from Hua1shan Hospital, 67 from Qilu Hospital, and 45 from Renmin Hospital of Wuhan University. The mean age of all patients was 60.6 ± 10.6 years old, ranging from 23 to 87. Male patients made up 63.1% (188/298) of all participants. The median lesion size was 36mm with a mean of 38.2 ± 16.1mm, ranging from 6 to 163 mm. Related previous surgery was defined as a history of any surgical procedure involving the target of EUS-FNA or interfering with the FNA pathway.

Malignancies counted for 267 cases (89.6%) and benign lesions added up to 31 cases (10.4%). Pancreatic adenocarcinoma accounted for most malignancies (196/267, 73.0%) and chronic pancreatitis was the most common (15/31, 48.4%) benign lesion [Table 2].

Specimen quality

We scored blood contamination of EUS-FNA specimens as 0, 1, and 2 for blood clots present,

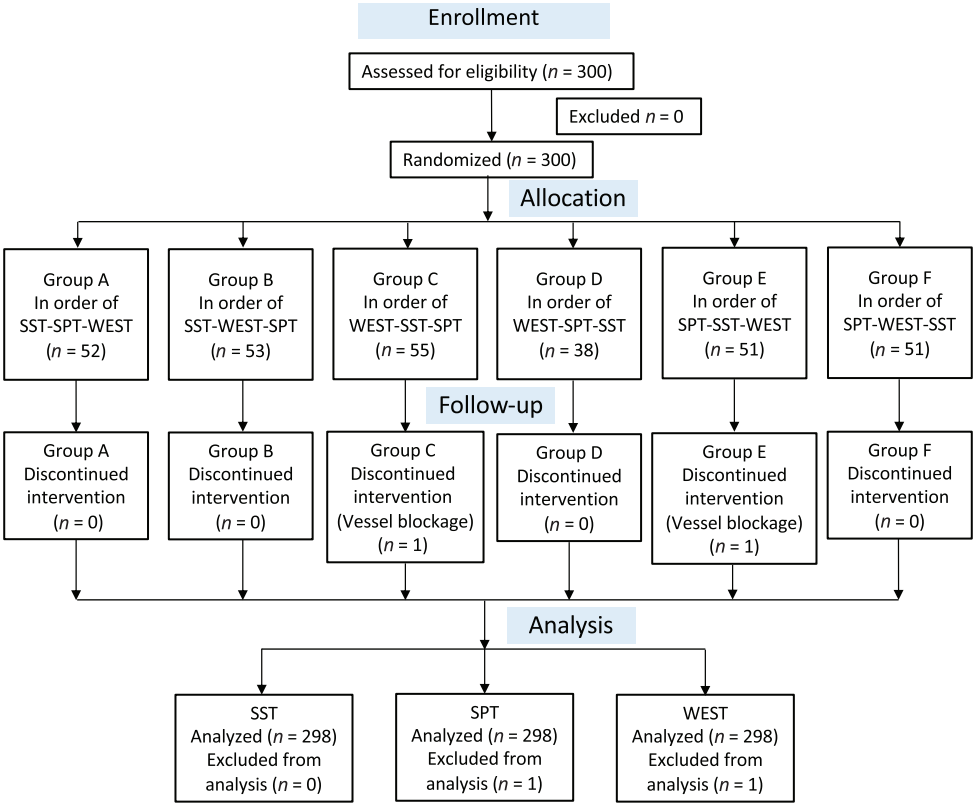

Figure 2. CONSORT diagram of the randomization assignments of the study patients

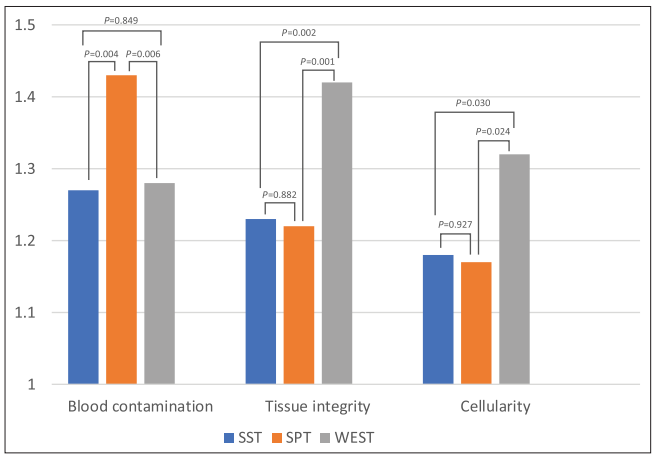

Figure 3. Quality scores for blood contamination, tissue integrity, and cellularity of specimens acquired by the standard suction technique, slow-pull technique, and wet suction technique

red blood cells contaminated, and free of blood, respectively. SPT was superior (mean score of 1.43 ± 0.69) to SST (1.27 ± 0.72, P = 0.004) and WEST (1.28 ± 0.71, P = 0.006) [Table 3 and Figure 3]. Tissue integrity and cellularity were both graded on a scale of 0 to 2. WEST offered the best tissue integrity with a mean score of 1.42 ± 0.74 and highest cellularity with a mean score of 1.32 ± 0.80 as compared to SST (tissue integrity 1.23 ± 0.78, P = 0.002; cellularity 1.18 ± 0.84, P = 0.030) and SPT (tissue integrity 1.22 ± 0.77, P = 0.001; cellularity 1.17 ± 0.82, P = 0.024) [Table 3 and Figure 3]. The overall specimen quality, as defined by the sum of the three scores, was the best for WEST (mean score 4.02 ± 1.51), followed by SPT (3.83 ± 1.55, P = 0.370) and SST (3.67 ± 1.57, P = 0.018) [Table 3 and Figure 4].

Subgroup analysis

A post-hoc analysis was made regarding lesion size as well as pancreatic and non-pancreatic lesions.

All lesions were divided into four groups according to quartile of lesion size (≤26mm, >26mm to ≤36mm, >36mm to ≤46mm, and >46mm). There was a tendency for the final score of specimen quality in SPT to be higher than the other two techniques with larger lesion sizes, without reaching statistical significance (P = 0.479) [Supplement Table 2].

The final score of specimen quality between pancreatic lesions and non-pancreatic lesions with the three techniques were evaluated. There was no significant difference between pancreatic lesions and non-pancreatic lesions (P = 0.309) [Supplement Table 2].

Table 2. Baseline patient characteristics

Characteristic	No. patients (%)
Age, mean±SD, y/o	60.6±10.6 (23-87)
Sex, *n* (%)	
Male	188 (63.1)
Female	110 (36.9)
Size of the lesion, mm	
Mean±SD (range)	38.2±16.0 (6-163)
Lesion location, *n* (%)	
Pancreas	226 (75.8)
Lymph nodes	28 (9.4)
Upper GI tract	26 (8.7)
Abdominal mass	9 (3.0)
Mediastinal mass	4 (1.3)
Liver, rectum, and common bile duct	5 (1.7)
Pathological type	
Malignancies, *n*	267 (89.6)
Pancreatic adenocarcinoma	195 (73.0)
GIST	15 (5.6)
Metastatic lymph nodes	13 (4.9)
Metastatic squamous cell carcinoma/adenocarcinoma	12 (4.5)
Upper GI tract carcinoma	9 (3.4)
Neuroendocrine tumor	8 (3.0)
Lymphoma	3 (1.1)
Other sporadic malignancies	12 (4.5)
Benign lesion, n	31 (10.4)
Chronic pancreatitis	15 (48.4)
Reactive lymphadenopathy	8 (25.8)
Other sporadic benign lesions	8 (25.8)

SD: Standard deviation; GIST: gastrointestinal stromal tumor; GI: gastrointestinal

Table 3. Comparison of scoring of different techniques among SST SPT WST groups

	SST (*n*=298)	SPT (*n*=297)	WEST (*n*=297)	*P*
Specimen quality				
Blood contamination	1.27d0.72	1.43d0.72	1.28d0.72	0.005
Tissue integrity	1.23ue in	1.22ue in	1.42ue in	0.001
Cellularity	1.18ular4	1.17ular4	1.32ular4	0.039
Total	3.67llar4	3.83llar4	4.02llar4	0.022
Diagnostic accuracy, %	64.4	65.0	74.7	0.010

SST: Standard suction technique; SPT: Slow-pull technique; WEST: Wet suction technique

Diagnostic accuracy

WEST achieved a diagnostic accuracy of 74.7% (222/297), which was higher than SST (64.4%, 192/298, $P = 0.007$) and SPT (65.0%, 193/297, $P = 0.012$) [Figure 4]. The diagnostic accuracy of EUS-FNA with all three passes was 93.3% (278/298).

Safety and adverse events

Only one patient (1/298, 0.3%) with a pancreatic lesion in the uncinate process experienced pulsatile bleeding after the first EUS-FNA pass with SST and was managed with metal clips successfully. The following two passes were suspended due to the risk of re-bleeding. EUS-FNA specimen and follow-up result confirmed the lesion was chronic pancreatitis. No other patients had severe bleeding nor other significant EUS-FNA related adverse events during and one week after the procedure.

DISCUSSION

The wet suction technique was first reported in 2015,[12] and only a few studies evaluated its performance. The 2017 ESGE EUS-FNA technical guideline[24] mentioned this technique, with only limited evidence supporting its use.

The quality of the sample was chosen as the major outcome in this study as this is a direct indicator of the technical performance of the FNA. A more clinically relevant outcome will be the diagnostic yield. However, diagnostic yield can be affected by multiple factors other than the effectiveness of the sampling method, such as methods used for pathology processing, experience of the pathologist, and also the case mix (*e.g.*, percentage of malignancy). Using sample quality as the major outcome measurement, in addition to the direct head to head randomized trial design, took these confounding factors out of the equation, and thus provides valuable information on the effectiveness of the different techniques.

The results of our study suggested that in terms of the overall specimen quality, the wet suction technique is comparable to the slow-pull technique and is superior to the SST. In clinical practice, we noticed that inserting the stylet into the needle to release the aspirate was difficult with the SST, probably due to the high viscosity of the clots.[25] When a clot forms, the ability to aspirate will decrease, which leads to lower cellularity, tissue integrity, and diagnostic yield. This may be one of the reasons why the SST received a lower score in our study compared to the slow-pull technique, which aspirates little blood, or the wet suction technique, where the saline-solution column prevents clot formation.

There was a tendency for the slow-pull technique to perform better in larger lesions (mean final score 4.14 ± 1.58 vs. 3.93 ± 1.55 in wet suction technique and 3.85 ± 1.60 in SST for lesions larger than 46mm).

Lee's study suggested a tumor size >40 mm is associated with increased diagnostic accuracy,[26] and El Haddad's study suggests that more tissue is acquired using the slow-pull technique.[27] Our results backed up both findings from these studies. One theory behind these findings begins with the assumption that large lesions run out of blood supply leading to central necrosis. With higher negative pressure, it is more likely to aspirate fragile material like necrosis. However, since the slow-pull technique only provides minimal negative pressure, chances of acquiring visible tissue are higher than mere necrosis. Therefore, the aspirate of large lesions using the slow-pull technique may result in more viable tissue compared to other techniques. Moreover, we noticed that some of the studies which reported relatively low diagnostic efficacies were conducted using a 20G needle,[19] which might weaken the siphoning effect. Accordingly, we propose that in large lesions with necrosis, a combination of wet suction and slow-pull techniques may be a better option for EUS-FNA.

The safety of EUS-FNA with the three techniques has been well established in previous studies. The most common reported adverse events were acute pancreatitis, pain, fever, and bleeding, with an incidence rate of 0.56% to 2.54%.[28,29] In our study, one patient with a pancreatic uncinate process lesion experienced pulsatile bleeding after the first EUS-FNA pass using the SST and was managed successfully with metal clips. The incidence rate of bleeding was 0.3%, confirming the safety of EUS-FNA.

This study has a few limitations. The majority of lesions were pancreatic adenocarcinomas; therefore, there may not be sufficient power to detect a possible difference for non pancreatic lesions. In a future study, a larger sample size of nonpancreatic lesions may provide new insights.

CONCLUSIONS

In conclusion, the slow-pull technique acquired specimens with the least blood contamination. In terms of overall specimen quality, using a 22G EUS-FNA needle, the wet suction technique was superior to the SST and comparable to the slow-pull technique. In terms of tissue integrity, cellularity and diagnostic accuracy, the wet suction technique was superior to both the standard suction and the slow pull techniques.

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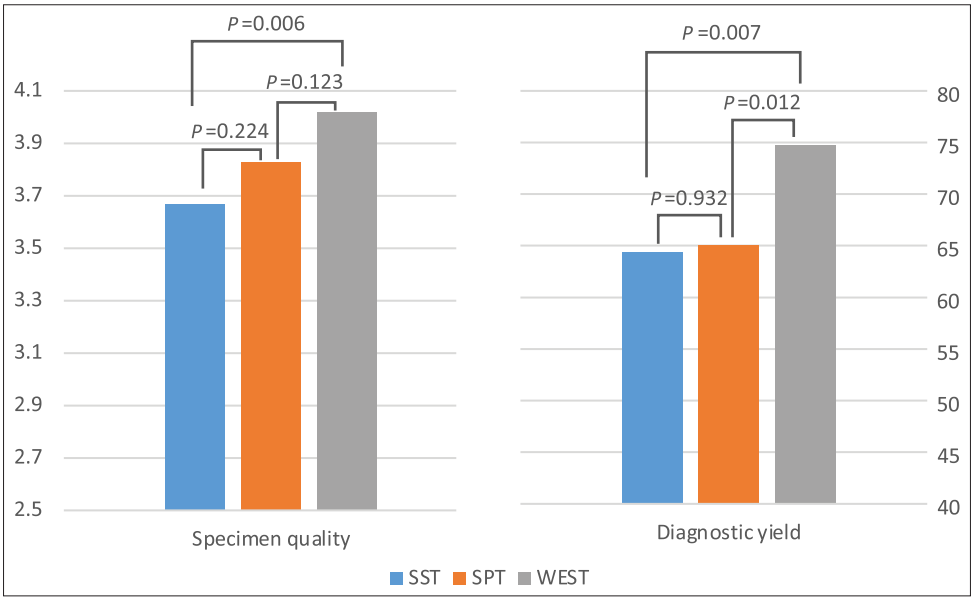

Figure 4. Quality and diagnostic yield of the specimens acquired with the standard suction technique, slow-pull technique, and wet suction technique

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Conflicts of interest

There are no conflicts of interest.

Supplementary Materials

Supplementary information is linked to the online version of the paper on the Endoscopic Ultrasound website.

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Supplement Table 1. Baseline patient characteristics

	Group A	Group B	Group C	Group D	Group E	Group F	Total	*P*
Age, mean±SD, y/o	59.6±9.3	61.1±9.6	58.4±10.3	61.1±12.7	60.2±12.1	63.4±9.6	60.6±10.6 (23-87)	0.244
Sex, *n* (%)								
Male	34 (65.4)	34 (64.2)	40 (74.1)	21 (55.3)	26 (52.0)	33 (64.7)	188 (63.1)	0.249
Female	18 (34.6)	19 (35.8)	14 (25.9)	17 (44.7)	24 (48.0)	18 (35.3)	110 (36.9)	
Size of the lesion, mm								
Mean±SD (range)	42.5±21.8 (16-163)	36.4±11.6 (12-68)	38.6±17.5 (12-100)	36.7±14.2 (6-80)	37.9±12.0 (18-67)	36.7±16.2 (6-80)	38.2±16.0 (6-163)	0.395
Lesion location, *n* (%)								
Pancreas	35 (67.3)	45 (84.9)	37 (68.5)	32 (84.2)	34 (68.0)	43 (84.3)	226 (75.8)	0.417
Lymph nodes	7 (13.5)	2 (3.8)	7 (13.0)	3 (7.9)	6 (12.0)	3 (5.9)	28 (9.4)	
Upper GI tract	4 (7.7)	5 (9.4)	6 (11.1)	3 (7.9)	5 (10.0)	3 (5.9)	26 (8.7)	
Abdominal mass	3 (5.8)	0	3 (5.6)	0	2 (4.0)	1 (2.0)	9 (3.0)	
Mediastinal mass	1 (1.9)	1 (1.9)	1 (1.9)	0	0	1 (2.0)	4 (1.3)	
Liver, rectum, and common bile duct	2 (3.8)	0	0	0	3 (6.0)	0	5 (1.7)	
Pathological type (%)								
Malignancies	45 (86.5)	51 (96.2)	47 (87.0)	35 (92.1)	45 (90.0)	44 (86.3)	267 (89.6)	0.511
Benign lesions	7 (13.5)	2 (3.8)	7 (13.0)	3 (7.9)	5 (10.0)	7 (13.7)	31 (10.4)	

SD: Standard deviation, GI: gastrointestinal

Supplement Table 2. Subgroup analysis of lesion size and lesion origins

	Suction	Slow-pull	Wet suction	*P*
Lesion size				0.479
≤0.479	3.64±1.48	3.77±1.51	4.12±1.38	0.123
>26 mm, 38zes	3.54±1.63	3.58±1.59	4.14±1.55	0.032
>36 mm, 546 mm	3.68±1.56	3.84±1.45	3.89±1.57	0.702
>46 mm	3.85±1.60	4.14±1.58	3.93±1.55	0.526
Lesion origins				0.309
Pancreatic lesions	3.64±1.49	3.77±1.53	4.12±1.39	0.123
Nonpancreatic lesions	3.69±1.59	3.85±1.55	3.99±1.55	0.122