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Original Article

Current Practice Patterns of Endoscopic Ultrasound-Guided Tissue Sampling for Pancreatic Solid Mass in Korea: Outcomes of a National Survey

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Background/Aims: Although endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) and fine needle biopsy (FNB) are widely used for tissue acquisition of pancreatic solid mass, the optimal strategy of this procedure has not been established yet. The aim of this nationwide study was to investigate the current practice patterns of EUS-FNA/FNB for pancreatic solid mass in Korea.

Methods: The Policy-Quality Management of the Korean Pancreatobiliary Association (KPBA) developed a questionnaire containing 22 questions. An electronic survey consisting of the questionnaire was distributed by e-mail to members registered to the KPBA.

Results: A total of 101 respondents completed the survey. Eighty respondents (79.2%) performed preoperative EUS-FNA/FNB for operable pancreatic solid mass. Acquire needles (60.4%) were used the most, followed by ProCore needles (47.5%). In terms of need size, most respondents (>80%) preferred 22-gauge needles regardless of the location of the mass. Negative suction with a 10-mL syringe (71.3%) as sampling technique was followed by stylet slow-pull (41.6%). More than three needle passes for EUS-FNA/FNB was performed by most respondents (>80%). The frequency of requiring repeated procedure was significantly higher in respondents with a low individual volume (<5 per month, p=0.001). Prophylactic antibiotics were routinely used in 39 respondents (38.6%); rapid on-site pathologic evaluation was used in 6.1%.

Conclusions: According to this survey, practices of EUS-FNA/FNB for pancreatic solid mass varied substantially, some of which differed considerably from the recommendations present in existing guidelines. These results suggest that the development of evidence-based quality guidelines fitting Korean clinical practice is needed to establish the optimal strategy for this procedure. **(Gut Liver 2023;17:328-336)**

Key Words: Endoscopic ultrasound-guided fine needle aspiration; Pancreatic neoplasms; Survey; Korea

INTRODUCTION

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) and fine needle biopsy (FNB) are the standard methods for tissue diagnosis of pancreatic solid mass. These are effective methods to achieve definite diagnosis of pancreatic solid mass with a reported sensitivity of 85% to 95%, specificity of 95% to 98% and diagnostic accuracy of 78% to 95%.[1,2]

To date, many studies have evaluated factors affecting diagnostic accuracy of EUS-FNA/FNB including skills and experience of endoscopists, target lesion characteristics, needle size and type, variable sampling techniques, and the presence of on-site cytopathology assessment.[3-23] Some practice guidelines addressing these techniques have been issued by the European Society of Gastrointestinal Endoscopy (ESGE) and the Papanicolaou Society of Cytopathology.[24-26]

However, in some aspect of EUS-FNA/FNB techniques, scientific evidence is not sufficient yet. There is no consensus on how to effectively utilize these techniques to optimize their diagnostic potential. Thus, it is thought that today's real clinical practice might vary and rely on clinicians' experience and preference and hospital protocols. To date, little is known about the practice patterns in EUS-FNA/FNB due to insufficient number of related studies. Thus, the objective of this nationwide study was to investigate the current practice patterns of EUS-FNA/FNB for pancreatic solid mass in Korea.

MATERIALS AND METHODS

1. Design of the questionnaire

This nationwide survey was conducted by the Policy-Quality Management in the Korean Pancreatobiliary Association (KPBA). A questionnaire draft was developed to explore hot topics and controversial issues in EUS-FNA/FNB practice patterns based on literature review and consensus of members of the Policy-Quality Management in the KPBA. The draft was then circulated among 43 expert members in the KPBA in July 2019. Revision was made based on expert review. After in-depth discussion by members of the Policy-Quality Management in the KPBA, the final version of questionnaire was developed. The final questionnaire consisted of a total of 22 questions. It was designed to take less than 10 minutes to complete (Supplementary Materials). Contents of the questionnaire were classified into four categories: (1) demographics including type of hospital, volume of current practice, and years of experience; (2) indication, tissue acquisition techniques, and equipment; (3) tissue processing and analysis; and (4) post-procedure management and complications. This study was conducted in accord with the Helsinki Declaration and approved by the Institutional Review Board at Seoul National University Boramae Medical Center (IRB number: 10-2022-39). In accordance with Institutional Review Board guidelines for anonymous surveys, the need for documentation of informed consent among participants was waived.

2. Conduct the survey

The survey was distributed by e-mail and administered through a web-based survey platform (SurveyMonkey, San Mateo, CA, USA, https://surveymonkey.com). Potential respondents were identified using the database from the KPBA. The e-mail was sent to expected respondents five times with an interval of a week. All data from respondents were anonymized and analyzed using a web-based soft-

Table 1. Demographic Characteristics of the Respondents

Characteristics	Overall (n=101)	TA medical center (n=63)	PS care hospital (n=38)	p-value
Experience of EUS, yr				0.344
<1	6 (5.9)	2 (3.2)	4 (10.5)	
1–5	34 (33.7)	20 (31.7)	14 (36.8)	
5–10	30 (29.7)	19 (30.2)	11 (28.9)	
>10	31 (30.7)	22 (34.9)	9 (23.7)	
Hospital volume of EUS-FNA/FNB, mo				<0.001
<5	26 (25.7)	9 (14.3)	17 (44.7)	
5–10	38 (37.6)	20 (31.7)	18 (47.4)	
10–30	26 (25.7)	24 (38.1)	2 (5.3)	
>30	11 (10.9)	10 (15.9)	1 (2.6)	
Individual volume of EUS-FNA/FNB, mo				0.001
<5	50 (49.5)	22 (34.9)	28 (73.7)	
5–10	30 (29.7)	23 (36.5)	7 (18.4)	
10–30	16 (15.8)	14 (23.8)	1 (2.6)	
>30	5 (5.0)	3 (4.8)	2 (5.3)	

Data are presented as number (%).
TA, tertiary/academic; PS, primary/secondary; EUS, endoscopic ultrasound; FNA, fine needle aspiration, FNB, fine needle biopsy.

ware platform.

3. Statistical analysis

Only completed surveys were used for data analysis. Differences in categorical variables were analyzed using the chi-square test or the Fisher exact test. Continuous variables, expressed as means±standard deviations, were compared using the Student t-test. To analyze the impact of individual volume on practice of sampling techniques and clinical outcomes after EUS-FNA/FNB, the individual volume was categorized into two categories using a cutoff level of five cases per month that was at least one case per week. All statistical analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as p-value <0.05.

RESULTS

1. Demographics of respondents

The survey was distributed to 1,010 e-mail addresses through the KPBA membership directory, of whom 111 (11.0%) responded. Ten responses were discarded because they were incomplete. Thus, a total of 101 complete responses were included and analyzed. Demographic characteristics of the 101 respondents are shown in Table 1.

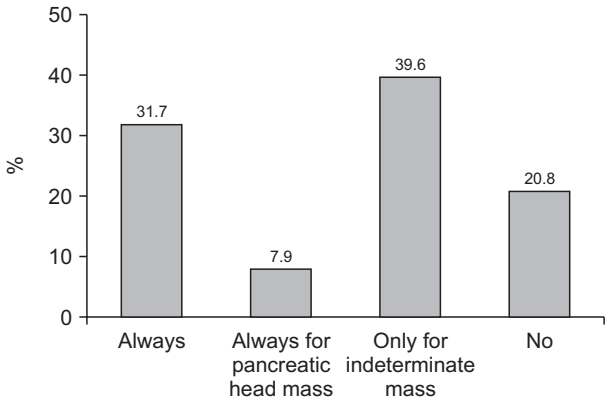

Fig. 1. Frequency of preoperative endoscopic ultrasound guided-fine needle aspiration and biopsy according to the location of pancreatic solid mass.

There were 63 (62.4%) respondents working in a tertiary/academic medical center, while one and 37 respondents worked in primary and secondary hospitals respectively. Experience of EUS-FNA/FNB was more than 10 years in 31 (30.7%), 5 to 10 years in 30 (29.7%), 1 to 5 years in 34 (33.7%), and less than 1 year in six (5.9%). More than 60% of respondents (61/101) had experience of ENS-FNA/FNB more than 5 years. We evaluated hospital and individual volume of EUS-FNA/FNB by examining the number of EUS-FNA/FNB per month both in each hospital (hospital volume) and each respondent (individual volume). There was a trend of higher hospital and individual volume in tertiary/academic medical center than in primary/secondary hospital. Fewer respondents in a primary/secondary hospital were performing more than five EUS-FNA/FNB per month than those in a tertiary/academic medical center (26.3% vs 65.1%, p<0.001).

2. Indication, tissue acquisition techniques, and equipment

Eighty respondents (79.2%) performed preoperative EUS-FNA/FNB for operable pancreatic solid mass (Fig. 1). Among them, 32 respondents (31.7%) performed preoperative EUS-FNA/FNB routinely, and eight performed (7.9%) preoperative EUS-FNA/FNB routinely only for pancreatic head mass, and another 40 (39.6%) performed the preoperative EUS-FNA/FNB selectively only for indeterminate solid mass (Fig. 1). Thirty-six respondents (35.6%) used radial EUS scope for anatomical evaluation before EUS-FNA/FNB, while 65 respondents (64.4%) used linear EUS scope initially.

For routine EUS-guided sampling of solid mass, about half of respondents preferred using Acquire FNB needles (60.4%; Boston Scientific, Marlborough, MA, USA) or EchoTip ProCore needles (47.5%; Cook Medical, Bloomington, IN, USA). However, 27 respondents (26.7%) preferred using the EZ Shot 3 Plus needle (Olympus America, Center Valley, PA, USA) for cytologic evaluation. In terms of need size, most respondents (>80%) preferred 22-gauge needles regardless of the location of the target lesion (Fig. 2). However, 43 respondents (42.6%) also preferred 25-gauge needles for sampling of solid mass in pancreatic

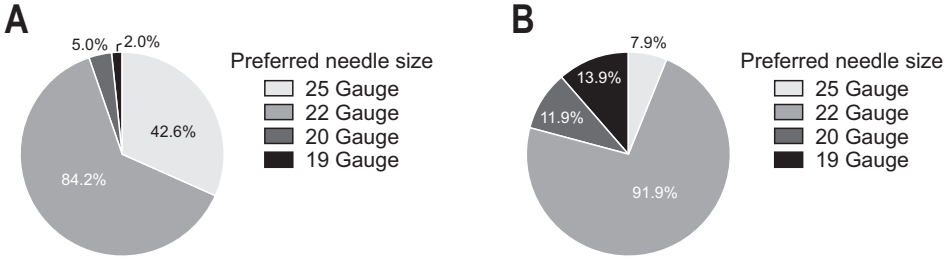

Fig. 2. Preferred needle size for sampling of (A) pancreatic head mass and (B) pancreatic body or tail mass.

head.

Eight-six respondents (85.1%) preferred using length fixing knob for depth adjustment before puncturing target lesion, while 15 respondents (14.9%) preferred adjusting the puncture depth manually. Preferred scope position during EUS-FNA/FNB was long scope position in 62 (61.4%) and short scope position in 39 (38.6%).

Generally, more than three needle passes for EUS-FNA/FNB was performed in most respondents (81.2%). Among them, six respondents (5.9%) performed more than five needle passes for EUS-FNA/FNB. After puncturing the target lesion, most respondents (90.1%) performed more than 10 needle movements for tissue acquisition including 36 respondents (35.6%) who performed more than 20 needle movements. Fanning technique was the preferred needle movement technique for tissue acquisition in most respondents (80.2%), while 20 respondents (19.8%) preferred the "to-and-fro" technique. Some additional techniques were employed to increase yield of tissue acquisition during EUS-FNA/FNB (Fig. 3). The most common additional technique was conventional negative suction technique using 10-mL syringe (72/101, 71.3%), followed by stylet slow-pull technique (42/101, 41.6%). Fourteen respondents (13.9%) used both the negative suction and stylet slow-pull technique according to target lesion. While most respondents (97.0%) used at least one of these two techniques, three respondents (3.0%) used only a non-suction technique.

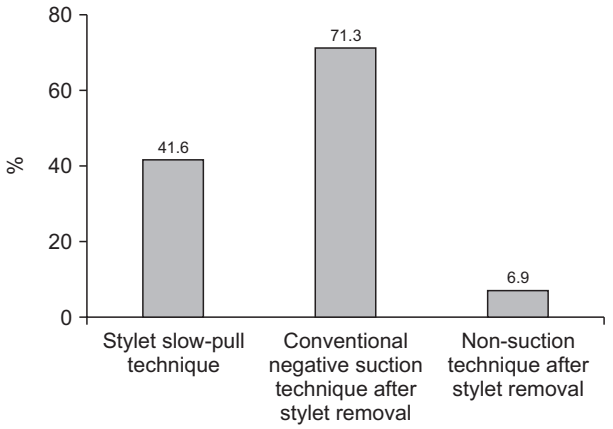

Fig. 3. Additional techniques for tissue acquisition.

Practice of sampling techniques according to individual volume is shown in Table 2. Fewer respondents with high individual volume (≥5 per month) performed radial EUS evaluation (25.5% vs 46.0%, p=0.039) and used length fixing knob (78.4% vs 92.0%, p=0.049). The rate of respondents who preferred long scope position tended to be higher in respondents with high individual volume (≥5 per month) although it was not statistically significant (68.6%

Table 2. Practice of Sampling Techniques According to Individual Volume

Variable	Overall (n=101)	Individual volume		p-value
		Low (<5/mo) (n=50)	High (≥5/mo) (n=51)	
Radial EUS before EUS-FNA/FNB				0.039
Yes	36 (35.6)	23 (46.0)	13 (25.5)	
No	65 (64.4)	27 (54.0)	38 (74.5)	
Length fixing knob before puncture				0.049
Yes	86 (85.1)	46 (92.0)	40 (78.4)	
No	15 (14.9)	4 (8.0)	11 (21.6)	
Scope position				0.155
Long	62 (61.4)	27 (54.0)	35 (68.6)	
Short	39 (38.6)	23 (46.0)	16 (31.4)	
No. of needle passes				0.701
1–2	19 (18.8)	10 (20.0)	9 (17.6)	
3–4	76 (75.2)	38 (76.0)	38 (74.5)	
>5	6 (5.9)	2 (4.0)	4 (7.8)	
No. of needle movement				0.486
<10	10 (9.9)	5 (10.0)	5 (9.8)	
10–20	55 (54.5)	30 (60.0)	25 (49.0)	
>20	36 (35.6)	15 (30.0)	21 (41.2)	
Needle movement technique				0.583
Fanning	81 (80.2)	39 (78.0)	42 (82.4)	
To-and-fro	20 (19.8)	11 (22.0)	9 (17.6)	

Data are presented as number (%).
EUS, endoscopic ultrasound; FNA, fine needle aspiration, FNB, fine needle biopsy.

vs 54.0%, p=0.155). Among 13 respondents with both high EUS experience (>10 years) and high individual volume (≥5 per month), most respondents (92.3%) except one used linear EUS scope initially. Other practices were not significantly different according to the individual volume (Table 2).

3. Tissue processing and analysis

After EUS-FNA/FNB, various methods for tissue processing were used including formalin fix of core tissue specimen for histologic evaluation (75.3%), conventional smear method for cytology (65.4%), and liquid-based cytology (56.4%) (Fig. 4). We examined practice about slide smear and rapid on-site pathologic evaluation (ROSE) in 66 respondents who had used the conventional smear method for cytology. The slide smear after EUS-FNA was performed by endosonographers in 46 (69.7%), while this process was performed by assistants in 20 (30.3%). ROSE was used only in four (6.1%) of 66 respondents.

4. Post-procedure management and complications

After EUS-FNA/FNB, nil per os was kept for more than 6 hours in 68 respondents (67.3%). Sixty-five respondents (64.4%) used prophylactic antibiotics for EUS-FNA/FNB, including 26 (25.7%) who selectively used prophylactic antibiotics depending on endosonographer's discretion and 39 (38.6%) who used antibiotics routinely.

Seventy-two respondents (71.3%) had an experience of post-procedure complications. Among them, 52 (51.5%) and 33 (32.7%) experienced post-procedure hemorrhage and pancreatitis, respectively. Three respondents experienced post-procedure infection and nine respondents experienced perforation.

The frequency of inconclusive pathologic diagnosis requiring repeated EUS-FNA/FNB is shown in Table 3. It was less than 5% in 40 (39.6%), 5% to 10% in 35 (34.7%), 10% to 20% in 22 (21.8%), and more than 20% in four (4.0%). The frequency of requiring repeated procedure was significantly (p=0.002) higher in respondents with low individual volume (<5 per month) than in respondents with high individual volume (≥5 per month).

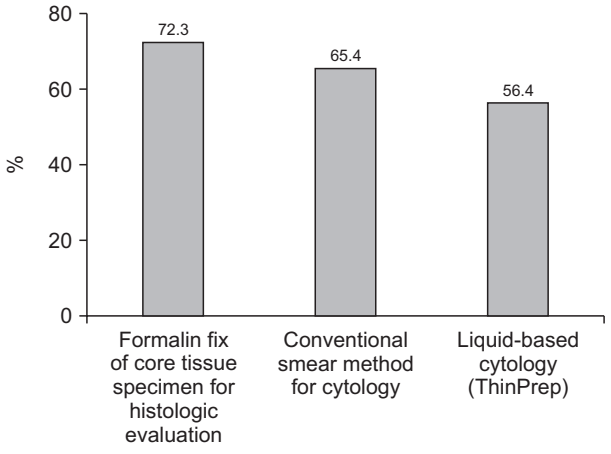

Fig. 4. Methods for tissue processing.

DISCUSSION

EUS-FNA/FNB has become an essential tool to obtain pathologic diagnosis of gastrointestinal tract or adjacent lesions including pancreatic solid tumor.[27] However, optimal strategy of this procedure to improve the diagnostic accuracy and safety remains a matter of debate. Investigating practice patterns of EUS-FNA/FNB in real current practice and the impact of this practice on diagnostic accuracy and safety could help us establish an optimal strategy. However, studies investigating this issue are limited.[27,28] Studies addressing the impact of this practice on clinical outcome have not been reported yet. Thus, we have conducted this nationwide study to investigate the current practice patterns of EUS-FNA/FNB and clinical implication of this practice in Korea. According to the survey, several substantial differences were identified among endosonographers even within Korea. Some routine practices such as choice of needle size and antibiotics prophylaxis differed considerably from recommendations expressed in existing guidelines.

Table 3. Frequency of Requiring Repeated EUS-FNA/FNB According to Individual Volume

	Overall (n=101)	Individual volume		p-value
		Low (<5/mo) (n=50)	High (≥5/mo) (n=51)	
Frequency of repeated EUS-FNA/FNB, %				0.002
<5	40 (39.6)	11 (22.0)	29 (56.9)	
5–10	35 (34.7)	21 (42.0)	14 (27.5)	
10–20	22 (21.8)	14 (28.0)	8 (15.7)	
>20	4 (4.0)	4 (8.0)	0	

Data are presented as number (%).
EUS, endoscopic ultrasound; FNA, fine needle aspiration, FNB, fine needle biopsy.

In our survey, most respondents (79.2%) performed preoperative EUS-FNA/FNB for operable pancreatic solid mass, including about 31.7% of respondents performing preoperative EUS-FNA/FNB routinely. Routine EUS-FNA/FNB for solid mass in pancreatic body/tail might matter. However, the current study did not have subgroup analysis according to the location of solid mass because of limitations of the survey with no detailed questions about location. While there is a concern about tumor seeding after EUS-FNA/FNB, several studies have shown that preoperative EUS-FNA/FNB did not affect clinical outcome after surgery.[29,30] One study has reported that preoperative EUS-FNA is not associated with adverse perioperative or long-term outcomes in patients undergoing distal pancreatectomy for pancreatic solid neoplasms.[29] Another study using database of pancreatic cancer has reported that preoperative EUS-FNA does not impair survival of patients.[30]

The choice of FNA or FNB and needle type has been a hot topic among EUS experts.[27] Many studies about this issue have been performed.[3,5-7,9,10,12,17,18,22] To date, there is no established answer whether FNB is superior to FNA for tissue acquisition.[27] Facciorusso *et al.*[17] have conducted a thorough pairwise and network meta-analysis of randomized trials to compare diagnostic performances of different needle types (FNA and FNB) for sampling pancreatic solid masses. In their meta-analysis, no specific tissue sampling technique was superior. Two methods (FNA and FNB) had the same diagnosis performance. However, another meta-analysis showed conflicting results, reporting that FNB was superior to FNA in specimen adequacy and diagnostic accuracy.[3] One retrospective study comparing Franseen FNB needle and standard FNA needle showed that Franseen FNB needle was associated with a higher first-pass tissue acquisition rate.[22] ESGE guideline equally recommends the use of FNA and FNB needles for sampling of solid masses.[24] With regard to needle type, both Acquire and ProCore needles might be commonly used in current practice. An international survey reported that most (65.7%) endoscopic experts preferred Acquire needles.[27] Our survey reported similar results. In our survey, more than half of respondents (60.4%) preferred Acquire FNB needles. In Korea, ROSE is not available in most institutions as shown from data in our study. Furthermore, histologic diagnosis is essential to provide chemotherapy with support from the national health insurance system, which might explain the preference of the Acquire FNB needles in our study. However, in our survey, some respondents (26.7%) preferred using EZ Shot 3 Plus needles for cytologic evaluation. The reason of choosing EZ Shot 3 Plus needles might be due to the high performance of these needles in pancreatic head lesion and their cost-effectiveness due to relatively low cost of EZ Shot 3 Plus needle.

The choice of needle size is another hot topic. Two meta-analyses have found no significant differences between 25-gauge and 22-gauge needles with regard to diagnostic accuracy, the number of needle passes, and complications.[19,20] However, two recent randomized trials have revealed that 25-gauge needles are inferior to 22-gauge or 20-gauge needles in sample acquisition for histological analysis.[31,32] Furthermore, one recent randomized crossover trial has reported that 22-gauge Acquire needles can provide more tissues for histological analysis and better diagnostic accuracy than 20-gauge ProCore needles.[33] Based on results of these recent studies, 22-gauge needles might be preferred when histological analysis is essential for determination of pancreatic solid mass. ESGE guideline recommends both 25-gauge and 22-gauge needles and suggests the use of 19-gauge FNA or FNB needles or 22-gauge FNB needles when the primary aim of sampling is to obtain a core tissue specimen.[24] An international survey has reported that 25-gauge and 22-gauge needles are equally used among respondents for sampling pancreatic solid mass.[28] Our survey revealed that most respondents (>80%) preferred 22-gauge needles regardless of the location of target lesion. However, about half of respondents (42.6%) also preferred 25-gauge needles for sampling of pancreatic head mass. The 25-gauge needle performs somewhat better regarding number of required needle passes, presumably due to its higher flexibility especially during sampling of pancreatic head mass, which might result in the preference of 25-gauge needles for sampling pancreatic head mass in our survey. One responder might make multiple choices in the question about needle size (both pancreatic head and body/tail). Since many respondents have chosen both 25-gauge and 22-gauge needles as preferred size in case of pancreatic head, the sum of the rate of 22-gauge needle and 25-gauge needle was over 100%.

ROSE after EUS-FNA/FNB is also an important topic. In our survey, ROSE was utilized only in a few respondents (<10%). An international survey has shown intercontinental variations in the availability of ROSE.[28] In that survey, ROSE was used nearly all US respondents whereas only half (48%) of respondents from Europe and Asia (55%) used ROSE. That survey also investigated reasons for omitting ROSE and found that limited pathology staffing was the most common reason for omitting ROSE. However, more than two-thirds of respondents also mentioned that they had doubts with regard to added benefit of ROSE. A meta-analysis about the use of ROSE including seven studies has reported that ROSE is not associated with an improvement of diagnostic yield or adequate rate.[21] Furthermore, a recent multicenter, randomized, and nonin-

feriority study has reported that EUS-FNB demonstrates high diagnostic accuracy in evaluating pancreatic solid mass independently on execution of ROSE. Based on this result, the authors suggested that ROSE should not be routinely recommended when new-generation FNB needles (SharkCore, Acquire, or ProCore needles) are used.[34] ESGE guideline states that panel could not find sufficient reasons to recommend that centers not using ROSE should change their practice.[24] ESGE guideline suggests performance of three to four needle passes with an FNA needle or two to three passes with an FNB needle.[24] In our survey, most respondents performed more than three needle passes including some respondents performing more than five needle passes.

The American Society for Gastrointestinal Endoscopy and ESGE guidelines do not recommend antibiotics prophylaxis for EUS-FNA/FNB for pancreatic solid mass.[24,35] However, in our study, nearly 40% of respondents used antibiotics routinely. Thus, there is a need for education led by an academic society that recommends not to use prophylactic antibiotics routinely. The KPBA is going to provide this education. The KPBA is planning to conduct a second survey in 5 years to investigate changed practice patterns about antibiotics prophylaxis.

In our survey, more respondents with high individual volume (≥5 per month) tended to prefer long scope position. Generally, scope position matters only for mass in pancreatic head or uncinate process. Although long scope position can provide stability in scope position during tissue sampling, elaborated skills are often required to depict target lesion or to manipulate a puncture needle in this long scope position, which can explain the preference of long scope position in respondents with high individual volume (≥5 per month).

In our survey, fewer respondents with high individual volume (≥5 per month) used radial EUS scope for anatomic evaluation and length fixing knob for depth adjustment. In these respondents with high individual volume, the frequency of inadequate diagnosis requiring repeated EUS-FNA/FNB was significantly lower compared to that in respondents with low individual volume (<5 per month). Generally, EUS procedures including EUS-FNA/FNB requests elaborated skills of endoscopists. The diagnostic accuracy of EUS-FNA/FNB is known to be affected by the skills and experience of endoscopists. High individual volume might help endoscopists escape learning curve more promptly, which could explain results of our study. Given these results, there might be a need for discussion led by an academic society on ways to improve the quality of EUS training program in each institution.

To date, there have been two studies performing surveys on EUS-FNA/FNB.[27,28] These two studies performed international survey about practice patterns of EUS-FNA/FNB consisting of preprocedural aspects, sampling techniques, and equipment. However, these studies did not address the impact of this practice on clinical outcome. To the best of our knowledge, our survey is the first to investigate both practice patterns and clinical implication of this practice. Our survey investigated the frequency of inadequate diagnosis requiring repeated EUS-FNA/FNB and post-procedure complications as clinical outcomes of the current practice. However, further studies with more elaborately defined items of clinical outcomes are needed to clarify the clinical implication of the current practice.

As mentioned above, the current study is the first to investigate both practice patterns and clinical implication of this practice in Korea. Despite this advantage, the current study has several limitations. First, it seemed conceivable that results of the current study were subjected to a response bias considering a response rate of 10%. It might result in a selection toward more active and academic endosonographers given that more than 60% of respondents were working in tertiary/academic medical centers in this survey. Second, this survey was distributed only to members registered in the KPBA. Although results of this survey would be representative of the status of practices in Korea, it might be difficult to generalize results of this survey to other countries. Third, this survey did not address some preprocedural practices (such as coagulation status or sedation) and issues about EUS training program. In return, this survey focused on practical issues consisting of equipment and technical aspects. Fourth, recall bias might not be avoided as in other retrospective surveys. Fifth, time dependent factors were not surveyed in the current study. For instance, the used EUS-FNA/FNB needle type could change over time.

In conclusion, this survey revealed that there was a considerable variation in the practice of EUS-FNA/FNB even within Korea. Furthermore, some routine practices differed considerably from recommendations present in existing guidelines. Some practices and clinical outcomes were affected by individual volume. These results suggest that the development of evidence-based guidelines fitting Korean clinical practice is needed to establish an optimal strategy of this procedure.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: D.W.A., C.H.P., K.B.C. Data acquisition: D.W.A., S.H.M., S.W.P., W.H.P., C.N.P., B.K.S., T.J.S., E.S.L., Y.N.L., Y.S.L., J.M.L., T.J.J., H.J.K., S.B.Y., K.H.C., J.S.P. Data analysis and interpretation: D.W.A., H.K.C., C.H.P., D.W.L. Drafting the manuscript: D.W.A. Critical reversion of the manuscript for important intellectual content: C.H.P., K.B.C. Statistical analysis: D.W.A. Study supervision: C.H.P. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220131.

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