TECHNICAL REVIEW

EUS-guided tissue acquisition: an evidence-based approach (with videos)

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EUS-guided tissue acquisition (EUS-TA) by fine needle aspiration (FNA) (EUS-FNA) and fine-needle biopsy (EUS-FNB) have become integral to the diagnosis and staging of GI and other malignancies. The common indications for EUS-TA include diagnosis and staging of pancreaticobiliary, esophageal, gastric, and rectal malignancies and lung cancer along with evaluation of GI subepithelial lesions and lymphadenopathy. In addition, EUS-TA can be used for numerous nonmalignant processes and mediastinal lesions such as tuberculosis, sarcoidosis, abscesses, and cysts.[1,2] The ideal EUS-TA technique needs to be safe and accurate and achieve a high diagnostic yield.

The key relevant outcomes of EUS-TA include specimen adequacy, diagnostic yield, accuracy, and adverse events. There are several limitations and technical challenges associated with this procedure. Low diagnostic yield (false-negative diagnosis) is the most important pitfall, with the potential to negatively impact patient outcomes by inappropriate patient care. A recent review reported a false-negative diagnoses rate of 4% to 45% in solid pancreatic masses, 21% to 53% in pancreatic cystic neoplasms, and 6% to 14% in lymph nodes.[3] This usually is as a result of sampling errors (related to improper EUS-TA, errors in image recognition, experience of the endosonographer, and lesion characteristics).[3-5] Several variables have been studied to optimize outcomes associated with EUS-TA. These include performance of EUS-FNA versus FNB, needle gauge, use of a stylet and suction, number of passes, sampling technique, presence of an on-site cytopathology evaluation (OCE) during the procedure, and the skill and experience of the endosonographer and the cytopathologist.

Abbreviations: AET, advanced endoscopy trainee; CEA, carcinoembryonic antigen; ETP, Echo Tip Procore; EUS-FNA, EUS-guided FNA; EUS-FNB, EUS-guided fine-needle biopsy; EUS-TA, EUS-guided tissue acquisition; OCE, on-site cytopathology evaluation; RCT, randomized controlled trial.

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The aims of this technical review were as follows: (1) perform a systematic review of variables that impact outcomes (diagnostic yield/accuracy and adverse events) related to EUS-TA and (2) provide evidence-based recommendations regarding techniques related to EUS-TA.

METHODS

Search strategy

This review encompasses the available scientific literature on the topic identified in Medline and PubMed (January 1992 to March 2014) and abstracts from national meetings (2013-2014), with search terms that included *endoscopic ultrasound, endoscopic ultrasonography, endosonographer, fine-needle aspiration, fine-needle biopsy, core biopsy, histology, needle gauge, suction, stylet, experience, learning curves, cytopathologist, cancer, malignancy, diagnostic yield, accuracy,* and *adverse events.*

Eligible studies

Clinical trials or observational studies that described the efficacy and effectiveness of EUS-FNA and EUS-FNB with regard to lesion site (pancreas, lymph nodes, subepithelial lesions, pancreatic cystic lesions, others) and technique (needle gauge, suction, stylet, on-site cytopathologist) were eligible for inclusion in this review. Only studies that reported outcomes in at least 20 patients were included.

Outcome measures and data extraction

Studies reporting on the impact of variables related to the efficacy of EUS-FNA and FNB had to provide information on at least one of the following measures: (1) diagnostic yield, (2) specimen adequacy, (3) accuracy for the diagnosis of malignancy, and (4) adverse events related to the procedure. For the purpose of this review, *diagnostic yield* is defined as a percentage of the lesions sampled for which a tissue diagnosis is obtained. *Specimen adequacy* is defined as the percentage of lesions sampled in which the obtained material is representative of the target site and sufficient for diagnosis. *Accuracy* is defined as the percentage of lesions sampled by EUS-TA techniques that correspond to the final diagnosis at surgical histopathology or clinical follow-up (at least 6 months).

TABLE 1. Strength of recommendation with the use of the GRADE classification and implications for patients, clinicians, and policy makers

Strength of recommendation	Recommendation
Strong	
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator
For policy makers	The recommendation can be adapted as policy in most situations
Weak	
For patients	The majority of individuals in this situation would want the suggested course of action but many would not. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences
For clinicians	Examine the evidence or a summary of the evidence individually
For policy makers	Policy making will require substantial debates and involvement of many stakeholders

Other than the outcome measures stated, additional relevant information regarding study design, patient characteristics, and relevant EUS-TA technique details were collected. Titles and abstracts of all studies identified by the search strategy and full articles for all potentially relevant studies were independently screened by at least 2 authors. Only articles published in the English language were included. The full text of these reports was assessed independently for eligibility. Any disagreements between the two assessors were resolved by discussion with the third assessor. A spreadsheet was developed to extract relevant information from each included study and was maintained in an Excel spreadsheet.

Level of evidence

The recommendations in this technical review are intended for use by healthcare providers and apply to adult patients. These recommendations are not intended to replace clinical judgment but rather to provide general guidelines applicable to the majority of patients. Clinicians need to integrate recommendations with their own clinical judgment, and with individual patient circumstances, values, and preferences. The recommendations are intended to be flexible, in contrast to standards of care, which are inflexible policies designed to be followed in every case. Specific recommendations are based on relevant published information. The quality of evidence and strength of recommendations have been assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Tables 1-2), a system that has been adopted by multiple national and international societies. The GRADE system is based on a sequential assessment of quality and level of evidence (high—randomized controlled trials [RCTs], moderate—downgraded RCTs or upgraded observational studies, low—well-done observational studies with control groups, very low—case reports or case series), followed by assessment of the balance between benefits versus downsides (harms, burden, and costs) and subsequent judgment about the strength of recommendation. This technical review is not intended to be a guideline document and should be distinguished from strict methodologically fixed guidelines.

VARIABLES AND OUTCOMES DURING EUS-TA

EUS-FNA

A variety of EUS-TA needles are available in the United States and are summarized in Table 3.

Use of a stylet

All commercially available EUS-FNA needle systems include a removable stylet. It was hypothesized that the use of a stylet during EUS-FNA prevents clogging of the needle lumen by GI wall tissue as the needle traverses this to reach the target lesion, which could limit the ability to aspirate cells.[6] Based on this theoretical belief of improving specimen quality, the use of a stylet is routine practice for some endosonographers during EUS-FNA. Several studies have evaluated the role of a stylet during EUS-FNA, assessing endpoints of specimen quality (cytologic characteristics such as adequacy, cellularity, contamination, amount of blood) and diagnostic yield of malignancy (Table 4).[6-10] Results of all available trials showed no difference in the diagnostic yield of malignancy or adequacy between the groups with and without use of a stylet.

TABLE 2. Quality and level of evidence—definitions and determinants

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
	Underlying methodology: randomized controlled trials
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
	Underlying methodology: downgraded randomized controlled trials or upgraded observational studies
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
	Underlying methodology: well-done observational studies with control groups
Very low	Any estimate of effect is very uncertain.
	Underlying methodology: case reports or case series

TABLE 3. Commercially available EUS-guided tissue acquisition needles in the United States

Manufacturer	Device name	Available sizes (gauge)
Boston Scientific	Expect	19, 22, 25
	Expect Flex	19
	Expect SL	19, 22, 25
	Expect SL Flex	19
ConMed Corporation	ClearView	19, 22, 25
Cook Medical	Echo Tip	22
	Echo Tip Ultra	19, 22, 25
	Echo Tip ProCore	19, 22, 25
	Quick-Core	19
Covidien GI Solutions	BNX FNA system	19, 22, 25
Olympus	EZ Shot	22
	EZ Shot 2	19, 22, 25
	EZ Shot 2 with side port	22

There are limited data evaluating the ideal technique for expressing EUS-FNA aspirates. A recent RCT evaluated whether expressing aspirates from the needle by reinserting the stylet was more effective than by air flushing. This study showed that bloodiness was in fact greater in the group of samples in which the stylet was reinserted to express aspirates compared with the group that underwent air flushing (odds ratio [OR] 1.16; 95% confidence interval [CI], 1.03-1.3). There were no differences between groups with regard to the number of diagnostic samples, overall accuracy, cellularity, and air-drying artifact.[11] Air flushing in a slow, controlled fashion appears to be superior to reinsertion of a stylet to express EUS-FNA aspirates. The traditional technique of reinserting the stylet to express EUS-FNA aspirates may be required only in cases in which the aspirates cannot be expelled because of clotting or drying. In addition, the use of a stylet during EUS-FNA is labor intensive, increases the procedure time because the stylet needs to be withdrawn after puncturing the lesion and then carefully reinserted through the needle before each pass, and increases the risk of accidental needle stick injuries.[12]

The routine use of a stylet during EUS-FNA to improve diagnostic yield of malignancy and specimen quality is not recommended. The quality of evidence for this recommendation is high, and the strength of recommendation is strong.

Use of suction

The role of suction during EUS-FNA is unclear. The proposed mechanism for the use of suction with a 5 to 10 cc syringe to improve the diagnostic yield during EUS-FNA is by holding the tissue against the cutting edge of the needle as it is moved through the target lesion and drawing up cells. Some endosonographers perform EUS-FNA without suction to achieve the same result. The capillary method involves slow withdrawal of the stylet after the needle has been passed into the lesion (Video 1, available online at www.giejournal.org). This creates negative pressure (suction) while the endosonographer moves the needle back and forth in the lesion. Although some endosonographers routinely use suction during EUS-FNA or tailor the use of suction based on OCE, others have abandoned the use of suction during

TABLE 4. Summary of studies evaluating the role of a stylet during EUS-guided FNA of solid lesions

Author	Study design	No. of patients/lesions	EUS-guided FNA with stylet	EUS-FNA no stylet	*P* value
Sahai[7]	RCT	111/135			
Adequate specimens			75%	87%	.013
Bloodiness			75%	52%	< .0001
DY of malignancy			87%	83%	NS
Rastogi[10]	RCT	101/118			
Adequate specimens			57%	62%	.26
Bloodiness			17%	14%	.61
DY of malignancy			23%	28%	.29
Wani[8]	Retrospective	162/228			
Adequate specimens			94.3%	91%	.45
Bloodiness			40.6%	45.9%	.42
DY of malignancy			38.7%	36.1%	.49
Wani[6]	RCT	100/100			
Adequate specimens			68.4%	71.6%	.34
Bloodiness			25.1%	24.4%	.6
DY of malignancy			40%	34.2%	.2
Gimeno-Garcia[9]	Retrospective	3078/3364			
Overall yield of malignancy			58.7%	61.5%	NS
Pancreas					
Adequacy			97.7%	97.8%	.88
DY of malignancy			84.3%	88.8%	NS
Lymph node					
Adequacy			95.9%	96.2%	.8
DY of malignancy			83.1%	81.6%	NS

RCT, Randomized controlled trial; *DY,* diagnostic yield; *NS,* not significant.

EUS-FNA of solid lesions and reported a high diagnostic yield with this technique.[13]

The following studies evaluated the role of suction during EUS-FNA (pancreatic masses, lymph nodes, others) (Table 5). A recent RCT by Lee et al[11] compared diagnostic yield and cytologic characteristics during EUS-FNA of pancreatic masses with and without suction. A total of 81 patients and 324 EUS-FNA passes were included in the final analysis. Samples in the suction group were associated with a higher diagnostic yield (72.8% vs 58.6%; $P = .001$), cellularity (OR 2.12; 95% CI, 1.3-3.3; $P < .001$), and bloodiness (OR 1.46; 95% CI, 1.2-1.6; $P < .001$) compared with samples obtained without suction. Overall, samples in the suction group had higher accuracy (82.4% vs 72.1%; $P = .005$) compared with those obtained without suction.[11] Puri et al[14] compared EUS-FNA with and without suction in an RCT that included 52 patients with solid lesions (19% pancreatic lesions, 66% lymph nodes, 15% adrenal lesions). The use of suction was associated with a higher sensitivity (85.7% vs 66.7%). On the other hand, another study showed that there was no difference in quality and diagnostic accuracy of specimens obtained with and without suction.[15] An RCT that evaluated the effect of suction in 43 patients undergoing EUS-FNA of lymphadenopathy showed that the use of suction had no impact on the diagnostic yield and was in fact associated with excessive bloodiness (OR 4.7; 95% CI, 1.9-11.2).[16] Similarly, another RCT demonstrated no difference in specimen quality and diagnostic yield of malignancy in 138 patients undergoing EUS-FNA with and without suction.[17] A recent prospective RCT compared the standard suction technique to the capillary

TABLE 5. Summary of randomized controlled trials evaluating the role of suction during EUS-FNA of solid lesions

Author	Study design	No. of patients/lesions	EUS-FNA with suction	EUS-FNA without suction	*P* value
Puri[14]	RCT	52/52			
		19% pancreas			
		66% lymph nodes			
Adequate specimens			100%	100%	NS
Bloodiness			76.9%	88.5%	.14
DY of malignancy			85.7%	66.7%	.05
Wallace[16]	RCT	43/46			
Adequate specimens			Higher	NA	.01 (OR 2.8; 95% CI, 1.2-6.6)
Bloodiness			Higher	NA	.0004 (OR 4.7; 95% CI, 1.9-11.2)
DY of malignancy			No difference		.19 (OR 1.5; 95% CI, 0.8-2.8)
Lee[11]	RCT	81/81			
		Pancreas only			
Adequate specimens			72.8%	58.6%	.001
Bloodiness			6.2%	0.6%	< .001
DY of malignancy			82.4%	72.1%	.005

EUS-FNA, EUS-guided FNA; *RCT,* randomized controlled trial; *NS,* not significant; *DY,* diagnostic yield; *NA,* not available; OR, odds ratio; *CI,* confidence interval.

technique by using a 25-gauge needle among 65 patients undergoing EUS-FNA (alternating techniques until adequate specimen noted on OCE). Overall, the capillary technique was superior to standard suction in cellular quality and diagnostic yield. Subgroup analysis showed that these differences were significant for pancreatic and liver masses only, with no difference in lymph nodes and other lesions.[18] The wet suction EUS-FNA technique is a novel one that involves flushing the needle with 5 mL of saline solution to replace the column of air in the EUS-FNA needle with saline solution. This technique was shown to be superior to the standard EUS-FNA technique with suction with regard to cellularity and diagnostic yield in an RCT that involved sampling of 117 lesions.[19] Another recent RCT showed that high negative pressure suction by using a 60-mL syringe was superior to suction applied by using a 10-mL syringe with regard to the diagnostic yield in patients with pancreatic masses undergoing EUS-TA.[20] These results need to be validated in future trials.

The use of suction should be considered during EUS-FNA of pancreatic masses, based on available evidence. However, suction should not be used during EUS-FNA of lymph nodes because it increases bloodiness of specimens obtained and has no impact on the overall diagnostic yield. The quality of evidence for this recommendation is moderate, and the strength of recommendation is weak.

Needle gauge

EUS-FNA can be performed by using 25-gauge, 22-gauge, or 19-gauge needles. Needle size has been investigated extensively as a predictor of cytologic adequacy and diagnostic yield of malignancy. There are several factors that determine the choice of needle gauge—approach (transesophageal, transgastric, or transduodenal), type, and location of the lesion. Although the 22-gauge needle was considered as the default needle by many endosonographers, a recent change in this trend has been noted among many endosonographers, who use 25-gauge needles increasingly.[21]

Several studies have assessed the performance characteristics of 22-gauge and 25-gauge needles for sampling pancreatic mass lesions.[22-31] Most studies, (specifically RCTs) have demonstrated no difference in diagnostic yield of malignancy between groups, and this may be related to lack of adequate sample size of individual studies to achieve statistical significance independently (Table 6). A recent meta-analysis of 8 studies that included surgical histology or at least 6 months of clinical follow-up compared the diagnostic accuracy of EUS-FNA for pancreatic masses by using 22-gauge and 25-gauge needles. This study involved 1292 patients undergoing EUS-FNA (22-gauge = 799 and 25-gauge = 565 patients) and showed that a 25-gauge needle was more sensitive than a 22-gauge needle for diagnosing pancreatic malignancy (pooled sensitivity, 25-gauge 0.93 [95% CI, 0.91-0.96]

TABLE 6. Summary of studies comparing DY of malignancy between 22-gauge and 25-gauge needles during EUS-FNA of pancreatic masses

Author	Study design	No. of patients 22 g/25 g	Sensitivity (95% CI) 22 g	Sensitivity (95% CI) 25 g
Imazu[22]	Prospective	12/12	0.83 (0.36-1.00)	1.00 (0.54-1.00)
Lee[23]	Prospective	10/10	1.00 (0.72-1.00)	1.00 (0.72-1.00)
Siddiqui[24]	RCT	64/67	0.88 (0.77-0.94)	0.96 (0.87-0.99)
Yusuf[25]	Retrospective	540/302	0.84 (0.80-0.88)	0.92 (0.87-0.95)
Siddiqui[26]	Retrospective	26/17	0.85 (0.62-0.97)	0.91 (0.59-1.00)
Camellini[27]	RCT	43/41	0.86 (0.70-0.95)	0.89 (0.75-0.97)
Uehara[28]	Retrospective	54/66	0.88 (0.74-0.96)	1.00 (0.91-1.00)
Fabbri[30]	Prospective	50/50	0.85 (0.71-0.94)	0.94 (0.82-0.99)

DY, Diagnostic yield; *EUS-FNA,* EUS-guided FNA; *g,* gauge; *CI,* confidence interval; *RCT,* randomized controlled trial.

vs 22-gauge 0.85 [95% CI, 0.82-0.88]; $P = .0003$).[32] Similar results were reported in another meta-analysis for the endpoints of specimen adequacy and overall sensitivity.[33] There are limited data comparing the diagnostic yield between the two needles during EUS-FNA of lymph nodes, subepithelial lesions, and other miscellaneous lesions.[22,27] A single prospective study showed no difference in the diagnostic yield of malignancy between the two needles in subepithelial lesions (22-gauge 80% vs 25-gauge 60%; P = not significant [NS]).[22] Fewer studies have compared 19-gauge with 22-gauge/25-gauge needles.[29,34-36] Data from RCTs suggest that there is no incremental diagnostic yield by using the 19-gauge needle compared with 22-gauge/25-gauge.[34,35,37] Lower technical success rates associated with the 19-gauge, especially via the transduodenal route, have precluded uniform adoption of this needle for EUS-FNA of pancreatic masses.

The use of a 25-gauge needle is associated with a higher diagnostic yield compared with a 22-gauge needle in patients undergoing EUS-FNA of pancreatic masses. The quality of evidence for this recommendation is moderate, and the strength of recommendation is weak.

The role of OCE

Obtaining an adequate sample is fundamental to making an accurate diagnosis with EUS-TA and requires a team effort between the endosonographer and cytopathologist. The goal of immediate OCE (Video 2, available online at www.giejournal.org) is to provide real-time feedback about the content and adequacy of a specimen in order to make the most accurate diagnosis, with the minimum number of passes, thus maximizing the efficiency of the procedure. Another potential advantage of OCE is high-quality specimen preparation and the adequate triage of limited specimens for ancillary tests such as immunohistochemistry, flow cytometry, culture, and cytogenetics or molecular studies.[38]

Initial observational data suggested that the absence of OCE was associated with a 10% to 15% reduction in definite diagnosis and number of adequate specimens (Table 7).[39-45] Klapman et al[40] compared the EUS-FNA cytology results obtained by the same endosonographer at two centers, one with and the other without OCE. The diagnostic yield with a cytopathologist (positive for malignancy) was higher in the group with a cytopathologist present (58% vs 41.5%; $P = .006$), with a lower number of inadequate specimens (9% vs 20%; $P = .035$). However, comparing these two endpoints specifically for pancreatic masses, there was no difference in the diagnostic yield (56% vs 49%) or number of inadequate specimens (13% vs 15.5%).[40] Similarly, in another retrospective study, Iglesias-Garcia et al[43] showed that the presence of OCE was associated with a significantly lower number of passes, lower number of inadequate samples, higher diagnostic yield, and higher accuracy for malignancy. On the other hand, investigators have reported comparable diagnostic yield of EUS-FNA, especially at centers where OCE was not available.[45-49] In a large series of patients undergoing EUS-FNA of solid pancreatic masses without OCE, a diagnostic accuracy of 97% was reported, with 1 to 4 passes.[46] Results from 3 meta-analyses that evaluated the diagnostic accuracy with regard to the role of OCE are conflicting, with 1 reporting improved adequacy rates in centers with low adequacy rates (<90%).[50-52]

The only data from RCTs evaluating the clinical impact of OCE on the diagnostic yield of malignancy during EUS-FNA of pancreatic masses were provided in a recent multicenter prospective RCT. Wani et al[53] compared the diagnostic yield of malignancy and proportion of inadequate specimens between patients (n = 241) undergoing EUS-FNA of pancreatic masses with (n = 121) and without (n = 120) OCE. There was no difference between groups in the diagnostic yield of malignancy (with OCE 75.2% vs without OCE 71.7%; $P = .53$) and proportion of

TABLE 7. Summary of studies evaluating the clinical impact of on-site cytopathology evaluation during EUS-FNA

Author	Study design	No. of patients	Site	With OCE	Without OCE	*P* value
Klapman[40]	Retrospective	195	Pancreas/LN/liver/other			
Overall						
DY				58%	41.5%	.006
Inadequate specimens				9%	20%	.03
No. of passes, mean				2.46	2.26	.49
Pancreas						
DY				56%	49%	NS
Inadequate specimens				13%	15.5%	NS
Cleveland[42]	Retrospective	247 276	Pancreas LN			
Inadequate specimens						
Pancreas				1%	0%	1.00
LN				4%	10%	.002
Iglesias-Garcia[43]	Retrospective	182	Pancreas			
DY				96.2%	78.2%	.002
Inadequate specimens				1%	12.6%	.002
No. of passes, mean				2	3.5	< .001
Overall accuracy				96.8%	86.2%	.013
Cermak[48]	Retrospective	381	Pancreas			
Inadequate specimens				25.8%	24.3%	.75
Ecka[44]	Retrospective	375	Pancreas/LN/others			
DY				97.7%	64.8%	.001
Inadequate specimens				5.6%	29.3%	.001
No. of passes, mean				3.24	3.12	.30
Wani[53]	RCT	241	Pancreas			
DY				75.2%	71.7%	.53
Inadequate specimens				9.9%	13.3%	.4
No. of passes, mean				3.7	7	< .001

EUS-FNA, EUS-guided FNA; *OCE,* on-site cytopathology; *LN,* lymph node; *DY,* diagnostic yield; *NS,* not significant; *RCT,* randomized controlled trial.

inadequate specimens (9.9% vs 13.3%; $P = .4$). Procedures with OCE had significantly lower numbers of passes (3.7 vs 7; $P < .001$). There were no significant differences between groups with regard to overall procedure time, adverse events, number of repeat procedures, and cytologic characteristics of specimens.

Conflicting data regarding clinical impact, clinical demands, and lack of proper billing of the procedure time along with poor reimbursement all have contributed to the practice of OCE not being universal throughout all centers performing EUS. The role of real-time dynamic telecytopathology has been explored in some centers.[54-56]

The use of OCE does not impact the diagnostic yield of malignancy and the number of inadequate specimens, based on available evidence. An on-site cytopathologist may have a role during training and in centers with a low adequacy rate (<90%). The quality of evidence for this recommendation is moderate, and the strength of recommendation is strong.

Experience and training of the endosonographer and cytopathologist

EUS is operator dependent, and training in EUS requires the development of technical and cognitive skills beyond that required for standard endoscopic procedures. It is intuitive that the success of EUS imaging and EUS-TA, and quality of EUS in provision of patient care is directly proportional to the training, skill, and experience of the endosonographer. With the establishment of a number of training programs in therapeutic endoscopy, standardization of the performance of EUS and definition of competency is of paramount importance. The American Society for Gastrointestinal Endoscopy recommends a minimum of 150 total supervised procedures, 75 of which have pancreatobiliary indications, and 50 cases of FNA (25 of which are pancreatic FNA) before competency can be determined, based on expert opinion.[57] Similar guidelines have been proposed by other gastroenterology societies.[58,59] However, these guidelines have not been validated. These recommendations do not account for the different rates at which people learn, and, in fact, many experts believe that the majority of trainees will require double the number of proposed procedures to achieve competency in EUS.[60-62]

In a prospective pilot study, Wani et al[63] used a novel comprehensive EUS competency tool and defined learning curves in EUS among 5 advanced endoscopy trainees (AETs) by using cumulative sum analysis. Two AETs crossed the threshold for acceptable performance at case numbers 255 and 295, 2 AETs showed a trend toward acceptable performance, whereas one demonstrated the need for ongoing training. These results demonstrate substantial variability in achieving competency and a consistent need for more supervision in all AETs.[63] A recent, large, multicenter consortium evaluated learning curves and competency in EUS among 17 AETs at 15 centers. Only 2 AETs crossed the threshold for acceptable performance at cases 225 and 245, respectively, 2 AETs showed a trend toward acceptable performance, and 8 AETs demonstrated the need for ongoing training and observation. Results from this study showed that a specific case load does not ensure competency in EUS and suggests that 225 cases should be the minimum caseload in EUS training programs.[64] There are limited data with regard to learning curves outside of formal advanced endoscopy training programs, specific disease states, and for EUS-TA techniques.[65-70] There are limited data demonstrating learning curves and impact of experience on diagnostic yield of malignancy among cytopathologists.[71]

Available data suggest that the current recommendations for procedure numbers during advanced endoscopy training may be inadequate to achieve competency in EUS, and emphasis needs to be shifted away from the number of procedures performed to performance metrics with defined and validated competency thresholds of performance. The quality of evidence for this recommendation is low, and the strength of recommendation is weak.

EUS-FNB

Although the diagnostic yield of EUS-FNA for pancreatic masses remains high, it continues to be suboptimal for non-pancreatic lesions.[67,72] Technical limitations include availability of cytologic expertise, scant cellularity of specimens, and inability to demonstrate lesion morphology and architecture.[73] Histologic specimens or core biopsies may (1) improve assessment of tissue architecture, (2) provide a more representative sample of the lesion, (3) allow for immunohistochemistry or vital stains, and (4) potentially eliminate the need for OCE, resulting in significant cost savings.

Methods to procure a histologic specimen

Core biopsies with FNA needles. Multiple studies, prospective cohort and retrospective studies only, have attempted to obtain core samples by using existing FNA needles with various degrees of diagnostic yield by using both 19-gauge and 22-gauge needles (Supplemental Table 1, available online at www.giejournal.org).[36,74-87] The overall specimen adequacy for core samples ranged from 27% to 100%, whereas the final diagnostic yield ranged from 43% to 98%. There is a trend toward higher diagnostic yield with the 19-gauge needle, but this is limited by difficult transduodenal access.

Core biopsies with use of the Tru-cut biopsy technique. The Quick-Core (Cook Medical, Limerick, Ireland) was the first dedicated tru-cut core biopsy needle. This 19-gauge needle uses a traditional spring-loaded mechanism as in previous percutaneous core needles and has the ability to obtain up to an 18-mm tissue core. There has been one RCT comparing Tru-cut to EUS-FNA, which did not demonstrate an increase in yield.[88] The remainder of the studies are prospective cohort studies or retrospective series, with diagnostic yields ranging from 52% to 95% (Supplemental Table 2, available online at www.giejournal.org).[29,36,88-109] Despite the novel aspects of this needle, it was significantly limited by (1) a 19-gauge-only platform, (2) lack of flexibility, (3) failure of the spring-loading charging mechanism, and (4) inability to reliably obtain tissue across the duodenum, with a failure rate up to 40%. As a result, the Quick-Core needle did not improve diagnostic yield significantly over FNA.

Core biopsies with use of a high-definition EUS-FNB needle. More recently, a newer generation of high-definition core biopsy needles was released (Echo Tip Procore [ETP], Cook Medical, Limerick, Ireland). The ETP needle is available in 19-gauge, 22-gauge, and 25-gauge sizes. The ETP is a nitinol needle with a reverse cutting bevel designed for procurement of a core specimen. The flexibility of this needle allows for sampling without difficulty from the stomach or duodenum. Multiple prospective cohort studies have shown a significant improvement in diagnostic yield with ETP, whereas multiple retrospective series have shown varying results

TABLE 8. Literature to date that used the Procore needle for EUS-FNB

Author	Study design	No. of patients	Cohort	Needle gauge FNB	Suction or capillary technique	SA FNB (%)	DY FNB (%)	DY FNA (%)	*P* value
Iglesias-Garcia[43]	Prospective cohort (MC)	114	P and NP	19	S	89	86	n/a	n/a
Bang[130]	RCT	28	P	22	S	89	80	67	.66
Larghi[119]	Prospective cohort (MC)	61	P	22	S	89	89	n/a	n/a
Hucl[277]	Prospective cohort	144	P and NP	22	S	86	86	87	.73
Iwashita[118]	Retrospective	38	P	25	C	n/a	86/96	n/a	n/a
Krishnan[121]	Retrospective	60	P and NP	19/22/25	C	58	83	62	n/a
Nagula[201]	RCT (MC)	102	P and NP	22/25	n/a		87	89	.81
Korenblit[284]	RCT	119	P and NP	22	n/a	n/a	80	63	.006
Vanbiervliet[285]	RCT (CO)	80	P	22	n/a	n/a	84	88	NS
Strand[286]	Prospective cohort	32	P	22	n/a	n/a	28	93	< .001
Ramay[287]	Retrospective	24	NP	22	n/a	n/a	100	88	NS
Choi[288]	Retrospective	80	P	22	n/a	n/a	90	62	< .005
Singh[289]	Retrospective	40	P	22	n/a	n/a	100	93	NS
De La Mora-Levy[290]	Retrospective	103	NP	22	n/a	n/a	87	82	NS
Aadam[117]	RCT (MC)	128	P and NP	19/22/25	C	56	89	69	.009

EUS-FNB, EUS-guided fine-needle biopsy; *FNB,* fine-needle biopsy; *SA,* specimen adequacy; *DY,* diagnostic yield; *P/NP,* pancreas/nonpancreas; *S,* suction; *n/a,* not available; *MC,* multicenter; *RCT,* randomized controlled trial; *C,* capillary.

(Table 8). To date, 10 RCTs have been performed comparing FNA and FNB, with 6 showing no significant difference and 4 demonstrating higher diagnostic yields with the ETP needle.[110,111-115] All but one RCT that studied pancreatic masses alone showed no difference by using the ETP needle. In a recent multicenter cross-over design RCT of 128 patients, the overall diagnostic yield was significantly greater for FNB by using the ETP needle compared with FNA. This difference was limited to nonpancreatic lesions (86% vs 56%; $P = .02$), because there was no difference in diagnostic yield in pancreatic lesions. The differences in yield were independent of lesion size, number of passes, use of suction or stylet, and needle gauge. Kim et al[115] similarly demonstrated a significantly higher yield of EUS-FNB for gastric subepithelial masses (75% vs 20%; $P < .010$). Finally, another recent multicenter RCT compared the ETP needle to the previous generation QuickCore needle and showed that the ETP needle had a higher frequency of diagnostic histology (85% vs 57%; $P = .006$).[116]

EUS-FNB can be effective as a salvage technique when FNA results in inadequate specimens. A recent RCT demonstrated a 96% salvage effect of EUS-FNB when FNA was inadequate.[117]

The high-definition FNB needle (ETP) is highly effective for acquisition of core specimens. EUS-FNB should be considered first-line for tissue sampling of nonpancreatic mass lesions, as a salvage technique after inadequate FNA samples, and for lesions requiring immunohistochemistry. The quality of the evidence for this recommendation is high, and the recommendation is strong.

Techniques for tissue procurement and specimen handling

Impact of suction, stylet, or needle gauge. There are currently no studies comparing use of suction, stylet, or different needle gauges and yield of EUS-FNB.

Use of the capillary technique

The optimal method of tissue procurement for EUS-FNB is unclear. Iwashita et al[118] studied the "slow-pull" or "capillary technique" by using the 25-gauge ETP needle and demonstrated a final diagnostic accuracy of 96%. The diagnostic yield in a recent RCT that used the capillary method was 96.5%,[117] compared with 88.5% (95% CI, 82-97)[119] in a previous multicenter study in which standard suction was used.

The routine use of the capillary technique is preferable to standard suction and should be used for EUS-FNB for histologic specimens. The quality of the evidence for this

recommendation is moderate, and the strength of recommendation is weak.

Impact of OCE on EUS-FNB

The impact of OCE on EUS-FNB has not been evaluated as extensively for FNA.[104] A retrospective study of EUS-FNB by using the ETP needle demonstrated a significantly greater diagnostic yield with OCE (97.2%; 95% CI, 91.7-99.4) than without OCE (84.7%; 95% CI, 76.7-90.3; $P = .002$).[120] Krishnan et al[121] studied 60 consecutive patients who underwent EUS-FNB with the ETP needle and found a specimen adequacy of 58% (95% CI, 45.1-71.2) and final diagnostic yield of 83% (95% CI, 71.9-91.5). Although the specificity of OCE for FNB was 100%, the sensitivity was only 65%, suggesting that OCE might not be necessary for EUS-FNB, given that the impression of an inadequate specimen on OCE appears to be of limited value. Another retrospective study compared 43 patients undergoing EUS-FNB without OCE to a matched cohort of patients who underwent EUS-FNA with or without FNB with OCE found no difference between groups, with a final diagnostic accuracy of 83.7% (95% CI, 72.7-94.7) and 84.9% (95% CI, 75.3-94.5; P = NS), respectively.[122] A more recent RCT comparing EUS-FNA and FNB also demonstrated on-site adequacy for EUS-FNB of 81%, whereas the overall diagnostic yield was 89%.[117] These current data suggest that OCE has no significant impact on the final diagnostic yield of EUS-FNB.

The routine use of OCE for EUS-FNB, based on available evidence, does not improve diagnostic yield. The quality of the evidence for this recommendation is moderate, and the strength of the recommendation is weak.

Specimen handling

The appropriate handling of a core specimen is essential to ensure optimal diagnostic yield (Video 3, available online at www.giejournal.org). If OCE is not used, the specimen should be expelled with air, stylet, or water flush directly into 10% formalin. If OCE is used, the specimen should be expelled onto the slide in full. The presence or absence of fragmented tissue or a visible core should be documented. If the tissue acquired is a visible core, standard touch preparation is used. The core is slowly and carefully touched to the slide and then placed into a specimen container with formalin. In the event that only fragmented or scant tissue is obtained, the tissue is placed on a slide, and a second slide should be used to gently crush the tissue and prepare an air-dried crush preparation. Any residual tissue should be fixed in 10% formalin for subsequent hematoxylin and eosin staining.

DIAGNOSTIC YIELD OF EUS-TA BASED ON LESION TYPE

Solid pancreatic lesions

Solid pancreatic lesions (Video 4, available online at www.giejournal.org) are typically the most commonly targeted site for EUS-TA.[123] Multiple studies, including 5 meta-analyses, have reported the utility of EUS-FNA for identifying malignant pancreatic lesions (Supplemental Table 3, available online at www.giejournal.org).[32,50,51,124,125] The reported pooled sensitivity from these meta-analyses has ranged from 85% to 89%. The diagnostic accuracy appears to be higher in prospective, multicenter studies, with an improved sensitivity for detecting malignancy observed in more recently performed studies.[50,125]

Relevant variables related to EUS-TA in solid pancreatic masses other than those discussed earlier are highlighted in this section. The ability to detect malignancy is reduced in patients with underlying chronic pancreatitis because of the difficulty in identifying a discrete mass lesion in this setting.[126,127] One study of 282 patients found a reduction in sensitivity for EUS-FNA to diagnose malignancy in patients with chronic pancreatitis compared with those without chronic pancreatitis (73.9% vs 91.3%; $P = .02$).[127] In addition, more passes were required (median pass number 5 vs 2; $P < .001$) to establish a diagnosis. The presence of an indwelling biliary stent, whether plastic or metal, does not appear to influence diagnostic yield or result in technical difficulty in patients undergoing EUS-FNA of solid pancreatic lesions.[128] A specific method of tissue acquisition, the use of a "fanning" motion of the needle in which multiple areas of the lesion are sampled during each pass, was superior to sampling a single region of the lesion per pass in an RCT.[129] This study found that a significantly higher percentage of patients (57.7% vs 85.7%; $P = .02$) were given a diagnosis on the first pass when the fanning technique was used, compared with standard to-and-fro needle motion confined to a single region of the lesion. The use of this method also significantly reduced the number of passes required to achieve a diagnosis.[50,51]

In the absence of OCE, an important consideration is the appropriate number of FNA passes needed to obtain an acceptable diagnostic yield. An initial study of 33 pancreatic lesions suggested that obtaining 7 passes was necessary to achieve 83% sensitivity for malignancy in solid pancreatic lesions without OCE and noted a 16.7% first-pass sensitivity. However, several recent studies have demonstrated that a diagnostic yield for malignancy of above 85% can be achieved in solid pancreatic lesions with ≤ 3 passes.[118,129,130] As noted, FNB does not improve the diagnostic yield of malignancy compared with FNA.[36,91,118,130,131] However, the ability to obtain histologic specimens can aid in diagnosing benign conditions such as autoimmune or chronic pancreatitis, in which the assessment of tissue architecture is necessary to achieve a diagnosis.[99,118,119,132] In addition, EUS-FNB should be considered in lesions with prior nondiagnostic EUS.

Although most solid pancreatic lesions are ductal adenocarcinomas, additional diagnoses include pancreatic neuroendocrine tumors, solid pseudopapillary epithelial neoplasms, lymphomas, and metastatic lesions. To date, there are no prospective studies comparing the diagnostic yield of EUS-FNA

for these lesions with that of ductal adenocarcinoma. However, several large cases series have shown the utility of EUS-FNA in diagnosing pancreatic neuroendocrine tumors, with diagnostic yields of up to 90.1% having been reported.[133-136] A variety of lesions metastatic to the pancreas have been diagnosed successfully by EUS-FNA and include melanoma as well as renal, breast, thyroid, and lung cancers.[137-139]

Cystic lesions

EUS-FNA is predominantly used to characterize cystic pancreatic lesions and occasionally to evaluate mediastinal and foregut cysts. However, although cytology can accurately diagnose many foregut and mediastinal cysts,[140,141] concerns regarding needle puncture leading to cyst infection coupled with the uncertain incremental value of cytology over EUS morphology alone have led to declining use of EUS-FNA in the assessment of these lesions.[142-145] In contrast, with pancreatic cystic lesions being identified in 2.5% to 10% of patients undergoing abdominal imaging,[146] EUS-FNA has been used increasingly to obtain fluid and tissue to aid in their characterization. Obtained fluid is most commonly sent for analysis of carcinoembryonic antigen (CEA), amylase levels, and cytology. The presence of a CEA level of $\geq$192 ng/mL has been associated with a sensitivity of 73% and a specificity of 84% for diagnosing mucinous cystic lesions, whereas elevated amylase levels suggest pancreatic fluid in communication with the main pancreatic duct.[147] However, a recent multicenter study of 1861 patients with cystic pancreatic lesions who underwent EUS-FNA with a criterion standard of confirmed surgical pathology or malignant cytology on FNA found that a cyst fluid CEA level of 192 ng/mL only had a sensitivity of 59% and a specificity of 73% for diagnosing mucinous cystic lesions.[148]

There are no RCTs comparing techniques of EUS-FNA for pancreatic cystic lesions. The reported performance characteristics for EUS-FNA–acquired cytology in diagnosing mucinous pancreatic lesions have varied widely, in part because of variability in the definition of what constitutes a positive EUS-FNA result.[149-163] A meta-analysis of 11 studies totaling 969 patients that used a reference standard of surgical histology or clinical follow-up of at least 6 months showed that cytology had a pooled sensitivity of 0.54 (95% CI, 0.49-0.59) and a specificity of 0.93 (95% CI, 0.90-0.95) for mucinous cysts.[164] Thus, the overall EUS-TA cytologic yield is suboptimal.

Several techniques have been evaluated to improve the diagnostic yield and accuracy of EUS-FNA for cystic pancreatic lesions. FNA of the cyst wall may provide additional cytologic material, and it offers the advantage of obtaining material from small cysts with insufficient fluid for aspiration. A retrospective study of 107 patients found an increase in the diagnostic yield for mucinous lesions of 37% by using this technique.[165] The same group used this technique prospectively and found that it was associated with a 36% reduction in inadequate specimens and a 29% increase in the diagnostic yield for mucinous or malignant cysts when compared with standard cyst fluid CEA and cytology ($P = .0001$).[166] In patients with a cyst containing a solid component, the diagnostic yield may be increased from 44% to 78% ($P = .016$) when more than 1 pass of the solid region is performed.[167]

A cytology brush (EchoBrush, Cook Endoscopy, Winston-Salem, NC) that could traverse a 19-gauge needle was developed with the aim of improving the cytologic yield of EUS-FNA. In 5 studies involving 115 pancreatic cystic lesions, diagnostic yields from 50% to 91% were achieved by using the cytology brush.[168-172] Three studies found superior results by using this brush compared with the standard FNA needle.[168,169,171] However, it should be noted that in several of these studies, EUS-FNA was used only to obtain cyst fluid, and active sampling of the cyst wall via a to-and-fro motion with FNA was not performed. Although 2 studies reported no adverse events,[170,172] 3 had rates of $\geq$10%, including pancreatitis, intracystic bleeding, hemosuccus pancreaticus, and retroperitoneal bleeding.[168,169,171] This device has had limited adoption to date because of concerns regarding its incremental value over standard EUS-FNA and the nature and rates of observed adverse events.

Studies assessing whether DNA or molecular analysis can improve the diagnostic accuracy of EUS-FNA of pancreatic cystic lesions have reported variable results. The sensitivity and specificity for these tests in detecting mucinous or malignant cysts has ranged from 50% to 86% and 80% to 100%, respectively.[173-177] The combination of CEA, cytology, and molecular markers appears to achieve the highest rates of diagnostic accuracy, but the exact role of DNA and molecular analysis in characterizing cystic pancreatic lesions remains undefined. Newer techniques that require the use of a 19-gauge needle, such as performance of cystoscopy by using a fiberoptic probe and the use of confocal laser endomicroscopy, have shown promising results and need to be confirmed in future studies.[178-182]

Subepithelial lesions

Standard mucosal biopsies are generally inadequate for diagnosis. Multiple other techniques have been studied for improving diagnostic yield including (1) unroofing biopsy, (2) snare unroofing biopsy, (3) and large forceps tunneling, among a few.[183-187] These techniques provide improved diagnostic yield over standard mucosal biopsies, but results remain suboptimal. The majority of data for EUS-TA has been centered on GI stromal tumors. Although EUS-FNA has higher accuracy for identifying spindle cells, it often does not procure enough tissue for immunohistochemistry, which is critical for the differentiation and final diagnosis of most GI subepithelial masses. Published diagnostic yields for EUS-FNA for evaluation of GI stromal tumors range from 46% to 93% (Supplemental Table 4, available online at www.giejournal.org),[74,184,188-199] but no RCTs have been conducted to date. EUS-guided core biopsies have provided slightly increased diagnostic yields for subepithelial

masses. Four studies that used the Tru-cut core biopsy needle for subepithelial masses demonstrated final diagnostic yields ranging from 35% to 79%, but the needle was limited by stiffness when the echoendoscope had any significant torque.[95,100,200] Three RCTs have been done comparing EUS-FNA and EUS-FNB with inclusion of subepithelial lesions by using the ETP needle. Kim et al[115] found the yield for FNB significantly greater than for FNA (75% vs 20%; $P < .010$). Nagula et al[201] demonstrated a 67% diagnostic yield for FNB compared to 33% for FNA. The most recent RCT demonstrated a diagnostic yield of 86% for FNB with the ETP needle versus 56% for FNA in nonpancreatic lesions.[117]

Lymphadenopathy

Tissue acquisition from lymph nodes can be difficult, especially when there is concern for hematologic malignancy (eg, lymphoma) (Video 5, available online at www.giejournal.org). Lymphoproliferative disorders often require histologic specimens to best delineate architecture and allow for performance of flow cytometry (immunophenotyping). Although FNA specimens can have a high yield for metastatic lesions, FNA generally is not ideal for hematologic malignancy.[67,202] Multiple observational studies have shown a range of diagnostic accuracy of FNA for the diagnosis of abnormal lymphocytes (70%-90%), but more importantly, these studies have shown much lower rates of accurate classification of lymphoma (Supplemental Table 5, available online at www.giejournal.org).[39,101,203-223] A single RCT of EUS for diagnosis of malignant lymphadenopathy in 43 patients demonstrated a diagnostic yield of FNA of 100%.[16] Two studies in which FNB with Tru-cut sampling was assessed for lymph nodes produced diagnostic yields ranging from 69% to 73%.[101,105]

Miscellaneous lesions

Suspected cholangiocarcinoma and/or indeterminate bile duct strictures. EUS offers excellent visualization of the intrahepatic and extrahepatic bile duct for evaluation of indeterminate strictures. FNA of bile duct strictures has been somewhat controversial because of the perceived risk of track contamination in the event the patient should undergo liver transplantation for intrahepatic strictures. A recent study refutes the potential risk of contamination in extrahepatic malignancy.[224] An early study of 28 patients by Eloubeidi et al[225] showed a sensitivity and accuracy of 86% and 88%, respectively, with a negative predictive value of 57%. Dewitt et al[226] evaluated 291 bile duct strictures after negative ERCP brushing and found the sensitivity and accuracy of EUS-FNA to be 77% (95% CI, 54-92) and 79% (95% CI, 58-93), respectively. Furthermore, they identified a low negative predictive value of 29% (95% CI, 4-79), making a negative cytology result unreliable in ruling out malignancy. Studies evaluating the role of EUS-TA in this category are highlighted in Supplemental Table 6 (available online at www.giejournal.org).[225-240] The majority of strictures studied had a concurrent mass lesion, thus creating some inconsistencies when EUS-FNA was evaluated for strictures alone. Although EUS-FNA offers increased overall sensitivity and yield for tissue acquisition in indeterminate bile duct strictures, the low negative predictive value limits its widespread applicability.

Adrenal masses and liver biopsy

EUS-FNA of adrenal masses can provide valuable information in the staging of lung cancer and diagnosis of metastatic lesions. Available data suggest that sampling from the left adrenal gland is feasible and can obtain adequate samples (Supplemental Table 7, available online at www.giejournal.org).[241-245] In addition, EUS-FNA of the right adrenal gland was feasible in a few patients in these series. There is one prospective study of 22 patients investigating EUS-guided liver biopsy by using a 19-gauge FNA needle.[84] The authors found an adequacy and diagnostic yield of 91% without significant adverse events. Multiple retrospective series have reported a successful yield of EUS-guided sampling of liver masses.[246-248] One prospective study comparing EUS-FNA to CT-guided core biopsies demonstrated a diagnostic yield of 73% for FNA and 82% for CT-guided sampling.[249] A recent prospective study of EUS-FNB demonstrated significantly greater adequacy of 81% versus 31% with the ETP needle compared with the Tru-cut.[250] Further prospective data are needed to validate the use of EUS-guided tissue sampling for hepatic parenchymal disease or mass lesions.

ADVERSE EVENTS ASSOCIATED WITH EUS-TA

The performance of EUS-FNA is generally safe, and adverse events are rare. In a systematic review of 51 studies involving 10,941 patients, adverse events were reported in 0.98%.[251] Two deaths attributable to performing EUS-FNA were identified, one from cholangitis and one from pancreatitis, for a mortality rate of 0.02%. Higher rates of adverse events were identified in prospective studies compared with retrospective studies (1.72% vs 0.64%; $P < .001$). EUS-FNA procedures targeting ascites and pancreatic cysts were associated with the highest rates of adverse events. Pain, pancreatitis, bleeding, fever, and infection were the most frequently reported adverse events. Tumor seeding and perforation are additional serious, but infrequently reported, adverse events from EUS-FNA.

Pancreatitis has been reported in up to 2% of FNAs of pancreatic lesions, with a rate of 0.44% in the aforementioned systematic review.[252-254] Given this low rate of occurrence, no specific factors such as needle size, needle type, lesion type, or lesion location have been identified. Extraluminal bleeding has been reported in 1.3% of cases in one study of 227 patients undergoing EUS-FNA, all of which were controlled via tamponade with the echoendoscope.[255] Self-limited intracystic bleeding, with rates as high as 6%, and hemosuccus pancreaticus have been reported from EUS-FNA of pancreatic cystic lesions.[256-258] The use of low molecular weight heparin, but not aspirin

or nonsteroidal anti-inflammatory drugs, was associated with an increased rate of bleeding events in 222 procedures with EUS-FNA or Tru-cut biopsy.[259] Bacteremia resulting from EUS-FNA is extremely uncommon and comparable to EUS without FNA. Prospective studies have found this to be true for both EUS-FNA of lesions in the upper and lower GI tract.[260-263] As a result of these data, routine antibiotic use is not recommended for EUS-FNA of solid lesions within or adjacent to the upper or lower GI tract. Cystic lesions are at higher risk of infection. Aspiration of mediastinal cysts has been associated with infection and mediastinitis and, given the limited cytologic yield of aspirating such lesions, FNA of these lesions is generally not recommended.[218] The data regarding the use of prophylactic antibiotics in pancreatic cysts undergoing EUS-FNA are equivocal. Although a cyst infection rate of 14% was reported in an initial series of 22 patients undergoing cyst FNA,[264] a recent retrospective cohort study of antibiotic prophylaxis for EUS-FNA of pancreatic cysts identified one possible infection each in 88 patients treated with antibiotics and 178 patients given no antibiotics.[265] Tumor seeding has been reported after aspiration of pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm, melanoma, and malignant adenopathy.[266-272,273] Caution in performing bile duct EUS-FNA for primary tumor diagnosis (cholangiocarcinoma) has been recommended because of the potential risk of tumor seeding associated with transperitoneal tissue acquisition, although 13 of 16 patients in this study underwent percutaneous procedures.[274] Perforations reported with EUS-FNA have been attributed to passage of the echoendoscope rather than the needle.[275] The rates of adverse events associated with needles designed to obtain histology via EUS-FNB have been comparable to those reported for EUS-FNA.[88,90,91,118,119,121,130,276-278] Finally, false-positive diagnoses associated with EUS-TA may occur, with reported incidences ranging from 1.1% to 5.3%.[279-281]

EUS-TA—AN EVIDENCE-BASED APPROACH

A pragmatic approach to EUS-TA, based on the available literature, has been summarized in Figure 1.

Future directions

The ideal EUS-TA technique is one that provides samples for cytology, histology, ancillary studies, and molecular markers, with few passes by using needles that are flexible, easily visualized, and cost effective. Pancreatic cancer is characterized by a variety of molecular alterations, and identification and quantification of potential molecular markers on samples obtained by EUS-TA techniques could be a promising approach. Preliminary studies have shown that EUS-FNA allows the extraction of sufficient quantities of RNA to perform quantitative, real-time, polymerase chain reaction analysis and other molecular tests such as broad panel microsatellite loss, k-*ras* point mutation, and mismatch excision repair gene analysis.[177,282] Future studies need to assess whether tissue samples can be obtained reliably for molecular markers to stratify risk and provide tailored chemotherapeutic regimens based on specific molecular characteristics. The methodology regarding tissue acquisition for molecular markers will then need to be standardized. The role of real-time dynamic telecytopathology needs to be evaluated in future large prospective trials. Also, the role of OCE feedback needs to be defined in the era of EUS-FNB. The putative advantages of a reduced number of passes, lack of need for OCE, provision of tissue providing architectural details, and the ability to perform ancillary studies with FNB tissue core specimens need to be confirmed in future prospective trials. With the availability of newer commercially available EUS-TA needles, the ability to obtain adequate samples along with improvement in diagnostic yield should be expected. Future prospective RCTs comparing devices should use standardized endpoints with clear definitions of diagnostic yield and accuracy.

A standardized and validated classification system to assess cytologic characteristics of EUS-FNA and/or FNB specimens (adequacy, cellularity, and bloodiness) is required. Studies that present data in terms of costs that should guide clinical decisions are limited and are needed. Finally, with the goal of high-value healthcare, endosonographers should monitor the following quality indicators related to EUS-TA in practice: (1) diagnostic rate of adequate samples in all solid lesions (adequate defined by the presence of cells and/or tissue from the representative lesion in question)—performance target 85%, (2) diagnostic rate of malignancy in patients undergoing EUS-TA of all pancreatic masses and sensitivity of malignancy among patients with pancreatic cancer (performance targets of 70% and 85%, respectively), and (3) monitor the incidence of adverse events (acute pancreatitis, bleeding, perforation, and infection) after EUS-TA.[283]

Conclusions

EUS-TA has evolved significantly over the past 25 years. Advances in needle technologies, further validation of EUS techniques, and the advent of flexible histology needles have significantly improved the impact of EUS. The current technical review offers an evidence-based algorithmic approach to EUS-TA for clinical application in practice. Although significant progress has been made, further well-designed RCTs are needed to optimize the EUS sampling technique.

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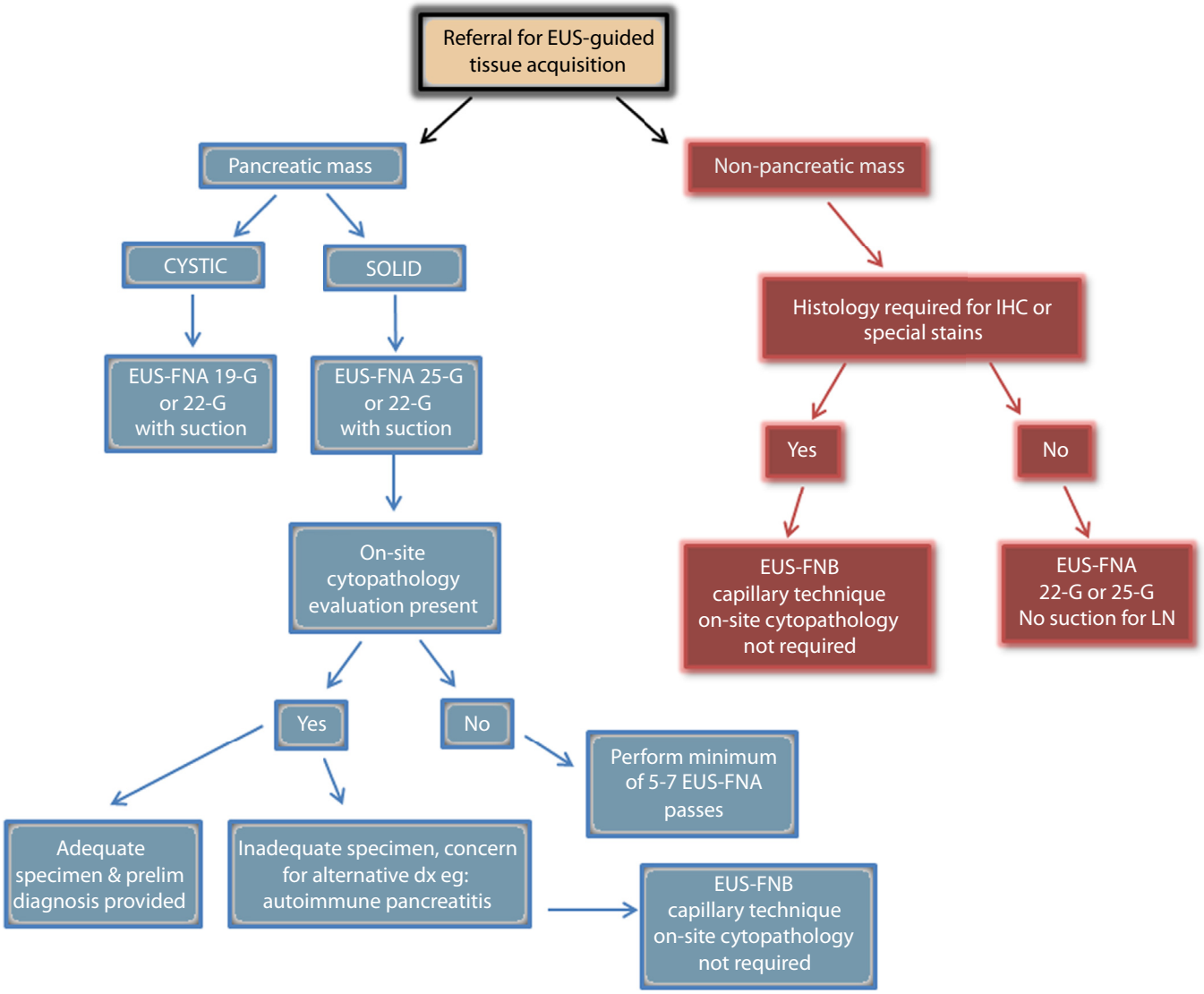

Figure 1. A pragmatic approach to EUS-guided tissue acquisition. *EUS-FNA,* EUS-guided FNA; *EUS-FNB,* EUS-guided fine-needle biopsy; *G,* gauge; *LN,* lymph node.

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SUPPLEMENTAL TABLE 1. Literature to date evaluating standard FNA needles for histologic specimens

Author	Study design	No. of patients	Cohort	Needle gauge	Adequacy (%)
Voss[86]	Prospective cohort	99	Pancreatic masses	22	81
Larghi[80]	Prospective cohort	27	Solid tumors	22	96
Yasuda[87]	Prospective cohort	104	Lymphadenopathy	19	100
Iglesias-Garcia[76]	Prospective cohort	62	Pancreatic masses	22	83.9
Iwashita[78]	Prospective cohort	41	Lymphadenopathy (sarcoid)	19	95
Gerke[75]		120	Solid tumors and lymph nodes	22	27.8
Moller[82]	Retrospective	192	Pancreatic masses	22	86.5
Noda[83]	Prospective cohort	32	Solid tumors and lymph nodes	22	N/A
Larghi[81]	Prospective cohort	120	All masses	19	96.7
Yasuda[204]	Prospective cohort	152	Suspected lymphoma	19	97
Iwashita[77]	Retrospective	44	Autoimmune pancreatitis	19	93
Larghi[79]	Prospective cohort	30	Pancreatic neuroendocrine tumors	19	93.3
Varadarajulu[85]	Prospective cohort	38	All masses	19	94.7
Stavropolous[84]	Prospective cohort	31	Liver	19	91
Eckardt[74]	Prospective cohort	46	Subepithelial masses	19	59
Al Haddad[291]	Prospective cohort	44	All masses	19	90.9

N/A, not available.

SUPPLEMENTAL TABLE 2. Literature to date regarding the EUS-guided fine-needle biopsy by using the Quick-Core (Tru-cut) needle

Author	Study design	No. of patients	Cohort	Adequacy EUS-TCB (%)	DY EUS-TCB (%)	DY EUS-FNA (%)
Larghi[91]	Prospective cohort	23	P	74	61	n/a
Wittman[90]	Prospective cohort	96	P and NP	88	73	77
Storch[104]	Retrospective	41	NP	n/a	76	76
Aithal[92]	Prospective cohort (MC)	167	NP	89	89	82
Saftoiu[102]	Prospective cohort	30	NP	89	68	73
Sakamoto[29]	Prospective cohort	24	P	50	54	92
Shah[103]	Retrospective	126	P	86	n/a	89
Storch[105]	Retrospective	48	NP	94	79	79
Berger[93]	Retrospective	70	NP	94	90	93
Dewitt[292]	Retrospective	21	NP	100	90	n/a
Polkowski[100]	Prospective cohort	49	NP	78	63	n/a
Thomas[106]	Prospective cohort	247	P and NP	87	75	n/a
Wahnschaffe[107]	Prospective cohort	24	NP	83	95	n/a
Gerke[88]	RCT	77	NP	95	88	n/a
Ribeiro[101]	Retrospective	24	NP	100	73	0
Dewitt[95]	Prospective cohort PC	38	NP	97	79	76
Lee[97]	Retrospective	65	NP	57	n/a	n/a
Cho[94]	Retrospective	27	NP	n/a	67	78

EUS-TCB, EUS-guided tru-cut biopsy; *DY,* diagnostic yield; *EUS-FNA,* EUS-guided FNA; *MC;* multicenter, *P/NP;* pancreas/nonpancreas, *n/a:* not available.

SUPPLEMENTAL TABLE 3. Summary of meta-analyses assessing the performance of EUS-guided FNA in diagnosing solid pancreatic neoplasms

Author	No. of studies included	Total no. of patients included	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
Hewitt[50]	33	4984	0.85 (0.84-0.86)	0.98 (0.97-0.99)
Chen[124]	31	4840	0.89 (0.88-0.90)	0.96 (0.95-0.97)
Hebert-Magee[51]	34	3644	0.89 (0.87-0.90)	0.99 (0.99-1.00)
Madhoun[32]	8	799 (22 G needle)	0.85 (0.82-0.88)	1.0 (0.98-1.00)
		565 (25 G needle)	0.93 (0.91-0.96)	0.97 (0.93-0.99)
Puli[125]	41	4766	0.87 (0.86-0.88)	0.96 (0.95-0.97)

CI, Confidence interval; *g*, gauge.

SUPPLEMENTAL TABLE 4. Studies evaluating EUS-guided tissue acquisition for subepithelial masses

Author	Study design	No. of patients	FNA or FNB	No. of passes (mean)	Adequacy	DY/DA FNA (%)	DY/DA FNB (%)
Ando[189]	Prospective cohort	23	FNA	n/a	n/a	91	n/a
Okubo[195]	Retrospective	21	FNA	2.4	n/a	86	n/a
Chen[192]	Prospective cohort	42	FNA	3.9	n/a	98	n/a
Akahoshi[188]	Prospective cohort	51	FNA	2.4	82	82	n/a
Hoda[184]	Retrospective	112	FNA	5.3	n/a	62	n/a
Philipper[196]	Prospective cohort	47	FNA	n/a	74	46	n/a
Polkowski[100]	Prospective cohort	49	TC	4.0	n/a	n/a	63
Sepe[197]	Retrospective	37	FNA	n/a	n/a	78	n/a
Yoshida[199]	Prospective cohort	49	FNA	n/a	71	63	n/a
Fernandez-Esparrach[200]	Prospective cohort	40	FNA/TC	2.1/1.9	70/60	52	55*
Mekky[194]	Retrospective	141	FNA	2.5	83	49	n/a
Bean 2011[190]	Retrospective	39	FNA	n/a	n/a	68	n/a
Dewitt[95]	Prospective cohort	38	FNA/TC	4/3	n/a	76	79
Watson[198]	Retrospective	65	FNA	2.2	n/a	68	n/a
Eckardt[74]	Prospective cohort	46	FNA (19)	1-4	46	52	n/a
Caglar[191]	Retrospective	67	FNA	3	n/a	85	n/a
Larghi[193]	Retrospective	121	FNA (FWFV)	2.7	93	93	n/a

FNB, Fine-needle biopsy; *DY,* diagnostic yield; *DA,* diagnostic accuracy; *NS,* not significant; *TC,* tru-cut; *FV,* forward viewing.
*P = NS.

SUPPLEMENTAL TABLE 5. Studies evaluating EUS-guided tissue acquisition for lymphadenopathy

Author	Study design	No. of patients	Cohort	Needle type	DY/DA FNB (%)	DY/DA FNA (%)
Wallace[16]	RCT	46	LN	FNA	n/a	100
Stelow[214]	Retrospective	185	All LN	FNA	n/a	88
Caddy[206]	Prospective cohort	34	NSCLC	FNA	n/a	92
Chen[203]	Prospective cohort	137	All LN	FNA	n/a	99
Mehra[207]	Retrospective	29	Lymphoma	FNA	n/a	90
Eloubeidi[68]	Prospective cohort	35	NSCLC	FNA	n/a	98
Tournoy[39]	Prospective cohort	67	Mediastinal LN	FNA	n/a	92
Storch[105]	Retrospective	48	Mediastinal LN	TC	79	79*
Naini[215]	Retrospective	88	All LN	FNA	n/a	n/a
Nakahara[216]	Retrospective	57	Intra-abdominal LN	FNA	n/a	96
Al Haddad[205]	Retrospective	54	Lymphoma	FNA	n/a	65 (76)
Iwashita[211]	Prospective cohort	62	All LN	FNA	n/a	98
Fritscher-Ravens[209]	Prospective cohort	72	All LN	FNA	n/a	89
Ribeiro[101]	Retrospective	24	Lymphoma	FNA/TC	73	0
Hirdes[201]	Retrospective	213	Mediastinal LN	FNA	n/a	96
Dhir[293]	Prospective cohort	66	Intra-abdominal LN	FNA	n/a	92
Songur[219]	Prospective cohort	57	All LN	FNA	n/a	96/92*
Zeppa[220]	Prospective cohort (MC)	57	Mediastinal LN	FNA	n/a	76
Eloubeidi[294]	Retrospective	116	Mediastinal LN	FNA	n/a	100
Yasuda[204]	Retrospective	240	Lymphoma	FNA	n/a	88 (79.6)
Korenblit[213]	Retrospective	147	Intra-abdominal	FNA	n/a	94
Puri[217]	Prospective cohort	142	Tuberculosis	FNA	n/a	91
Srinivasan[295]	Retrospective	69	Mediastinal LN	FNA	n/a	54
Kim 2013[212]	Prospective cohort	95	Intra-abdominal LN	FNA* (core with FNA)	69	82
Mehmood[221]	Retrospective	119	All LN	FNA	n/a	96
Vazquez-Sequeiros[222]	Retrospective	73	Mediastinal LN	FNA	n/a	97
Coe[223]	Retrospective	225	All LN	FNA	n/a	85

DY, Diagnostic yield; *DA,* diagnostic adequacy; *FNB,* fine-needle biopsy; *RCT,* randomized controlled trial; *LN,* lymph node; *TC,* Tru-cut; *NS,* not significant; *n/a;* not available, *NSCLC;* non small cell lung cancer, *MC;* multicenter.
*P = NS.

SUPPLEMENTAL TABLE 6. Literature to date for EUS-guided FNA of indeterminate bile duct strictures

Author	Study design	No. of patients	Mass present (%)	Sensitivity	NPV	DA/DY
Fritscher-Ravens[232]	Prospective	10	100	80	n/a	n/a
Fritscher-Ravens[233]	Prospective cohort	44	98	89	n/a	91
Byrne[240]	Retrospective	35	71	86	n/a	n/a
Lee[228]	Retrospective	40	25	47	50	n/a
Eloubeidi[225]	Prospective cohort	28	89	86	57	88
Rosch[230]	Prospective cohort	50	n/a	43	n/a	n/a
Dewitt[226]	Prospective cohort	24	96	77	29	79
Meara[229]	Prospective cohort	46	n/a	87	n/a*	n/a*
Mohamadnejad[237]	Prospective cohort	81	94	73	n/a	n/a
Tummala[235]	Retrospective	342	50	92	72	92
Weilert[231]	Prospective cohort	51	71	94	50	94

NPV, Negative predictive value; *DA,* diagnostic adequacy; *DY,* diagnostic yield *n/a;* not available.
*Abstract only available (presence of mass, NPV, and DA/DY not given in abstract).

SUPPLEMENTAL TABLE 7. Literature to date for EUS-guided FNA of adrenal masses

Author	Study design	No. of patients	Left or right adrenal gland	No. of passes (median)	SA (%)	DY/DA
Jhala[241]	Prospective cohort	24	L and R	3-5	100	n/a
Stelow[245]	Retrospective	24	L and R	n/a	100	100
DeWitt[242]	Retrospective	38	L	3.6	n/a	76
Bodtger[296]	Retrospective	40	L	2	n/a	n/a
Eloubeidi[244]	Prospective cohort	54	L and R	3	100	n/a
Schuurbiers[243]	Retrospective	85	L	3	n/a	95

L, Left; *R,* right; *SA,* specimen adequacy; *DY,* diagnostic yield; *DA,* diagnostic adequacy; *n/a,* not available.