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Endoscopic ultrasound fine needle aspiration vs fine needle biopsy for pancreatic masses, subepithelial lesions, and lymph nodes

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Abstract

Endoscopic ultrasound tissue acquisition, in the form of both fine needle aspiration (EUS-FNA) and fine needle biopsy (EUS-FNB), is utilized for pancreatic mass lesions, subepithelial lesions, and lymph node biopsy. Both procedures are safe and yield high diagnostic value. Despite its high diagnostic yield, EUS-FNA has potential limitations associated with cytological aspirations, including inability to determine histologic architecture, and a small quantitative sample for further immunohistochemical staining. EUS-FNB, with its larger core biopsy needle, was designed to overcome these potential limitations. However, it remains unclear which technique should be used and for which lesions. Comparative trials are plagued by heterogeneity at every stage of comparison; including variable needles used, and different definitions of endpoints, which therefore limit generalizability. Thus, we present a review of prospective trials, systematic reviews, and meta-analyses on studies examining EUS-FNA vs EUS-FNB. Prospective comparative trials of EUS-FNA vs EUS-FNB primarily focus on pancreatic mass lesions, and yield conflicting results in terms of demonstrating the superiority of one method. However, consistent among trials is the potential for diagnosis with fewer passes, and a larger quantity of sample achieved for next generation sequencing. With regard to subepithelial lesions and lymph node biopsy, fewer prospective trials exist, and larger prospective studies are necessary. Based on the available literature, we would recommend EUS-FNB for peri-hepatic lymph nodes.

Key Words: Endoscopic ultrasound fine needle aspiration; Endoscopic ultrasound fine needle biopsy; Pancreatic lesions; Subepithelial lesions; Lymph node biopsy

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Core Tip: Endoscopic ultrasound fine needle aspiration (EUS-FNA) and fine needle biopsy (EUS-FNB) provide two methods for endoscopic ultrasound tissue acquisition for pancreatic mass lesions, subepithelial lesions, and lymph node biopsy. Both methods are safe and provide high diagnostic yield. Prospective comparative trials of EUS-FNA vs EUS-FNB primarily focus on pancreatic lesions. EUS-FNB provides diagnostic accuracy with fewer needle passes, and may provide higher diagnostic yield for peri-hepatic lymph nodes.

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INTRODUCTION

As medical and surgical therapeutics continue to evolve, there is a renewed emphasis on timely diagnosis of various illnesses. This mantra certainly holds true in gastrointestinal (GI) diseases, including pancreatic malignancies and GI tumors, where early and specific diagnosis guides management and impacts morbidity and mortality [1]. While cross-sectional imaging can characterize lesions, a tissue diagnosis is often required for a definitive diagnosis prior to therapy [2-5]. Endoscopic ultrasound tissue acquisition (EUS-TA) has improved the ability for tissue diagnosis using a minimally invasive technique. The two modalities for EUS-TA, endoscopic ultrasound fine needle aspiration (EUS-FNA) and endoscopic ultrasound fine needle biopsy (EUS-FNB) vary in technique and utility. Common indications for EUS-TA include the diagnosis and staging of pancreaticobiliary and luminal GI malignancy, and assessing lymphadenopathy associated with luminal GI and lung cancers [6]. Additionally, EUS-TA aids in the evaluation of potentially neoplastic GI subepithelial lesions [6]. Comparative studies on the diagnostic ability of EUS-FNA and EUS-FNB have yielded conflicting results. Here we review prospective comparative data on EUS-FNA vs EUS-FNB for pancreatic masses, subepithelial lesions, and lymph node biopsy (Table 1-3).

EUS-FNA

EUS-FNA was first introduced in 1992. It is often combined with rapid onsite evaluation (ROSE) to improve diagnostic ability [7,8]. EUS-FNA is now standard of care for sampling pancreatic solid masses, subepithelial lesions, and lymph nodes, among others. The European Society of Gastroenterology and American Society of Gastroenterology recommend EUS-FNA as first line for diagnosing pancreatic lesions [9-11].

Marked variability exists in EUS-FNA equipment and technique. Several different needle sizes are available including 19 G, 20 G, 22 G, and 25 G. Additionally, variability exists in aspiration technique, including the use of negative pressure suction (used with either a 5 mL or 10 mL syringe) or slow stylet pull. The aspirate from EUS-FNA is often sufficient for cytology and adequate for diagnosis, with diagnostic accuracy ranging from 77% to 95% for pancreatic masses [9,10]. Given its minimally invasive technique and small needle size, EUS-FNA has low rates of morbidity [12].

However, several limitations exist for EUS-FNA which obtains a cytological specimen. EUS-FNA is limited by an inability to obtain histological architecture, and the inability to perform immunohistochemical analysis and molecular profiling. This is of particular importance as certain neoplasms, such as stromal cell tumors and lymphomas, may be difficult to diagnose without histologic samples, as their tissue architecture and morphology are essential for accurate pathologic assessment and histochemical studies [9,13-17]. Furthermore, with the increased attention on personalized or precision medicine in oncology, a sufficient tissue sample to perform next generation sequencing is required. Current National Comprehensive Cancer Network guidelines recommend germline testing for any patient with confirmed pancreatic

Table 1 Prospective comparative trials of endoscopic ultrasound fine needle aspiration vs fine needle biopsy for solid pancreatic mass lesions

Ref.	Study design	Number of subjects	Needle size (FNA, FNB)	Diagnostic yield/specimen adequacy (EUS-FNA vs EUS-FNB)	Diagnostic accuracy (EUS-FNA vs EUS-FNB)	Number of passes needed (EUS-FNA vs EUS-FNB)	Comments
Bang <i>et al</i> [9], 2012	RCT	56	22 G, 22 G Procore	66.7% vs 80% (NS)	N/A	1.61 vs 1.28 (NS)	
Aadam <i>et al</i> [30], 2015	RCT	73	Variable, variable	78.4% vs 91.7% (NS)	67.5% vs 83.3% (NS)	N/A	
Tian <i>et al</i> [31], 2018	RCT	36	22 G, 22 G ProCore	83.3% vs 83.3%	N/A	1.83 vs 1.11 ($P = 0.049$)	
Hedenstrom <i>et al</i> [33], 2018	RCT, crossover	68	25G, 22G reverse bevel Wilson Cook	N/A	78% vs 69% (NS)	N/A	In a subset of non-pancreatic adenocarcinoma, combined modality (EUS-FNA + FNB) was significantly higher compared to EUS-FNA alone
Oppong <i>et al</i> [34], 2020	RCT, crossover	108	Variable, variable Sharkcore	71% vs 82% (OR 3.23, sig)	64% vs 79% (OR 4.79, sig)	N/A	Shorter sampling time and pathology viewing time with EUS-FNB. Equivalent cost analysis.
Kandel <i>et al</i> [35], 2020	RCT, crossover	50	25 G, variable Sharkcore	100% vs 86% (NS)	100% vs 100%	N/A	Primary outcome of DNA concentration, significantly higher in EUS-FNB than in EUS-FNA
Wang <i>et al</i> [26], 2017	Meta-analysis	921	Variable, variable	81.4% vs 88.3% (OR 0.57, sig)	84.0% vs 87.8% (NS)	Fewer in EUS-FNB	
Li <i>et al</i> [27], 2018	Meta-analysis	1382	Variable, variable	82.3% vs 89.4% (OR 1.83, sig)	84.3% vs 89.6% (OR 1.62, sig)	Fewer in EUS-FNB	

EUS-FNA: Endoscopic ultrasound fine needle aspiration; EUS-FNB: Endoscopic ultrasound fine needle biopsy; RCT: Randomized controlled trial; N/A: Not applicable; NS: Not significant.

cancer using comprehensive gene panels for hereditary cancer syndromes, as well as tumor/somatic gene profiling for patients with locally advanced or metastatic disease to identify mutations that may benefit from anti-cancer therapy. Testing on tumor tissue is preferred; however, cell-free DNA testing can also be considered[18]. There is uncertainty whether EUS-FNA will be able to routinely provide adequate material for these studies[6].

EUS-FNB

In an attempt to overcome the limitations of EUS-FNA, EUS-FNB was first introduced in the early 2000s to obtain tissue specimens as opposed to aspiration-based cytology. With the goal of evaluating tissue core, EUS-FNB provided novel needles for improved diagnostic accuracy.

Table 2 Prospective comparative trials of endoscopic ultrasound fine needle aspiration vs fine needle biopsy for subepithelial lesions

Ref.	Study design	Number of subjects	Needle size (FNA, FNB)	Lesions sampled	Diagnostic yield/specimen adequacy (EUS-FNA vs EUS-FNB)	Diagnostic accuracy (EUS-FNA vs EUS-FNB)	Number of needle passes needed (EUS-FNA vs EUS-FNB)	Comments
Kim <i>et al</i> [47], 2014	RCT	22	22 G, 22 G Procore	All SELs	20% vs 75% ($P = 0.01$)	N/A	4 vs 2 ($P = 0.025$)	
Iwai <i>et al</i> [43], 2017	RCT, crossover	23	Variable, variable Procore	Gastric SELs	73.9% vs 91.3% ($P = 0.12$)	N/A	N/A	Histology positive significantly higher in EUS-FNB for 21 mm-30 mm lesions
Hedenstrom <i>et al</i> [48], 2018	RCT, crossover	70	Variable, variable reverse-bevel Wilson-Cook	All SELs	N/A	49% vs 83% ($P < 0.001$)	N/A	Extramural lesions lower sensitivity for EUS-FNA but not EUS-FNB)
Nagula <i>et al</i> [49], 2018	RCT	18	Variable, variable Procore	All SELs	83.3% vs 75% (NS)	N/A	2 vs 2 (NS)	

EUS-FNA: Endoscopic ultrasound fine needle aspiration; EUS-FNB: Endoscopic ultrasound fine needle biopsy; RCT: Randomized controlled trial; N/A: Not applicable; NS: Not significant; SELs: Subepithelial lesions.

Table 3 Prospective comparative trials of endoscopic ultrasound fine needle aspiration vs fine needle biopsy for lymph node biopsy

Ref.	Study design	Number of subjects	Needle size (FNA, FNB)	Lymph nodes sampled	Diagnostic yield/specimen adequacy (EUS-FNA vs EUS-FNB)	Diagnostic accuracy (EUS-FNA vs EUS-FNB)	Number of needle passes needed (EUS-FNA vs EUS-FNB)	Comments
Nagula <i>et al</i> [49], 2018)	RCT	46	Variable, variable Procore	All lymph nodes	92.9% vs 94.4% (NS)	N/A	2 vs 2 (NS)	
de Moura <i>et al</i> [52], 2020)	Retrospective study of prospectively collected data	209	Variable, variable	All lymph nodes	N/A	78.8% vs 83.2% (NS)	N/A	For peri-hepatic lesions, EUS-FNB was significantly more accurate

EUS-FNA: Endoscopic ultrasound fine needle aspiration; EUS-FNB: Endoscopic ultrasound fine needle biopsy; RCT: Randomized controlled trial; N/A: Not applicable; NS: Not significant.

Early models of EUS-FNB utilized Trucut needle biopsy, with a tissue penetrating stylet within an outer cannula. The 19 G Trucut FNB proved more accurate than EUS-FNA for diagnosing lymphomas and stromal tumors, but was limited by mechanical failure when attempting to biopsy pancreatic head masses and duodenal lesions due to the torqued echoendoscope and mechanical friction[16,19]. Newer models, including EchoTip HD ProCore™ (Wilson-Cook Medical Inc., Winston-Salem, NC, United States) is available in 19-25 G, and provides two cutting surfaces, a tip and reverse bevel, to further preserve histological architecture[1]. The reverse or opposing cutting bevel design of the EUS-FNB needle allows for the biopsy of core histopathologic tissue. This

aspect has the potential advantage of improving diagnostic performance, but also allowing a wide range of follow-up testing[20]. Immunohistochemistry, which is required for the diagnosis of autoimmune pancreatitis, lymphoma, and metastasis, can be performed on the tissue core. Furthermore, molecular analysis, which is now standard of care for pancreatic malignancies, can also be performed. Other needles, including SharkCore™ (Medtronic Inc., Sunnyvale, CA, United States) and Acquire™ (Boston Scientific, Marlborough, MA, United States), (Figure 1) may achieve even higher diagnostic accuracy[21,22].

Studies have demonstrated high diagnostic yields of core specimens with EUS-FNB with fewer needle passes[23-25]. The potential concern for increased bleeding when using EUS-FNB is offset by the fewer passes required for diagnosis.

EUS-FNA VS EUS-FNB: OVERVIEW

Several comparative trials have evaluated EUS-FNA *vs* EUS-FNB. Interpreting the conflicting data is challenging, as trials are plagued by heterogeneity in every stage of comparison. Reported outcomes as well as definition of those outcomes vary between studies. For example, inconsistent use of the term “diagnostic accuracy” and “diagnostic adequacy” creates confusion. Furthermore, heterogeneity exists within equipment use (needle size), and technique (suction *vs* slow pull; specified number of passes). Additionally, designing strong randomized trials is limited by the inability to blind endosonographers, and sometimes cytopathologists, to the type of needle used [26-57].

METHODS

In compiling this review article, we performed a literature search utilizing PUBMED, EMBASE, and Google Scholar for comparative trials of EUS-FNA *vs* EUS-FNB for pancreatic mass lesions, subepithelial lesions, and lymph nodes. A total of 77 articles were identified. Trials were excluded if they were retrospective ($n = 26$), if they did not directly compare EUS-FNA and EUS-FNB ($n = 18$), or if they were incomplete manuscripts ($n = 6$). Any study performed on a variety of mass lesions without subcategories for the aforementioned groups was also excluded ($n = 4$).

PANCREATIC LESIONS

Pancreatic adenocarcinoma is characterized by a poor prognosis, with a 5-year survival rate of 5%-6%[27]. Pancreatic adenocarcinoma may be difficult to differentiate from other pancreatic mass lesions based on cross-sectional imaging and abdominal ultrasound[2-5]. The reported sensitivity of EUS in the detection of pancreatic cancer is between 94% and 100%[28]. Compared to computed tomography (CT), EUS can detect up to 14% of pancreatic tumors that were not visualized on CT, especially tumors smaller than 20 mm[11]. As such, EUS is currently the standard method for tissue diagnosis of pancreatic masses[11].

Tissue sampling of pancreatic mass lesions by EUS is vital in diagnosis. Several sampling approaches are possible depending on the location of the pancreatic mass lesion. A trans-duodenal approach may be optimal for lesions in the pancreatic head, while the transgastric approach is more appropriate for lesions in the pancreatic body and tail. Bang *et al*[29] proposed an algorithm for needle selection based on anatomical site; a 25 G needle for the trans-duodenal approach and a 22 G or 25 G for all other punctures.

Comparative trials of EUS-FNA *vs* EUS-FNB for pancreatic mass lesions focus mostly on safety, diagnostic accuracy, sample adequacy for diagnosis and further testing (Table 1).

Randomized controlled trials of pancreatic masses with EUS-FNA or EUS-FNB

Bang *et al*[9] performed the earliest randomized controlled trial (RCT) comparing EUS-FNA and EUS-FNB. The study randomized 56 patients to receive either EUS-FNA 22 G or EUS-FNB 22 G ProCore for pancreatic mass lesions, with the primary outcome being the number of passes required to establish a diagnosis with ROSE. They found no significant difference in the median number of passes required to establish on-site

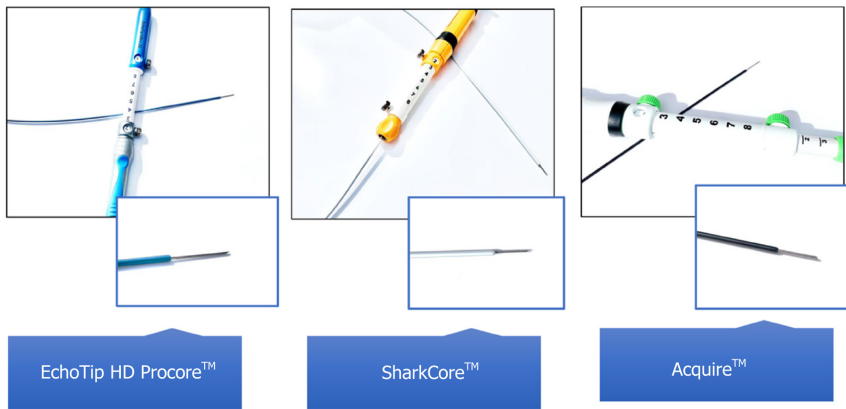


Figure 1 Fine needle biopsy needles.

diagnosis, and overall similar rates of diagnosis were achieved within 3 passes (100% EUS-FNA, 89% EUS-FNB). Incomplete diagnosis by EUS-FNB was due to diagnostic failure in two patients, and technical failure in 1 patient. Procedural complications among the two techniques were similar (one patient with post-procedural abdominal pain in the EUS-FNA cohort, and one patient with pancreatitis in the EUS-FNB cohort). With regard to secondary outcomes, EUS-FNA had a higher proportion of samples with histologic core tissue present (100% *vs* 88.3%, not-significant) but EUS-FNB had a higher percentage of histologic core tissue optimal for histochemical testing.

It is noteworthy that their technique varied from subsequent trials in several respects, and perhaps limited the study's generalizability. First, ROSE was carried out for all specimens, thereby possibly preferentially inflating the diagnostic ability of EUS-FNA. Additionally, they utilized an earlier model of FNB, the 22 G Echotip ProCore™ device. Lastly, they utilized fewer needle movements for the EUS-FNB cohort (only 4 movements to and fro).

A subsequent larger RCT by Aadam *et al*[30] similarly showed no difference in diagnostic yield or specimen adequacy between EUS-FNA and EUS-FNB in patients with pancreatic lesions.

A 2018 RCT by Tian *et al*[31] of 36 patients similarly showed no superiority in diagnostic accuracy between EUS-FNA and EUS-FNB; although they did find a difference in the number of passes needed to make a diagnosis. Similar to Bang *et al* [9], patients were randomized to either EUS-FNA or EUS-FNB ProCore for solid pancreatic masses, although ROSE was not performed on any of the specimens. For the primary outcome of diagnostic yield, the authors found identical results (83%). However, among their secondary outcomes, EUS-FNB required fewer passes to make a diagnosis (1.11 *vs* 1.83, $P < 0.05$). It is noteworthy that a smaller percentage of their cohort were diagnosed with pancreatic adenocarcinoma (66.7%) compared to other trials. There were no complications in either cohort in their study.

Similar findings were also demonstrated in a larger, more recent RCT performed by Chen *et al*[32]. The authors randomized 235 patients with pancreatic mass lesions to EUS-FNA + ROSE ($n = 120$) *vs* EUS-FNB (22 G or 25 G Fork-tip needle, $n = 115$). For the primary outcome of diagnostic accuracy, the authors found no difference (92.2% *vs* 93.3%, respectively). However, among the secondary outcomes, EUS-FNB was associated with fewer needle passes to make a diagnosis compared to EUS-FNA + ROSE (2.3 *vs* 3.0) and decreased procedure time (19.3 min *vs* 22.7 min). There were no adverse events in the EUS-FNB cohort, and three adverse events in the EUS-FNA cohort (2 pancreatitis, 1 bleeding).

Crossover trials

In contradistinction to the aforementioned articles, in several trials patients underwent both EUS-FNA and EUS-FNB in a crossover study design, thereby allowing direct comparison between specimen procurement in the same patients and providing an internal control. Hedenstrom *et al*[33] randomized 68 patients with a pancreatic mass to receive either EUS-FNA (25 G) followed by EUS-FNB (22 G), 1 pass each, or vice versa. A reverse bevel EUS-FNB 22 G needle was used (Wilson-Cook Medical) and further passes were performed by alternating the two needles. They utilized similar

suction (10 cc) and fanning techniques for both EUS-FNA and EUS-FNB. ROSE was carried out for the majority of both EUS-FNA and EUS-FNB samples. The primary outcome of diagnostic accuracy was not significantly different between the two methods of tissue acquisition. No adverse events were recorded.

Utilizing a newer model of EUS-FNB Fork tip (SharkCore™ FNB Needle), Oppong *et al*[34] randomized 108 patients with pancreatic mass lesions to EUS-FNA and then EUS-FNB, 3 passes each, or vice versa. The primary endpoint was diagnostic performance for malignancy (malignant yes/no), compared to a gold standard of unequivocal malignant pathology obtained by EUS sampling, surgical resection, or alternative biopsy. For non-operated patients, clinical and radiological disease progression consistent with malignancy at 6-mo follow-up was required. The authors found increased sensitivity for the diagnosis of malignancy with EUS-FNB compared to EUS-FNA (82% vs 71%). The study was unique in that it also assessed procedural time and pathology viewing time, both of which were significantly shorter for EUS-FNB (710 s vs 759 s, $P = 0.001$; 188 s vs 332 s, $P < 0.001$, respectively). The authors performed a cost-analysis and found no significant difference; however, they analyzed only materials used and did not factor in operational/labor time. The authors reported four serious adverse events (2 cholangitis, 1 pancreatitis, 1 abdominal pain), but did not specify which cohorts the patients belonged to.

Other studies have utilized alternative endpoints to diagnostic accuracy or adequacy. As discussed previously, obtaining a diagnosis for pancreatic adenocarcinoma may still require further testing for personalized medicine, and therefore additional tissue may be required. Kandel *et al*[35] performed a RCT of 50 consecutive patients to assess adequacy for genomic profiling. In their study, they randomized patients to EUS-FNA followed by EUS-FNB (or vice versa) in a randomized order. They also utilized the SharkCore™ FNB needle. The first pass with each needle was used for histology, and subsequent passes were used to collect DNA. They found that EUS-FNB yielded significantly higher mean DNA concentrations compared to EUS-FNA (5.930 µg/mL vs 3.365 µg/mL, $P = 0.01$).

These findings have unclear clinical significance, since despite the quantitative difference in DNA acquired, both acquisition techniques yielded sufficient DNA for next generation sequencing (approximately 10 ng/µL). Furthermore, it is noteworthy that the EUS-FNA utilized a smaller needle (25 G) compared to both EUS-FNB needles (19 G or 22 G). This was likely done to maximize diagnostic accuracy, which was similar in both cohorts (100% final diagnosis in both), but may come at the expense of the DNA quantity acquired.

Systematic reviews and meta-analyses

Several systematic reviews and meta-analyses have attempted to summarize the conflicting data on pancreatic lesions. However, heterogeneity in the studies included and outcomes measured further perpetuate the confusion.

In 2017, Wang *et al*[26] performed a meta-analysis on 8 RCTs to determine diagnostic accuracy. Significant variability existed within needle size and suction technique between the trials. For diagnostic accuracy, they found no significant difference between EUS-FNA (84%) and EUS-FNB (88%, OR 0.72; 95%CI: 0.49-1.07). Among the 5 trials that reported specimen adequacy, and the four trials reporting the number of needle passes required, EUS-FNB demonstrated superiority (OR 0.57, 95%CI: 0.37-0.89; and OR 0.86, 95%CI: 0.45-1.26, respectively). Among the five studies that reported adverse events, the rates were low and not significantly different between the two groups (2/313 in the EUS-FNA group, and 4/311 in the EUS-FNB group), and specific complications were not mentioned.

One year later, in 2018, Li *et al*[27] performed a meta-analysis with the same 8 RCTs, and included an additional 3 RCTs, and yielded different results. They found that EUS-FNB had significantly better specimen adequacy (OR 1.83, 95%CI: 1.27-2.64), and higher diagnostic accuracy (OR 1.62, 95%CI: 1.17-2.26) than EUS-FNA, again with fewer needle passes (MD -0.69, 95%CI: -1.18 to -0.2). There was no difference in complications or technical success.

However, a larger 2019 meta-analysis by Facciorusso *et al*[20] of 27 RCTs found different results. They evaluated diagnostic accuracy, and found no significance difference between needle type (EUS-FNA or EUS-FNB) or needle size. The authors summarized the adverse events as rare among their studies; however, most studies did not itemize the etiology of the adverse events. The only studies that specifically reported bleeding episodes, all reported bleeding in the EUS-FNA cohort. Of note, the authors performed a network meta-analysis technique, thereby utilizing both direct RCT (EUS-FNA vs EUS-FNB) as well as indirect evidence (RCT of EUS-FNA vs EUS-FNA, or EUS-FNB vs EUS-FNB) and then extrapolated the data. Only 14 of the 27 trials

included were actually EUS-FNA *vs* EUS-FNB. As such, their results should be interpreted with caution.

Summary of pancreatic mass studies

Conflicting data exist among prospective studies evaluating the superiority of different EUS-TA techniques. Taken together, both methods provide overall high, and comparable, diagnostic accuracy and specimen adequacy for diagnosis. Adverse events, including bleeding, are rare in both techniques, with pancreatitis being the most common adverse event. Multiple trials have demonstrated that fewer passes are required for EUS-FNB compared to EUS-FNA. The ramifications of this, with the resulting decreased procedural time and likely fewer adverse events, may prove beneficial when applied broadly, but larger trials are required for further elucidation. Additionally, clinical benefit from the increased quantity of tissue obtained remains unclear, if standardized testing and next generation sequencing can be performed on all samples.

SUBEPITHELIAL LESIONS

Subepithelial lesions (SELs) of the GI tract are tumors that originate from the muscularis mucosa, submucosa, or muscularis propria[36]. Initial management of SELs focuses on proper diagnosis and determination of malignant potential, to guide further resection recommendations. EUS is the most accurate imaging method for evaluating SELs of the GI tract[37-39], because it can delineate the individual histologic layers and likely site of tumor origin. Certain SELs have a distinct endoscopic appearance, such as lipomas, duplication cysts, and ectopic pancreas, and endoscopic appearance may be considered diagnostic[36]. However, endoscopic appearance alone is not sufficient for diagnosis in many cases, such as hypoechoic and heterogeneous lesions from the submucosal and muscularis propria, and tissue acquisition is often required. Standard biopsy forceps and jumbo biopsy forceps (bite on bite technique) have low diagnostic yield[40,41].

EUS-FNA is the most widely used method for obtaining SEL tissue arising from the submucosal and muscularis propria layer[36]. However, the diagnostic accuracy of EUS-FNA is variable, ranging from 34% to 93%[39,42]. Additionally, the amount of cytological material obtained by EUS-FNA is often insufficient for the immunohistochemical staining required to differentiate different SELs[43].

Comparative trials

There are few prospective comparison trials of EUS-FNA and EUS-FNB focused solely on SELs, although several larger prospective trials contained cohorts of SELs (Table 2). We excluded trials that did not perform subgroup analysis on this SEL subgroup in isolation[30,44-46].

The first RCT focused solely on SELs was performed by Kim *et al*[47] in 2014. The authors randomized 22 patients with GI SELs of all types to either EUS-FNA ($n = 10$) or EUS-FNB ($n = 12$, ProCore). The patients did not receive both methods of tissue acquisition. The cohort was comprised of mostly gastric SELs (17/22), and mainly arising from the muscularis propria (20/22). The needle size was dependent on tumor diameter at the time of EUS, with a 22 G needle used if the tumor was estimated to be < 30 mm, and 19 G used if the tumor was > 30 mm. The authors utilized the unique endpoint of the number of passes required to obtain macroscopically optimal core samples. Since ROSE was not carried out at all sites, the endoscopist immediately inspected the material for the presence of tissue core, defined as whitish pieces of tissue with apparent bulk. If present, no further passes were obtained. However, if absent, the endoscopist proceeded with an additional pass with a maximum of 3 passes. If the sample still did not contain macroscopic tissue core, the number of passes was recorded at 4, and the patient crossed over to the other cohort. The authors found that the median number of needle passes required to obtain macroscopically optimal core sampled by EUS-FNB was significantly lower than that by EUS-FNA (2 *vs* 4, $P = 0.025$). Despite being macroscopically defined as optimal core samples, the core samples were suboptimal for microscopic analysis in three cases. Overall, the rates of obtaining macroscopically and histologically optimal core samples with EUS-FNB (92% and 75%, respectively) were superior to EUS-FNA (30% and 20%, respectively). No technical difficulties were encountered, and one patient in the entire cohort developed post-procedural bleeding which was managed conservatively. A limitation of the study design was lack of blinding of the endoscopist who assessed the primary

endpoint.

A follow-up study by Iwai *et al*[43] in 2017, focused solely on gastric SELs arising from the muscularis propria and randomized 24 patients to receive either EUS-FNA followed by EUS-FNB or vice versa. The two needles were used alternatively to puncture the same lesion with a total of four punctures per session. Similar to Kim *et al* [47], needle size was dependent on tumor size on EUS, and the ProCore needle was used for all EUS-FNB. The primary outcome was diagnostic yield. The authors found that the rate of correct diagnosis on immunohistochemical staining tended to be higher for EUS-FNB (91.3%) than for EUS-FNA (73.9%, $P = 0.120$), although this failed to reach statistical significance. When sub-characterized by tumor size, they found that EUS-FNB had significantly higher rates of positive histology among tumors 21-30 mm. The study was limited by sample size and was underpowered, as several of their findings trended towards significance.

A larger 2018 RCT performed by Hedenstrom *et al*[48] similarly found superiority of EUS-FNB to EUS-FNA for SELs, utilizing the reverse bevel ProCore EUS-FNB needle. The study randomized 70 patients with GI SELs to dual sampling with EUS-FNA and EUS-FNB in an alternating fashion until the yield was regarded as satisfactory by the cytotechnician, with a maximum of six passes. Similar to Iwai *et al*[43], in the absence of ROSE, gross examination was performed by the endoscopist. The cohort consisted of mostly gastric SELs (66/70). The study found significantly higher overall diagnostic accuracy for EUS-FNB than EUS-FNA (83% *vs* 49%, $P < 0.001$). A trend of lower sensitivity of EUS-FNA for extramural lesions compared to intramural lesions was also observed, a trend that did not exist for EUS-FNB. The authors hypothesized that this may be related to increased mobility of extramural lesions, preferentially affecting EUS-FNA diagnostic accuracy. The characterization of intramural and extramural was based on appearance at EUS. The authors reported few adverse events.

These findings are in contrast to Nagula *et al*[49] who found in the SELs cohort ($n = 18$) that there was no significant difference in diagnostic yield between EUS-FNB ProCore and EUS-FNB (EUS-FNB 75% *vs* EUS-FNA 83.3%, $P = 0.754$).

LYMPH NODES

Lymphadenopathy may arise from many different etiologies, ranging from benign inflammatory or infectious, to malignant etiologies. Evaluation of lymphadenopathy must include tissue sampling, as lymph node size has demonstrated poor specificity for differentiating malignant from benign lymphadenopathy[50,51]. Clarifying the malignant potential of lymphadenopathy is essential for clinical management[52].

The modality for sampling lymph nodes depends on anatomic location. For mediastinal lymph node sampling, EUS-TA is safer and less invasive compared to alternative techniques[10]. Additionally, for abdominal lymph nodes, EUS-sampling is successful in 92% of patients[53].

EUS-TA for lymph nodes is typically performed with EUS-FNA. However, the sensitivity of EUS-FNA for providing material for cytological evaluation is suboptimal, with reported rates of 88%-96%[54]. The suboptimal results are often attributed to damaged lymph node architecture[51,54]. This limitation of EUS-FNA is important in the evaluation of lymphadenopathy of unknown etiology, where the differential diagnosis includes lymphoma, metastasis, mycobacterial infection, and sarcoidosis, and core biopsy with preservation of lymph node architecture is particularly important for diagnostic purposes[53,55,56].

Comparative trials

We found no published prospective RCTs of EUS-FNA *vs* EUS-FNB for only lymph node biopsy. In the large RCT by Nagula *et al*[49] mentioned above, the subgroup of lymph node biopsies ($n = 46$) found no difference between EUS-FNA and EUS-FNB Procore in diagnostic yield (92.9% *vs* 94.4%) or number of passes needed to make a diagnosis (median 2, $P = 0.43$) (Table 3).

De Moura *et al*[52] performed a prospective study comparing EUS-FNA *vs* EUS-FNB exclusively for lymph node diagnosis. The authors performed an analysis on a prospectively collected database of 209 patients undergoing either EUS-FNA ($n = 108$) or EUS-FNB ($n = 101$) to evaluate lymph nodes. No predefined protocol was used in the study, and as such several different EUS-FNB needles were used including Acquire, SharkCore, and ProCore. The cohort consisted mostly of peri-hepatic lymph nodes (60%) followed by peri-pancreatic (10.4%) and mediastinal (10.4%), and were mostly accessed *via* a transgastric approach (45%). The pathology of most specimens

was benign (61%). Their primary outcome was diagnostic yield from cytological and histological analysis with and without immunohistochemical staining.

Overall, the authors found similar diagnostic accuracy between EUS-FNA and EUS-FNB (78.8% vs 83.2%, $P = 0.423$). However, the specificity for EUS-FNB demonstrated significant superiority (100% vs 93.62%, $P = 0.01$). In the subgroup analysis, EUS-FNB showed significantly higher sensitivity and specificity for abdominal lymph nodes. The diagnostic accuracy tended to be greater in the EUS-FNB cohort, but this failed to reach statistical significance. Following further analysis of lymph node location, EUS-FNB was associated with significantly higher sensitivity, specificity, and overall diagnostic accuracy for peri-hepatic lesions (88.9% vs 70.5%, $P = 0.038$).

Taken together, the study forms an important backdrop for further research, and argues for consideration of EUS-FNB over EUS-FNA for lymph node biopsy, specifically for peri-hepatic lesions.

UTILIZING BOTH TECHNIQUES

Additional studies have assessed the additive benefit of sampling lesions with both EUS-FNA and EUS-FNB. One such study by Hedenstrom *et al* [33] found that EUS-FNA/FNB compared to EUS-FNA alone had a higher diagnostic sensitivity for pancreatic tumors (89% vs 69%, $P = 0.02$), but not for pancreatic adenocarcinoma. However, compared to the diagnostic accuracy of EUS-FNB in isolation, Keswani *et al* [57] found no additional diagnostic accuracy by including EUS-FNA for pancreatic adenocarcinoma.

CONCLUSION

Endoscopic ultrasound tissue acquisition is routinely utilized in the evaluation of pancreatic mass lesions, subepithelial lesions, and lymph node biopsies. Ongoing confusion surrounds the ideal modality for EUS-TA, whether by EUS-FNA or EUS-FNB. While more robust comparative clinical trials exist for pancreatic lesions compared to subepithelial lesions and lymph nodes, the data continue to be mixed. Randomized controlled trials with homogenous populations and homogenous sampling protocols are needed in order to truly understand which needle is superior.

Based on the literature reviewed in this article, the authors conclude the following: EUS-FNA and EUS-FNB both provide high diagnostic accuracy, with low technical failure and adverse events, and thus either needle can be utilized for EUS-TA of pancreatic lesions, subepithelial lesions, and lymph nodes. In our experience we prefer FNB with a new generation needle as it allows us fewer passes of the needle, allows us to forgo ROSE which adds significant time and resources to a procedure, and gives a sample suitable for molecular testing. When increased quantity of DNA is desired for next generation sequencing, the utilization of EUS-FNB should be considered. For extramural subepithelial lesions, the utilization of EUS-FNB should be considered. Despite the dearth of prospective literature, we would recommend EUS-FNB for lymph node biopsy, specifically for peri-hepatic nodes.

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