EUS-guided tissue acquisition: Do we need to shoot for a "core" to score?

EUS-guided tissue acquisition (EUS-TA) by FNA (EUS-FNA) and fine-needle biopsy (EUS-FNB) sampling play a pivotal role in the diagnosis of GI and other non-GI malignancies and numerous nonmalignant processes.[1,2] Obtaining an adequate sample and arriving at an accurate diagnosis are fundamental endpoints of EUS-TA. Significant efforts have been made in recent years to establish an ideal EUS-TA technique, one that is efficient, effective, and associated with high diagnostic yield, specimen adequacy, accuracy, and low adverse event rate (key relevant and meaningful outcomes of EUS-TA). These efforts have focused on several variables associated with EUS-TA outcomes and can be categorized as those related to technique (number of passes, use of suction and stylet, fanning and capillary technique), needle type (gauge and FNA vs FNB needles), endosonographer (experience and volume, training and competency), cytopathologist (experience, training and competency), and center (volume and availability of onsite cytopathology evaluation [OCE]).[2]

One variable in the field of EUS-TA that has garnered a great deal of interest is obtaining histologic specimens or core biopsy samples using EUS-FNB needles. Proposed advantages of EUS-FNB over EUS-FNA needles include the potential for improving diagnostic yield, especially for nonpancreatic lesions; improving assessment of tissue architecture and allowing for immunohistochemistry or vital stains required for certain diagnoses (such as autoimmune pancreatitis, GI stromal tumors, metastasis, and lymphoma); and obviating the need for OCE and thus potentially resulting in cost savings.[2] Recently, a new generation of core biopsy needles has been introduced with variable results.[3-7] In a recent multicenter, randomized, controlled crossover trial, Aadam et al[6] compared the diagnostic yield of EUS-FNB (Echotip Procore; Cook Medical, Winston-Salem, NC) with EUS-FNA needles in patients presenting with pancreatic and nonpancreatic masses. Results demonstrated a significantly higher diagnostic yield with specimens obtained by EUS-FNB compared with EUS-FNA needles (90% vs 67.1%, P = .002). Although there was no difference between the 2 groups for pancreatic masses, the diagnostic yield of the EUS-FNB needle was higher than the EUS-FNA needle for nonpancreatic masses. Finally, a decision analysis performed from a third-party payer perspective that compared 2 competing strategies of EUS-FNB needles without OCE to EUS-FNA needles with OCE showed that use of EUS-FNB needles saved costs compared with EUS-FNA needles over a wide range of cost and outcome probabilities.[6] Two studies published in this issue of *Gastrointestinal Endoscopy* add to the growing body of literature describing the utility of a EUS-FNB needles in obtaining core biopsy samples and diagnostic yield compared with EUS-FNA using a needle with a novel fork-tip needle design (Shark Core; Medtronic Corp, Boston, Mass).[8,9]

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Using a case-control study design that included 156 patients, Kandel et al[9] compared the histologic yield of EUS-FNB (n = 39, 25%) with EUS-FNA (n = 117, 75%) needles in patients presenting with pancreatic and nonpancreatic lesions at a tertiary care center. To account for the retrospective nature of this study, consecutive cases undergoing EUS-FNB sampling of variable gauges were matched in a 1:3 ratio by lesion site and needle gauge to cases that underwent EUS-FNA. All procedures were performed with OCE, and specimen slides were evaluated by 2 cytopathologists for histologic yield using a standardized scoring system (0 for no material, 1-2 for cytologic yield, and 3-5 for histologic yield) proposed by Gerke et al.[10] The median histology score for EUS-FNB samples was 4, whereas that of EUS-FNA was 2, and histology cores were obtained from most EUS-FNB samples compared with those obtained by EUS-FNA (95% vs 59%, P = .01). The median number of passes required to obtain adequate tissue was significantly lower in the EUS-FNB group (2 vs 4,

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2016.08.004

$P = .01$). These differences remained significant for all lesion locations and target organs. After adjusting for age and size of lesion, the histology score of EUS-FNB samples was significantly higher compared with the EUS-FNA group on multivariate analysis (odds ratio, 11.3; 95% confidence interval, 3.14-76.68). However, although not the intent of the study, information on diagnostic yield for detecting neoplasia between the 2 groups was not provided. Further, detail on what the customary practice was during the study period of number of passes obtained before OCE was not apparent. As an example, if 2 passes for FNA are obtained back-to-back while waiting for OCE but a "wait-and-see" approach is used for each FNB pass, then study results may be altered.

In another retrospective study of prospectively collected data by Rodrigues-Pinto et al,[8] EUS-FNB sampling without OCE was compared with EUS-FNA with OCE. All patients (n = 33, 42 lesions) underwent both EUS-FNB and EUS-FNA sampling of the same lesion and using the same-gauge needle; EUS-FNA samples were assessed by cytopathologists and EUS-FNB samples were assessed by surgical pathologists. Importantly, there was no difference in the diagnostic yield of malignancy between the 2 techniques (EUS-FNB sampling, 72.7%, vs EUS-FNA, 66.7%; $P = .72$). However, EUS-FNB sampling provided qualitative information (degree of differentiation in malignancy, origin of metastatic lesion, and rate of proliferation in neuroendocrine tumors) at a higher frequency compared with EUS-FNA specimens. Given the comparable performance of these EUS-TA techniques, the authors suggest that this new EUS-FNB needle may eliminate the need for EUS-FNA with OCE.

Several issues regarding these studies and EUS-FNB in general merit further discussion. The main limitation of these studies, as acknowledged by the authors, is the retrospective study design; hence, these results need to be validated in future randomized controlled trials before wider adoption. The design would require standardized definitions with regard to diagnostic yield, protocol for obtaining specimens (eg, slow stylet withdrawal, dry suction, etc), specimen adequacy, and accuracy for the diagnosis of malignancy. Further, the criterion standard for the final diagnosis of malignancy used to determine operating characteristics not only requires cytohistologic confirmation but clinical follow-up of at least 12 months for nondiagnostic sampling.

These advances raise the important issue of the role of cytopathologists and OCE in EUS-TA. The goal of immediate OCE is to provide real-time feedback regarding the adequacy of a specimen to make the most accurate diagnosis with the minimum number of passes, thus maximizing the procedure efficiency and providing on-the-spot information for our anxious patients. The value of the latter point cannot be underestimated. Further, another potential advantage of OCE is the appropriate triage of limited specimens for ancillary tests (such as immunohistochemistry, flow cytometry, cytogenetics. or molecular studies) and high-quality specimen preparation.[11] A recent randomized controlled trial conducted at 3 tertiary referral centers that compared EUS-FNA of pancreatic masses with and without OCE demonstrated no statistically significant difference in the diagnostic yield of malignancy and proportion of patients with inadequate specimens, although patients undergoing EUS-FNA with OCE required fewer passes. There was no difference between the two groups with regard to diagnostic characteristics, cytopathology characteristics, number of repeat procedures, and adverse events. These results, along with associated cost-minimization analysis, suggest that OCE may not change diagnostic yields in patients with pancreatic masses undergoing EUS-FNA at tertiary care centers.[11]

With the improvement in EUS-TA techniques and availability of newer EUS-FNB needles, the role of OCE will continue to evolve. Similar to the potential role of OCE during EUS-FNA among less-experienced endosonographers and at centers with low adequacy rates (<90%),[12] future studies need to demonstrate that the promising results seen in these preliminary EUS-FNB studies can be duplicated among less-experienced endosonographers before widely reassessing the practice of OCE during EUS-FNB sampling. Standardized validated systems for handling and assessment of EUS-FNB specimens are also required. The interobserver variability among cytopathologists with regard to EUS-FNA and FNB specimens needs to be clarified, which is an issue that has significant implications for patient management. In a pilot study, we evaluated the interobserver variability among 4 cytopathologists in assessing EUS-FNA cytology specimens of solid pancreatic lesions using a novel standardized scoring system and showed that the interobserver agreement for the final diagnosis was moderate ($\kappa = .45$; 95% confidence interval, .4-.49) with minimal improvement when combining suspicious and malignant diagnoses ($\kappa = .54$; 95% CI, .49-.6).[13] These results are currently being validated in a multicenter study. In addition, similar to the recent advances in EUS with regard to training, competence, and quality metrics,[1,14] cytopathologists need to address these critical issues in future studies.

It should be acknowledged that EUS-FNA would suffice for most cases in clinical practice (eg, pancreatic adenocarcinoma), and histologic specimens may only be relevant for certain diagnoses that require assessment of tissue architecture (eg, autoimmune pancreatitis and lymphoma). However, in an era of personalized medicine, there is a clear impetus to obtain core specimens for molecular analysis to determine biologic pathways driving tumorigenesis and aid in determining appropriate therapy for an individual patient. In fact, several ongoing oncologic studies require core specimens for patient enrollment. Although tissue block specimens are typically considered optimal for molecular testing, EUS-FNA cytopathology

specimens are increasingly recognized as potential sources as well. A recent study demonstrated the feasibility of targeted next-generation sequencing on residual FNA rinse specimens.[15] Gleeson et al[16] also showed that EUS-FNA cytology specimens in patients with pancreatic and ampullary adenocarcinoma can serve as a suitable surrogate for surgically acquired specimens in genotyping using targeted next-generation sequencing. These results raise questions about whether core biopsy samples are routinely required to aid patient stratification for optimal therapy selection, for trials assessing neoadjuvant and adjuvant therapies, and for biomarker development.

In conclusion, these studies have set the stage for future high-quality, multicenter, randomized controlled trials to clarify the role of EUS-FNB sampling. These trials should not only evaluate the key relevant and meaningful outcomes of EUS-TA but also address the cost-effectiveness of our rapidly expanding needle options. Finally, the "core" of EUS-FNB sampling may potentially be its role in the era of personalized medicine.

DISCLOSURE

The following authors disclosed financial relationships relevant to this publication: S. Wani: Consultant for Medtronic and Boston Scientific; R. J. Shah: Consultant for Boston Scientific and Cook Endoscopy; advisory board member of Boston Scientific.

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Abbreviations: EUS-FNB, EUS-guided fine-needle biopsy; EUS-TA, EUS-guided tissue acquisition; OCE, onsite cytopathology evaluation.

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