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Editorial

Should EUS-guided tissue acquisition for histologic examination replace fine needle aspiration for cytologic examination? Another brick in the wall

Since its initial description in 1992 (1), endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has become the procedure of choice to obtain samples to reach the definitive diagnosis and proper lymph nodal staging of lesions of the gastrointestinal (GI) tract and of adjacent organs (2). The sensitivity of EUS-FNA, however, is strongly dependent on the availability of an on-site cytopathology, which has been clearly demonstrated to significantly influence the diagnostic accuracy, as well as, the proportions of indeterminate and unsatisfactory samples (3-5). Cytopathology, however, requires a high degree of expertise and unfortunately, the access to rapid on-site cytopathology evaluation (ROSE) and the availability of a cytopathologist specifically trained to interpret EUS specimens is not possible in many centers (6). This has created a barrier to the dissemination of EUS in the community and in many countries because the lack of cytology expertise results in a low diagnostic accuracy and therefore in a limited overall perceived utility of EUS (7,8).

This main limitation of EUS-FNA can be overcome by the obtainment of a tissue biopsy specimen for histological examination. A tissue core biopsy with preserved architecture is critical to diagnose and fully characterize certain neoplasms, such as lymphomas and GI stromal tumors. Moreover, tissue specimens for histological examination also provides the opportunity: a) To easily immunostain the tissue, further increasing differential diagnostic capabilities; b) To reach a specific diagnosis for benign diseases not always obtainable with a cytological sample, thus sparing patients from more invasive and risky sampling procedures or costly and unnecessary follow up examinations; and c) to potentially perform tissue profiling and/or cell culture needed to guide targeted therapies for individualized treatment of patients with cancer of the GI tract (9-11).

In the past, the ability to obtain fragments of tissue for histological examination with FNA needles of various diameters had been tested (12-14), and a tru-cut biopsy needle, the Quick-Core® needle, dedicated to EUS-guided fine needle biopsy (EUS-FNB) was developed but without meaningful advantages over EUS-FNA (15-17). More recently, standard 19-gauge needles using an ordinary technique (18-20) or by removing the stylet before inserting the needle in the working channel of the echoendoscope in the so called fine needle tissue acquisition technique (EUS-FNTA) (21-23) have been successfully utilized to gathered tissue biopsy samples in different patient populations. Moreover, new needles, the Procore™ needles, specifically designed to obtain histological samples have become available in 19G, 22G, and the 25G (24-27). A multicenter preliminary feasibility experience the 19G Procore™ (24) provided excellent results, though additional studies with this needle have not been published.

A single-center study by Iglesias-García et al. (28) published in this issue of the *Revista Española de Enfermedades Digestivas (Spanish Journal of Gastroenterology)*

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has finally arrived to fill in this gap. The authors performed a retrospective analysis of all patients with solid lesions throughout and adjacent to the GI tract, who underwent EUS-FNB utilizing the 19G Procore™ over an 18 month period. Of the 494 EUS-FNA procedures performed over the study period, 87 procedures (17.6 %) were EUS-FNB performed using the 19G Procore™ needle. In 18 patients (20.7 %), EUS-FNB was performed through the duodenum, a difficult location where to use such a large caliber needle. The bending position of the echoendoscope in the duodenum can cause great difficulty in both advancement of the needle out from the working channel of the echoendoscope and in removing the stylet, as also observed in the present study. On the other hand, these difficulties did not seem to affect the technical feasibility of tissue sampling, which was successfully accomplished in all patients. A very high diagnostic accuracy of 95.4 % was achieved using only a single needle pass.

This study raises questions and considerations. The first and most important question is when should EUS-FNB be used as the sampling procedure of choice? In this single center study, the authors did not refine the criteria used to select patients in whom to perform EUS-FNB with the 19G Procore™, which represented about one sixth of the EUS sampling procedures (17.6 %) during study period. were done with the intent to gather a tissue core biopsy sample instead of a cytological one. When evaluating the entire cohort it seemed the authors elected to use the 19G Procore™ especially when there was a high pre-procedure probability for need to perform immunohistochemical studies. This is similar to criteria used in the study published by Larghi et al. using the EUS-FNTA technique (21). On the other hand, in a recent algorithm proposed by Bang et al. (29), the authors suggested a changing in the paradigm of EUS-guided tissue acquisition where the choice of the needle to be used should be driven by the availability of ROSE; when ROSE is available, it was suggested that 25G and 22G needles should be used, while in centers where ROSE is not available 19G needles should be used to retrieve tissue biopsy samples. The authors also recommend using standard 19G needles for trans-esophageal, -gastric, and -rectal biopsy and the 19G Flex from Boston Scientific for the trans-duodenal route (30). Their recommendations, however, are not evidence based and there are no studies directly comparing commercially available needles. Indeed, as shown in the present study and in the previous multicenter published experience (24,28), use of the 19G Procore™ is associated with very high technical success and performance rates even, when used transduodenally by expert endosonographers. Despite these results the use of a particular needle will likely be based upon personal preference of the echoendoscopist until more definitive data will become available. Changes in the proposed algorithm described above are expected in the near future as studies evaluating sample adequacy and accuracy between cytology, cell-block, and core biopsy for obtaining molecular markers or cell culture with chemo-sensitivity testing to guide individualized cancer therapies will be performed. This process will require close collaboration with expert pathologists.

Another important aspect is the best way to process the specimens obtained with EUS-FNB (30). As pointed out by Iglesias-Garcia et al. (28), in the first feasibility study using the 19G Procore™ (24) each of the participating centers did not apply a uniform protocol to retrieve the sample from the needle (some by reinserting the stylet, others by flushing with saline) and to prepare the sample before processing in the pathology lab [samples were placed in formalin or in a liquid-based preparation, ThinPrep® (Hologic Corp, Bedford, MA)]. Interestingly, the interobserver agreement among five expert pathologists in grading the quality of specimens obtained in the five participating centers was found to be excellent and particularly high (91.2 %) with

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regard to sample adequacy, with a Fleiss' κ of 0.73 (95 % CI 0.61-0.81) (31). This suggests that different methods of processing specimens after FNB might not affect the overall specimen quality. However, future studies specifically designed to answer the ideal processing techniques are warranted so that standardized protocols can be developed. Such protocols would then allow better comparisons of results between centers and between different types of needles.

Finally, one question that naturally occurred to us and for which there is no clear answer is why did it take so long, after the excellent results of the preliminary multicenter study with the 19G Procore™, to have a second experience reported? A possible explanation is the fear of using a large biopsy needle, which theoretically increases the risk of adverse events (complications) as well as possibly increasing risk of damaging the echoendoscope. However, no increase in adverse events has been reported in any of the studies in which a 19G needle was used, independently of design and brand. On the other hand, the lack of studies on the 19G Procore™ may indicate the need to change our way of thinking and search for the best needle (maybe smaller diameter) that will provide enough tissue to perform all histologic/cytopathologic diagnostic studies to obtain the correct diagnosis and to allow for individualized treatment. Such an ideal needle should not only be able to meet the needs of experts but also that of all levels of endosonographers. We firmly believe in and strongly encourage close collaboration between endosonographers and pathologists, which is of paramount importance to succeed in this balanced effort to develop the ideal EUS-FNB needle.

Whether all of these efforts will change the practice of EUS from cytological based to histological based remains to be determined. However, the article by Iglesias-García et al. (28) represents another brick in the wall of evidence that needs to be built before EUS-FNB can become the standard of practice.

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