EUS-guided fine-needle tissue acquisition for solid pancreatic lesions: Finally moving from fine-needle aspiration to fine-needle biopsy?

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Since its introduction 26 years ago,[1] EUS-guided tissue acquisition (EUS-TA) has become an irreplaceable tool in the diagnostic and staging algorithm of lesions of the gastrointestinal tract or adjacent to it. EUS-TA can be performed to acquire samples for cytological (EUS-FNA) or histological (EUS-FNB) evaluation, with the same safety profile.[2] Both techniques present pros and cons and which one should be the preferred is still a matter of debate.[3,4]

It is well established that for subepithelial lesions and for lymph nodes of unknown origin suspicious for lymphoma, the acquisition of a tissue core biopsy specimen to perform immunohistochemical studies is of paramount importance. On the other hand, the story for the need of cytological or histological samples for solid pancreatic lesions (SPLs) is much more complex. In the first 10 years, EUS-TA for SPLs was performed using 22-gauge needles to collect cytological samples and was associated with a diagnostic accuracy in between 70% and 80%.[5] To reduce the number of nondiagnostic and atypical samples, rapid on-site evaluation (ROSE) was introduced with a 10%–15% gain in diagnostic accuracy.[6] Despite the fact that subsequent studies have reported controversial results on the efficacy of ROSE in significantly increasing the diagnostic accuracy of EUS-FNA,[7-10] clear advantages definitively exist. ROSE can give a timely feedback on the adequacy of the specimens and the preliminary cytological diagnosis of an aspirate, with the possibility to reduce the diagnostic turnaround time.[11] In addition, ROSE of EUS-FNA specimens may help obtain samples for ancillary studies, such as immunohistochemical analysis, bacterial cell cultures, flow cytometry, and gene rearrangement studies for unsuspected cases of lymphoma.[11] However, the limited availability of ROSE in many centers throughout the world,

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associated with the lack of cytology expertise outside high-volume tertiary care centers,[11] has resulted in a limited perceived utility of EUS[12] and has created a barrier to the dissemination of the procedure in the community and in many countries.[13]

To overcome these limitations of EUS-FNA, efforts to develop devices and techniques to gather samples for histological evaluation have been made. The first device that was developed was a 19-gauge tru-cut biopsy needle, the Quick-Core® (Cook Medical, Bloomington, IN, USA) needle, which did not show any advantages over EUS-FNA.[14] Standard 19-gauge FNA needles were also used to sample SPLs with a good accuracy rate,[15-17] but never gained full acceptance by nonexpert endosonographers because of the fear of complications. The same occurred to the 19-gauge Procore™, which was specifically built to gather tissue core biopsy samples through a lateral opening with a reverse-bevel technology.[18,19] The middle brother of the 19-gauge Procore™, the 22-gauge Procore™, has been utilized more extensively. However, a meta-analysis including nine studies revealed no significant difference between the 22-gauge Procore™ and standard 22-gauge FNA needles in diagnostic adequacy, diagnostic accuracy, or rate of histological core specimen acquisition.[20] In a subsequent editorial, the same authors of the meta-analysis questioned the need for FNB needles for SPLs in view of the limited number of indications.[21] On the other hand, other authors suggested to direct the search to build up a needle able to give enough tissue to perform all studies needed to reach the diagnosis and to allow for personalized treatment of individual patients, and also to be able to be used by all individual endosonographers.[22]

Recently, other novel needles for EUS-FNB have become available on the market: (i) the 20-gauge Procore™ needle (Cook Medical), which has novel design features, including cutting edges that were changed from a reversed to a forward-facing bevel and the tip design from a Lancet to a Menghini type; (ii) the SharkCore™ needle (Medtronic Corporation, Newton, Mass), which is a fork-tip needle with two opposite cutting edges; and (iii) the Acquire™ needle (Boston Scientific Corporation, Natick, Mass) with a Franseen tip geometry with three incorporated cutting edges.

Preliminary studies on these three needles have reported very encouraging results, with diagnostic accuracies >90%.[23-27] However, they were mostly retrospective, with a relatively small sample size, and all without a comparison with the standard of care, *i.e.*, FNA with ROSE.

A paper just published by Bang *et al.* in Gastrointestina endoscopy may bring the never-ending story of EUS-TA for SPLs to a conclusion.[28] Fifty patients underwent sampling of SPLs using both the 22-gauge Acquire™ and the 22-gauge SharkCore™ needles, with randomization of the needle order. Two passes for each needle were performed and the specimens were sent for cell block. Subsequent passes were made for ROSE, utilizing the touch imprint cytology technique using both needles alternatively until diagnosis was established. This technique allows obtainment of cytological slides from the solid component of the FNB sample, by first separating it on a slide from the bloody material and then by gently push and rub it down with another slide.

No significant differences in the area of the total tissue acquired (median 6.1 mm^2 *vs.* 8.2 mm^2), tumor area (median 0.9 mm^2 *vs.* 1.0 mm^2), desmoplastic fibrosis (median 4.3 mm^2 *vs.* 5.2 mm^2), retained histological architecture (100% *vs.* 83%), diagnostic cell block (96% *vs.* 92%), and diagnostic adequacy at ROSE (94% *vs.* 98.0%) between the two study needles were found. Based on these impressive results, the authors concluded that these new-generation FNB needles may obviate the need for ROSE. This has important implications in term of costs and may favor, by assuring a high diagnostic accuracy, the expansion in the utilization of EUS outside high-volume centers and in countries where cytology is underdeveloped.

Bang *et al.*[28] should be congratulated for their study, which represents a real breakthrough in the practice of EUS-TA. However, some considerations need to be done. First of all, cytological samples from EUS-FNA are rich in pure tumor cells and seem to be a more reliable source of DNA compared with histological specimens, which are often rich in stroma. For this purpose, more than 1000 cells, corresponding to >10 ng DNA, are considered to be an adequate specimen for molecular analyses.[29] In the study by Bang *et al.*, no assessment of the degree of cellularity on the collected cell block samples was performed. Furthermore, alcohol-based fixation of FNA smears improves the preservation of nucleic acids, which are

partially degraded by formalin fixation of the histologic specimens.[30,31] Based on these premises in centers with ROSE, when evaluating patients with SPLs, it would be still important to continue performing the touch imprint cytology technique on the samples acquired with FNB needles to gather cells for DNA analysis. On the other hand, in centers without ROSE, training of the endosonographers by the cytopathology or the cytotechnician in performing the touch imprint cytology technique, which does not imply diagnostic consideration, should be strongly encouraged.

Second, up to now, the evidence that core biopsy tissue samples for histological examination are more adequate than cytological ones to perform predictive molecular markers or gene expression analyses to guide risk stratification of patients with pancreatic cancer or neuroendocrine tumors and to drive individualized therapies is still limited and needs further confirmations. Future studies to further clarify these issues are warranted.

Finally, the study is a single-center study with a cross-over design that allows decreasing the number of the required sample size, which, however, does not represent methodologically the best way to compare two different diagnostic tests or devices. Moreover, the reproducibility of their results needs to be proven in a multicenter study. In this regard, we are conducting a large, multicenter, international noninferiority study to compare FNB with FNB plus ROSE, obtained with the touch imprint technique (NCT03322592).

In conclusion, Bang *et al.*[28] added another brick in the wall in the practice of EUS-TA for the evaluation of SPLs. Until more data will be available, our suggestion is to continue to perform both cytological and histological evaluations using the same FNB needle and the touch imprint technique. More studies focused on addressing the value of cytological and histological samples to perform predictive molecular markers and gene expression analyses in order to pave the road for individualized treatment of pancreatic cancer are desperately needed.

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