EUS-Guided Fine Needle Aspiration of Gastrointestinal Stromal Tumors: The GIST of the Matter

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Our understanding of gastrointestinal stromal tumors (GIST) has evolved rapidly over the last few years. GISTs are now considered a distinct entity that arise from the interstitial cells of Cajal and exhibit a variable clinical course. One of the major breakthroughs was the discovery of CD117 antigen expression, also referred to as *c-kit*, on the tyrosine kinase receptor by GISTs. This antigen can be identified using immunohistochemistry (IHC), is expressed nearly universally by GISTs, and is critical in allowing differentiation of GISTs from myogenic, neurogenic, and other mesenchymal tumors. There has also been a paradigm shift in how the clinical behavior of GISTs is viewed; even though only 10–30% of GISTs are clinically malignant [1], all GISTs are now considered to have malignant potential with long-term follow-up [2]. This shift is based on a number of studies, one of which is a large series from Armed Forces Institute of Pathology (AFIP), where GISTs larger than 2 cm were found to have some finite risk of recurrence [3]. The natural history of smaller GISTs remains unclear at this point, though there have been reports of aggressive behavior in GISTs smaller than 2 cm in size [4]. Specific criteria that include size, mitotic count, and location of GISTs have been described to stratify risk of malignancy and tailor treatment [3, 5]. In this context, an accurate diagnosis, and if possible risk stratification of GISTs, is critical. Towards this end, endoscopic ultrasound (EUS) has become an important tool in our armamentarium.

GISTs are typically seen to arise from the fourth layer of the gastric wall. While EUS imaging alone can accurately determine tumor size, wall layer of origin, echogenicity, and tumor margins, it is unable to reliably discriminate GISTs from other subepithelial tumors in all cases [6, 7]. Whether specific endosonographic features alone can help define low-risk and high-risk lesions also remains uncertain [8–10]. Consequently, many experts recommend EUS-guided fine needle aspiration (EUS-FNA) for diagnostic sampling of subepithelial lesions when a diagnosis of GIST is being considered. However, in general, gastroenterologists continue to view EUS-FNA for subepithelial lesions with ambiguity. A recent survey of 134 members of the ASGE EUS special interest group found that only 58% believed that EUS combined with FNA was most predictive of a diagnosis of GIST [11]. This notion that EUS-FNA is unrevealing in GISTs has been supported by reports of inadequate tissue acquisition with EUS-FNA with yields as low as 33.3% in all specimens [12]. Nevertheless, there is a growing body of more recent literature that has reported steadily improved diagnostic yields of EUS-FNA for GISTs.

Watson et al. [13], in the current issue of *Digestive Diseases and Sciences*, provide additional data regarding the diagnostic yield and performance characteristics of EUS-FNA for GISTs. The authors retrospectively analyzed 65 consecutive patients who underwent EUS-FNA for 66 solid-appearing submucosal upper GI tract lesions over a 4-year period. A resection specimen was available and used as a reference in 28 patients. FNA was performed using either a 22-gauge or 19-gauge needle at the discretion of the endosonographer. A result was deemed diagnostic if a sufficient sample for cytopathologic evaluation and IHC analysis was obtained leading to a specific diagnosis. The authors found EUS-FNA to be diagnostic in 68%,

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suspicious in 12%, and non-diagnostic in 20% of the lesions. In univariate analysis, the diagnostic yield was higher for gastric lesions, lesion size ≥ 20 mm, and with the presence of on-site cytopathology. However, none of these differences were significant in multivariate analysis. The size of the FNA needle or the number of needle passes did not influence the diagnostic yield. EUS-FNA was diagnostic in 18/22 (82%) lesions that were confirmed to be GISTs on pathology. The performance characteristics of EUS-FNA for GIST based on cytology and IHC were as follows; sensitivity 82%, specificity 100%, and overall accuracy 86%. The authors concluded that EUS-FNA provides a high yield for sampling submucosal lesions and is highly accurate for diagnosing GISTs.

The diagnostic yield reported by Watson et al. is comparable to other recent studies where a definite diagnosis of GIST is made using cytology and IHC staining. Higher yields have been reported by other authors but these have included “suspicious” cytology findings without confirmatory IHC staining [14, 15]. The current study also reports a yield of 80% when both definite and suspicious diagnosis is considered. However, whether suspicious cytology should be included in the diagnostic yield remains a subject of debate, particularly given that the earlier misclassification of GISTs was in the era predating IHC staining for CD117. For now, a diagnosis that is confirmed by IHC staining should be considered as the true diagnostic yield.

The authors did not find any factors that conclusively and significantly affected the diagnostic yield of EUS-FNA. However, they did report an improved diagnostic yield with a gastric location and increasing size of the lesion as well as the presence of on-site cytopathology. These findings make sense conceptually, but they have not been replicated consistently in other studies. For instance, the anatomic location of GISTs has not been demonstrated to improve diagnostic yield [14, 16], whereas improved yield with increasing size of the lesion has been suggested [15, 16]. However, it has also been reported that the yield may actually decrease, presumably because of necrosis, if the lesion size is >10 cm [15]. The presence of on-site cytopathology has been associated with a higher diagnostic yield in FNA for GISTs as well as other lesions [15]. As the authors correctly point out in their discussion, given that a diagnosis of GIST is confirmed on IHC staining, the true value provided by an on-site cytopathologist is confirmation of acquisition of adequate tissue. Interestingly, there was no significant difference in diagnostic yield for the different needle sizes or the number of passes. There have been similar findings in other studies [14, 16].

The findings of this study also need to be considered in the context of study design. This was a retrospective case series that, in addition to being subject to an inherent

selection bias by virtue of its study design, was also not powered to detect differences in factors affecting the yield of EUS-FNA in GISTs. It is also unclear whether all patients with suspected GIST were selected for EUS-FNA or was FNA attempted in only select patients. Furthermore, there were patients in the study who underwent surgery despite a non-diagnostic FNA. This raises the very relevant issue of whether an FNA should be attempted in patients who are clearly destined for surgery regardless of the results. All these limitations notwithstanding, the 68% diagnostic yield and 82% accuracy rate for histologically confirmed GISTs does lend credence to the role of EUS-FNA as the sampling modality of choice for these lesions.

Finally, in spite of studies reporting encouraging results for EUS-FNA for diagnosis of GISTs, the area of sampling GISTs for diagnosis and risk stratification remains a subject of debate. Much of the angst stems from the challenge of distinguishing lesions that need surgery from those that can be observed. As mentioned above, the risk of malignancy for GISTs can be calculated according to the size of the lesion, location, and the mitotic rate. The mitotic index requires 50 high-powered fields (HPF) and cannot be calculated with cytology specimens. The core needle biopsy, which was greeted with much enthusiasm because it offered the theoretical benefit of obtaining a core of tissue rather than a cluster of cells, did not pan out to be the optimal device for tissue acquisition [17, 18]. Consequently, at this point, the mitotic rate can only be reliably calculated with surgical resection, the caveat being that surgical resection for all GISTs is not an optimal approach since some indolent lesions with low malignant potential may not require excision at all.

The crux of the matter remains the evolution of diagnostic sampling to a point where we can obtain tissue reproducibly and reliably not only for diagnosis but also for risk stratification of GISTs. This can be accomplished by either developing new sampling devices that provide adequate tissue for IHC staining, histological, or mutational analysis, or the development of new markers that will allow us to provide a preoperative, individualized risk assessment for these lesions. Ongoing interest in this research field may provide us with answers in the not-too-distant future.

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