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Approach to Gastric Subepithelial Lesions: From Differential Diagnosis to Histologic Confirmation

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The detection of gastric subepithelial lesions (SELs) has increased with the widespread use of endoscopic screening. While most SELs are benign, some, such as gastrointestinal stromal tumors, have malignant potential, underscoring the importance of accurate diagnosis. Histological confirmation is often challenging due to the submucosal location of these lesions, which limits the effectiveness of conventional biopsy techniques. Endoscopic ultrasonography (EUS) plays a central role in lesion characterization, providing information on the layer of origin, echogenicity, and internal features. When tissue sampling is required, techniques such as mucosal incision-assisted biopsy (MIAB) and EUS-guided fine-needle biopsy (FNB) offer complementary advantages. MIAB has demonstrated a diagnostic yield of approximately 89%, particularly for lesions <20 mm, whereas FNB provides sufficient tissue for immunohistochemical analysis. As international guidelines differ regarding indications and methods of tissue acquisition for SELs, tailored management based on EUS findings, patient-specific factors, and institutional capacity is essential for optimal diagnostic outcomes. This review aims to summarize the current understanding of gastric SELs based on evidence-based guidelines and recent studies and offer practical guidance for clinicians diagnosing these lesions in routine practice.

Keywords Gastrointestinal neoplasms; Subepithelial tumor; Endoscopic ultrasonography; Biopsy, fine-needle; Diagnosis, differential.

INTRODUCTION

The detection of gastric subepithelial lesions (SELs) has increased in recent years, largely because of the widespread use of esophagogastroduodenoscopy as part of routine health screening programs and the aging of the general population.[1] Gastric SELs are typically defined as protrusions covered by normal mucosa that are frequently discovered incidentally during endoscopy. Although many of these lesions are benign, they encompass a wide spectrum of histological entities, including tumors with malignant potential such as gastrointestinal stromal tumors (GISTs), neuroendocrine tumors (NETs), and lymphomas.

A key challenge in the clinical management of SELs is their submucosal location. As these lesions originate from deeper layers of the gastrointestinal wall, often beyond the reach of standard biopsy forceps, an accurate histological diagnosis is frequently difficult to obtain. Although endoscopic ultrasonography (EUS) has emerged as the most useful imaging modality for characterizing SELs by identifying the originating layer, echogenicity, and other internal features, in some cases, it cannot definitively differentiate between benign and malig-

nant lesions.[2] Therefore, tissue acquisition techniques, such as EUS-guided fine-needle aspiration (FNA) or fine-needle biopsy (FNB), bite-on-bite biopsy, and mucosal incision-assisted biopsy (MIAB), have been developed to improve the diagnostic accuracy in selected cases.[3-5]

Given the heterogeneity of SELs and their variable clinical significance, individualized diagnostic and therapeutic strategies are necessary. International guidelines, including those of the European Society of Gastrointestinal Endoscopy (ESGE) and American Society for Gastrointestinal Endoscopy (ASGE), offer differing recommendations based on lesion size, EUS features, and institutional capabilities.[4,5] This review aims to summarize the current understanding of gastric SELs based on evidence-based guidelines and recent studies and offer practical guidance for clinicians diagnosing these lesions in routine practice.

CLASSIFICATION AND EPIDEMIOLOGY OF GASTRIC SELs

SELs are most often detected incidentally in asymptomatic patients. Although rare, some lesions may present with significant clinical symptoms, such as bleeding or obstruction, and prompt endoscopic or surgical resection may be required for both diagnosis and treatment. However, the vast majority of SELs are asymptomatic; thus, the primary clinical objective is to assess the malignant potential of the lesion and determine whether it requires surveillance, close follow-up, or resection.

SELs encompass a wide spectrum of benign and malignant pathologies, including vascular lesions, cysts, lipomas, GISTs, leiomyomas, NETs, granular cell tumors, heterotopic pancreatic tissue, schwannomas, and lymphomas. Accurate differentiation between these subtypes is often challenging because conventional white-light endoscopy (WLE) and standard forcep biopsies are frequently insufficient for characterization and tissue acquisition.

Endoscopic features alone are generally inadequate for establishing a definitive diagnosis of gastric SELs, except for lipomas (Table 1). Lipomas typically appear yellowish on WLE and demonstrate a positive "pillow sign" or "cushion sign," characterized by indentation when gently compressed with biopsy forceps. Although granular cell tumors and NETs may also have a yellowish hue, they are usually firmer and do not display the pillow sign.[6] When a lesion is firm and does not indent on compression, its mobility can be assessed using the "rolling sign." A positive rolling sign, where the lesion shifts position when pushed, suggests that the mass originates from the muscularis mucosa or submucosal layers. Similarly, the "tenting sign," in which the overlying mucosa lifts while the lesion remains fixed, indicates a deeper origin, such as the muscularis mucosa or deeper layers.[7] Certain cases of heterotopic pancreatic tissue, particularly those located in the gastric antrum, may exhibit central umbilication, providing clues for diagnosis; however, these features are not consistently reliable.

Moreover, prior studies have shown that up to one-third of incidentally detected SELs are attributable to extrinsic compression rather than true intramural pathology.[8] In such cases, EUS plays a pivotal role in distinguishing intramural from

Table 1. Summary of gastric subepithelial lesions: clinical, endoscopy-based differentiation

Subepithelial lesion	Typical location	Layer	Endoscopy and history	Malignant potential
Lipoma	Antrum	3rd	Yellowish, soft, movable, cushion sign+	N
Leiomyoma	Cardia, HB	2nd/4th	Normal color, hard, movable/not movable	N
Schwannoma	Body	4th	Normal color, hard, not movable, mid-aged women	N
Heterotopic pancreas	Antrum	3rd, 4th	Normal color, hard, not movable, umbilication, younger patients	N
Varices	Cardia, fundus	3rd	Bluish color, soft, not movable, patients with portal hypertension	N
Duplication cyst	Fundus, HB	3rd	Normal color, soft, not movable	Y (extremely rare)
Gastritis cystica profunda	MB, antrum	3rd	Translucent color, soft, not movable	Y (extremely rare)
Gastrointestinal stromal tumor	Fundus, HB	2nd/4th	Normal color, hard, sometimes erosion/ulceration, movable/not movable, elderly patients	Y
Neuroendocrine tumor	Fundus, HB	2nd/3rd	Normal or light yellowish, hard, sometimes with erosion, not movable	Y
SEL-like carcinoma	Any	Any	Erosion, ulceration	Y
Metastatic cancer	Fundus, body	Any	Erosion, ulceration	Y

SEL, subepithelial lesion; HB, high body; MB, mid body.

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extramural origins. Compared to WLE, which has a reported sensitivity of 87% but a specificity of only 29%, EUS offers markedly superior diagnostic performance, with reported sensitivity and specificity of 92% and 100%, respectively.[9] Accordingly, EUS is strongly recommended in the evaluation of non-lipomatous SELs to enhance diagnostic accuracy.

SELs can occur throughout the stomach; however, certain subtypes exhibit a predilection for specific locations. GISTs and leiomyomas are most frequently found in the upper stomach, including the cardia and fundus, with leiomyomas particularly predominant in the cardia.[10] In contrast, heterotopic pancreatic tumors and lipomas are more frequently observed in the antrum. NETs also show location-specific patterns: type 1 lesions typically arise along the lesser curvature of the gastric body, reflecting the distribution of chronic atrophic gastritis, while type 3 lesions can occur throughout the stomach.[10]

Several large-scale Korean studies have reported on the epidemiology and natural history of gastric SELs, particularly those detected incidentally during routine endoscopic examinations. The prevalence of gastric SELs has consistently ranged from 1.6% to 1.9% among asymptomatic adults undergoing screening endoscopies, with a higher frequency noted in older populations.[1,11,12] The most commonly identified histological subtypes include GISTs (39.1%), ectopic pancreatic tissue (22.5%), and leiomyomas (18.3%).[11] Notably, up to one-third of these lesions, particularly those <1 cm in size, are caused by extrinsic compression rather than true intramural tumors. Longitudinal follow-up data indicate that while most SELs remain stable over time, approximately 8%–9% exhibit significant growth over a follow-up period of 4–5 years. Importantly, initial features such as irregular borders and lesion sizes ≥2 cm have been associated with an increased risk of progression.[12]

USE OF EUS FOR DIFFERENTIAL DIAGNOSIS

EUS is considered the gold-standard imaging modality for evaluating SELs because of its ability to provide high-resolution images of the lesion's internal characteristics (Fig. 1). By directly applying the ultrasound probe to the lesion's surface, often with water immersion, EUS offers detailed insights into the lesion's size, layer of origin, echogenicity, heterogeneity, growth direction, and vascularity.[8,13] These features facilitate the estimation of histological subtype and potential malignancy. Prior studies have confirmed the superior diagnostic performance of EUS over computed tomography, especially for small lesions, with a higher accuracy in both detection and histological prediction.[14-16]

However, despite its utility, EUS interpretation remains operator-dependent, and interobserver agreement is limited, especially for hypoechoic lesions in the submucosal or muscularis propria (MP) layers, where the diagnostic accuracy can be as low as 43% when compared with histological diagnosis.[8,17] Understanding the layer of origin is crucial for narrowing down the differential diagnosis.[7] For example, lesions arising from the second layer (muscularis mucosa) commonly include NETs and lymphangiomas, whereas those arising from the third layer (submucosa) typically include lipomas and ectopic pancreatic tissue. The fourth layer (MP) is the most common site of origin of SELs and includes leiomyomas, GISTs, and schwannomas. However, these distinctions are not absolute, as some lesions, such as NETs and ectopic pancreatic tissue, may span multiple layers as they grow. Echogenicity on EUS also aids in differentiation: cystic and lymphatic lesions are anechoic, lipomas are hyperechoic, and most solid tumors, including GISTs, are hypoechoic. The homogeneity further refines this assessment. Benign lesions, such as lipomas, leiomyomas, and low-risk GISTs, typically appear homogeneous, whereas heterogeneity is more commonly observed in high-risk GISTs and ectopic pancreatic tissue.

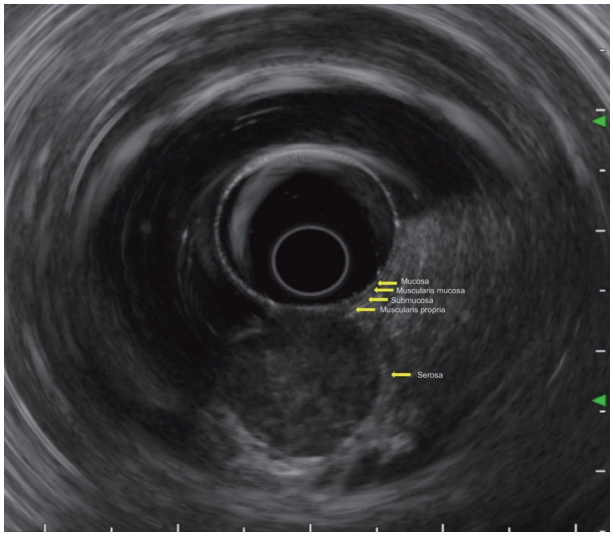

Fig. 1. Radial EUS image of a subepithelial lesion in the gastric body. EUS demonstrates an approximately 26×24 mm lesion arising from the muscularis propria, which is homogeneous and hypoechoic with a sharp border. EUS, endoscopic ultrasonography.

One of the most clinically important and diagnostically challenging tasks of EUS is differentiating between hypoechoic lesions arising in the fourth layer. Leiomyomas typically show a homogeneous, hypoechoic pattern that blends naturally with the adjacent muscle layer. Schwannomas may also be hypoechoic and are usually slightly more hypoechoic than the surrounding muscle. They may present with a marginal halo that appears as a hypoechoic rim around the lesion and histologically corresponds to a peripheral lymphoid cuff. In contrast, GISTs tend

to be more echogenic than muscles and exhibit a heterogeneous internal echotexture, particularly in high-risk cases. Features such as irregular borders, internal anechoic or hyperechoic foci, and heterogeneous echogenicity indicate malignant potential and should raise the suspicion of GISTs requiring further evaluation or resection.[18,19]

WHEN SHOULD ENDOSCOPIC TISSUE ACQUISITION BE CONSIDERED?

Tissue acquisition for histopathological diagnosis is considered the gold standard in the evaluation of SELs, as it directly informs clinical decision-making. Given the malignant potential of certain lesions, particularly GISTs, histological confirmation is essential in select cases. However, owing to the normal mucosa covering most SELs, conventional forcep biopsies typically fail to obtain sufficient diagnostic material.[20] One method for improving the tissue yield is the bite-on-bite biopsy technique, which involves obtaining repeated samples at the same site using either standard or large-bore forceps. Despite its utility, this technique has several limitations, including the need for multiple passes (at least 4–10), increased bleeding risk (up to 2.8%), and a relatively low diagnostic yield, ranging from 17% to 42%.[21] Therefore, it is generally reserved for lesions without rolling or tenting signs, such as NETs, lymphomas, or SEL-like carcinomas, or for those with visible mucosal openings (e.g., heterotopic pancreatic tissue, or gastritis cystica profunda) or surface changes, such as erosions or ulcerations,

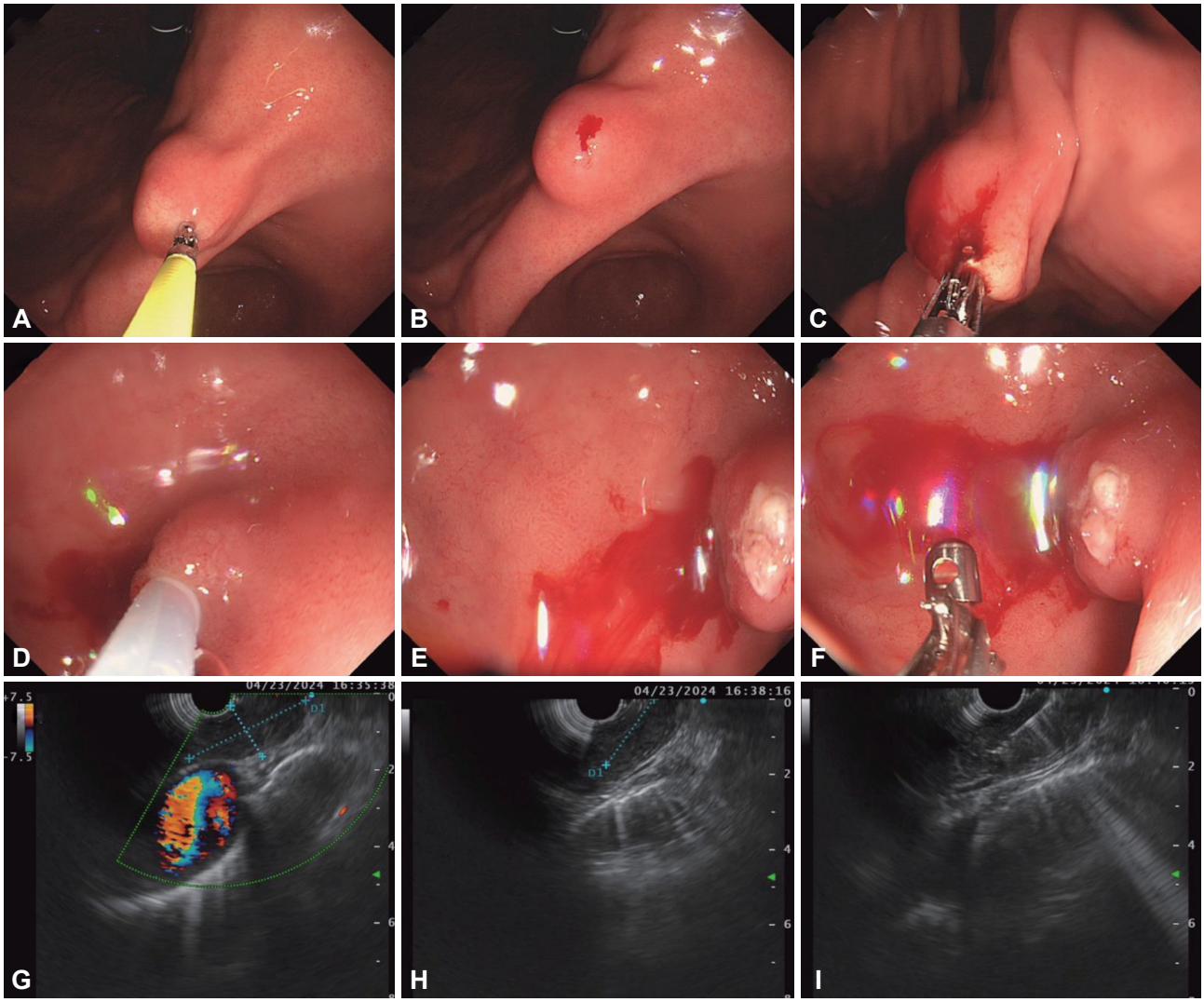

Fig. 2. Representative endoscopic and EUS-guided biopsy techniques for gastric and esophageal SELs. A-C: Bite-on-bite biopsy of a 15 mm SEL at the gastric angle. Mucosal tissue was sequentially removed to expose the subepithelial layer. D-F: MIAB of a 12 mm SEL. A mucosal incision was made to directly visualize the lesion, followed by forceps biopsy. G-I: EUS-guided fine-needle aspiration of a 34×15 mm SEL. A nearby large vessel was noted, requiring caution. Tissue sampling was performed using a 22G ProCore needle with a 21 mm safety margin. EUS, endoscopic ultrasonography; SELs, subepithelial lesions; MIAB, mucosal incision-assisted biopsy.

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where superficial sampling may be more informative.

The current guidelines provide additional clarity on when tissue sampling should be pursued. The ESGE suggests obtaining a tissue diagnosis for all SELs with features suggestive of GISTs when they are larger than 20 mm, present high-risk stigmata, or require surgical or oncological intervention.[4] However, this is a weak recommendation based on low-quality evidence. Other societies, including the European Society for Medical Oncology and the Japanese GIST Guideline Subcommittee, recommend that even small GISTs (<20 mm) should be resected if immunohistologically confirmed.[22,23] In contrast, the National Comprehensive Cancer Network (NCCN) advises close surveillance of small GISTs when high-risk features are absent.[24] Particularly in patients with severe bleeding in whom surgery is feasible, biopsy should be avoided, and resection should be planned within a multidisciplinary team approach. Therefore, there is no consensus on the optimal timing for endoscopic tissue acquisition in SELs. Decisions should be individualized based on EUS findings, patient symptoms, and clinical background as well as institutional resources and expertise.

TISSUE ACQUISITION TECHNIQUES OTHER THAN BIOPSY

To overcome the suboptimal diagnostic yield of the bite-on-bite biopsy technique, alternative methods that allow direct access to deeper tissue layers have been developed. These include MIAB, which exposes the lesion through a small mucosal incision; EUS-FNA; and EUS-FNB, which enables targeted sampling under ultrasound guidance (Fig. 2).[25] Despite these advances, preoperative histological confirmation remains challenging due to the deeply buried nature of many SELs.

In MIAB, the mucosa overlying the lesion is incised using a snare or an endoscopic submucosal dissection knife to expose the surface of the SEL, allowing direct tissue sampling. Its diagnostic accuracy is approximately 89% (95% confidence interval: 82.7%–93.5%), with the main adverse event being bleeding, observed in approximately 0.36%–12.9% of cases.[26] MIAB offers a relatively high diagnostic yield and is particularly effective for smaller lesions (<20 mm in diameter), where it may outperform EUS-FNA.[27] However, it required longer procedure times than EUS-FNA in a randomized crossover study (34 min vs. 26 min, p=0.0011)[28] and may not be suitable for patients with bleeding tendencies. Additionally, if subsequent endoscopic resection is scheduled, fibrosis induced by the MIAB may pose technical challenges.

EUS-guided tissue acquisition, including FNA and FNB, is a widely used approach for the histological diagnosis of SELs. FNB is generally preferred over FNA because of its higher diagnostic yield, greater ability to obtain core tissues suitable for immunohistochemical analysis, and fewer needle passes. Meta-analyses based on 17 studies involving 978 patients have reported that FNB achieved a diagnostic accuracy of approximately 60% (based on 17 studies involving 978 patients), with superiority over FNA in terms of sample adequacy, diagnostic yield, and technical efficiency.[3] Procedure-related adverse events are rare, with bleeding reported in less than 1% of cases.[29] Importantly, EUS-guided tissue acquisition does not increase the risk of tumor rupture in GISTs and has no known negative impact on the prognosis.[30] The diagnostic sensitivity of FNB is the highest when a visible white core (VWC) longer than 4 mm is obtained, highlighting the importance of an adequate sampling technique.[31] The VWC refers to the whitish, thread-like tissue obtained from the target lesion, which reflects diagnostically valuable material for histologic evaluation. Studies have shown that achieving a VWC length of at least 4 mm significantly increased diagnostic sensitivity, reaching up to 98.7%.[31] To ensure a high diagnostic yield, endoscopists must use a core biopsy needle (usually 22 gauge), perform at least three needle passes, and carefully process the sample.

Notably, international guidelines differ regarding their rec-

Table 2. Comparison of ESGE and ASGE guidelines on histologic diagnosis of SELs

Category	ESGE (2022)	ASGE (2017)
Indication for histologic diagnosis	SEL ≥20 mm or suspected GIST or high-risk EUS features	Hypoechoic lesion originating from the 4th layer (MP), lesion ≥2 cm, or with high-risk EUS features
Recommendation for SELs <20 mm	MIAB as first-line, FNB as second-line option - if suspected GIST or high-risk EUS features	Surveillance if no high-risk EUS features
Recommendation for SELs ≥20 mm	EUS-FNB or MIAB equally recommended	Tissue acquisition considered, using either FNA or FNB
View on FNA and FNB	FNB preferred over FNA; emphasizes securing ≥4 mm visible white core	Diagnostic yield varies (46%–93%), influenced by needle design and ROSE availability

ESGE, European Society of Gastrointestinal Endoscopy; ASGE, American Society for Gastrointestinal Endoscopy; GIST, gastrointestinal stromal tumor; MP, muscularis propria; EUS, endoscopic ultrasound; SELs, subepithelial lesions; MIAB, mucosal incision-assisted biopsy; FNB, fine-needle biopsy; FNA, fine-needle aspiration; ROSE, rapid on-site evaluation.

ommendations. The ESGE guidelines recommend histological diagnosis for all SELs measuring ≥20 mm and those measuring <20 mm with high-risk features suggestive of malignancy (Table 2).[4] In contrast, the ASGE guidelines emphasize that most SELs are benign, and tissue acquisition is not always required.[2] However, this finding suggests that hypoechoic lesions arising from the MP layer, such as GISTs and leiomyomas, should be evaluated using EUS-FNA or FNB.

Furthermore, the ESGE provides more structured guidance regarding sampling methods: for SELs ≥20 mm, either EUS-FNB or MIAB is recommended, while for lesions <20 mm, MIAB is considered the first-line option, with FNB as an alternative if MIAB is not feasible. In contrast, the ASGE guidelines list multiple sampling options, including standard forcep biopsies, bite-on-bite biopsies, jumbo biopsies, unroofing, and EUS-FNA/FNB, but do not specify the indications for each technique. For example, when considering a 15 mm SEL originating from the MP layer, the different approaches of the two guidelines become evident. Based on its structured criteria, the ESGE guidelines generally favor surveillance without tissue acquisition in the absence of high-risk features. In contrast, the ASGE recommends proceeding with tissue sampling, such as EUS-FNB or another available technique, given the lesion's hypoechoic nature and MP origin, which raises concerns about potential malignancy.

CONCLUSION

The diagnosis of gastric SELs requires a careful balance between lesion characteristics, patient-specific factors, and institutional capabilities. While most lesions are benign, selected cases, especially those with malignant potential, require histological confirmation using appropriate techniques such as MIAB or EUS-FNB. Understanding the indications, strengths, and limitations of each diagnostic method based on international guidelines is essential to optimize clinical outcomes.

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