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SYSTEMATIC REVIEW OPEN ACCESS

Practice Guidelines for the Diagnosis and Treatment of Subepithelial Lesion Observed in Upper Gastrointestinal Endoscopy

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Received: 9 June 2025 | **Revised:** 17 November 2025 | **Accepted:** 20 December 2025

Keywords: endoscopic treatment | guidelines | subepithelial lesion | systematic review

ABSTRACT

Subepithelial lesions (SELs) of the upper gastrointestinal tract are commonly detected during endoscopic examinations and encompass a broad spectrum of benign, potentially malignant, and malignant tumors. While most SELs are asymptomatic and incidentally found, accurate diagnosis remains challenging due to their subepithelial location, necessitating advanced imaging and tissue acquisition techniques. Endoscopic ultrasound (EUS) plays a crucial role in differentiating SELs, but its diagnostic accuracy remains limited. In response to the need for standardized clinical management, the Korean College of Helicobacter and Upper Gastrointestinal Research has developed evidence-based practice guidelines for the diagnosis and endoscopic treatment of SELs. These guidelines were established through a systematic review of existing literature and expert consensus, resulting in 11 key recommendations addressing diagnostic strategies, surveillance intervals, biopsy techniques, and indications for endoscopic or surgical resection.

Beom Jin Kim and Seung Joo Kang, both authors equally contributed as co-first authors.

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1 | Introduction

A subepithelial lesion (SELs) refers to a raised lesion arising from the gastrointestinal wall between the lamina propria and the serosa, located beneath the epithelium and covered by mucosa identical to adjacent tissue [1]. These lesions are classified as benign or potentially malignant/malignant. Common benign types include leiomyomas, granular cell tumors, lipomas, and fibromas; common malignant or potentially malignant types include gastrointestinal stromal tumors (GIST), neuroendocrine tumors (NET), glomus tumors, and lymphomas [2, 3].

In a study analyzing approximately 80 000 patients who underwent screening endoscopy, SELs were found in 1.94% of the upper gastrointestinal tract, and gastric SELs were found in 0.74% of patients [4]. The mean size of gastric SELs varies across studies, typically ranging from 8 to 15 mm [4–7], with screening cohort reporting mean sizes of 8.7 mm [4] and studies with histological confirmation showing mean sizes of 13.6 mm [7]. Most gastric SELs are asymptomatic and incidentally discovered, although they can occasionally cause dysphagia, pain, obstruction, or bleeding [6].

Their endoscopic appearance is typically uniform, making visual differentiation difficult. Due to their subepithelial location, histological diagnosis by forceps biopsy is often challenging. Although EUS helps in differential diagnosis, its accuracy is limited (43%–50%) [7].

To improve diagnostic yield, EUS-guided fine-needle biopsy (EUS-FNB) and mucosal incision–assisted biopsy (MIAB) have been developed. These guidelines aim to provide evidence-based recommendations for the diagnosis, surveillance, and treatment of upper gastrointestinal SELs. Where evidence is limited, expert consensus supports the guidance. To our knowledge, this represents the first comprehensive clinical practice guideline for gastric SELs developed by a Korean medical society and published in English. Developed in the context of Korea's widely implemented gastric cancer screening program, these guidelines address the increasing detection of incidental SELs and provide standardized recommendations for their diagnosis, surveillance, and treatment.

2 | Development Methods for the Guideline

1. Clinical Practice Guideline Committee and multidisciplinary approach
2. Clinical practice guideline development process
    1. Selection of key questions
       Key questions (KQs) were selected through review of international guidelines [8–11] and discussion among all committee members, based on the PICO framework. Eleven KQs were finalized.
    2. Literature search and selection
       A comprehensive literature search was conducted in MEDLINE, Embase, Cochrane Library, and KoreaMed in September 2022, without restriction by year, language, or publication status. Duplicates were excluded. Two reviewers per KQ screened and selected relevant studies following PRISMA guidelines [12].
    3. Literature quality assessment and meta-analysis
       Quality was assessed using validated tools: RoB 2.0 for RCTs [13], Revised Risk of Bias Assessment tool for Non-Randomized Studies (ROBANS) for nonrandomized studies [14], Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic studies [15], and A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2) for systematic review literature evaluations [16]. Meta-analyses were conducted using random-effects models when appropriate, and heterogeneity assessed by I^2. The most recent or largest study was selected when data duplication was suspected.
    4. Derivation of recommendations and determination of recommendation strength and evidence level
       Recommendations were formulated based on the GRADE approach. Strength (strong vs. conditional) reflected the balance of benefits and harms, while evidence certainty was rated from high to very low [17]. For insufficient evidence, expert consensus was used.
    5. Agreement of recommendations and adoption
       A modified Delphi consensus process was conducted with two rounds of voting among multidisciplinary experts. In the first round, 43 experts evaluated 11 key recommendations using a 5-point Likert scale. Consensus was defined as ≥70% agreement, where agreement included "strongly agree" (1 point) or "agree with reservations" (2 points). Recommendations achieving consensus were accepted, while those with <70% agreement underwent revision based on expert feedback and were subjected to a second round of voting. In the second round, 28 experts participated to evaluate the revised recommendations. Panel consistency between rounds was assessed to ensure reliability of the consensus process.
    6. Dissemination of clinical practice guidelines and revision plan
       The final guidelines will be published domestically and internationally and posted on the society's website. Future revisions will be considered by the KCHUGR guideline committee if significant new evidence emerges.

The Clinical Practice Guideline Committee comprised a steering, working, and internal/external review group. The steering committee, composed of society leadership, oversaw strategy, budget approval, stakeholder coordination, and ensured independence. The working group included 14 members from the Korean College of Helicobacter and Upper Gastrointestinal Research and experts recommended by the Korean Physicians' Association. Methodologists also participated. Internal and external review committees had two members each. Meetings began in May 2022, with ongoing discussions and internal votes until December 2023, followed by a public hearing with field experts in March 2024.

3 | Key Questions and Recommendations

3.1 | Delphi Consensus Process Results

The first round of voting involved 43 experts evaluating 11 key recommendations. Seven recommendations (Questions 1, 2, 4, 8, 9, 10, and 11) achieved immediate consensus with agreement

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rates ranging from 73.5% to 87.8%. Four recommendations did not reach the 70% threshold: Question 3 (69.4%), Question 5 (67.3%), Question 6 (69.4%), and Question 7 (63.3%), requiring revision and a second round of voting. Question 5 was subsequently divided into two sub-questions (5-1 and 5-2) for clarity.

In the second round, 28 experts participated, with 96.4% (27/28) having also participated in the first round, demonstrating high panel consistency. All five revised recommendations achieved consensus in the second round. Question 3 improved from 69.4% to 82.4% agreement, Questions 5-1 and 5-2 achieved 70.6% and 73.5%, respectively, Question 6 improved from 69.4% to 79.4%, and Question 7 showed the most substantial improvement from 63.3% to 79.4%.

The high retention rate of experts between rounds and the improved agreement rates in the second round indicate a robust consensus-building process. Final recommendations were adopted based on these voting results.

3.2 | KQ1: Is Endoscopic Ultrasonography Useful for the Diagnosis of Subepithelial Lesions Found on Endoscopy?

Statement 1. *EUS imaging is useful for the diagnosis of SELs because it can characterize the features of SELs (level of evidence: moderate; strength of recommendation: strong).*

EUS is a useful test for the diagnosis of SELs in the gastrointestinal tract because it can characterize the size, layer of origin, and presence of extrinsic compression. However, the accuracy of EUS varies depending on the size and type of SELs. Therefore, we conducted a literature search and analyzed studies that performed EUS on gastric SELs with confirmed histological findings.

In a review of 21 studies with histologically confirmed gastric SELs, EUS imaging accuracy (without tissue acquisition) ranged from 48% to 90.9% (Supplementary Figure 1) PRINTDATE * MERGEFORMAT [7, 18–37]. All studies were prospective or retrospective observational studies, and quality was assessed using QUADAS-2 (Supplementary Table 1). Histologically confirmed SELs included GISTs, leiomyomas, ectopic pancreas, NETs, lipomas, schwannomas, lymphomas, duplication cysts, inflammatory fibroid polyps, MALT lymphomas, and others.

The sizes of SELs in the 21 studies ranged from 3.3 mm (mean) to 40 mm (median). In 14 studies that evaluated the accuracy of EUS imaging alone, EUS accuracy for all SELs ranged from 48% to 90.9% [7, 18–30]. This variation appears to be related to lesion size among other factors. One study reported 48% accuracy with a mean size of 3.3 mm [30], whereas a Korean study with a mean size of 25.2 mm (range 10–45 mm) reported 74.6% accuracy for GISTs [31]. While these studies suggest that EUS accuracy may improve with larger lesion size, the optimal size threshold for EUS evaluation requires further investigation. Current international guidelines generally recommend EUS evaluation for SELs ≥10 mm based on clinical experience and expert consensus [8–11].

The main clinical concern with SELs is their malignant potential. Thus, we assessed EUS diagnostic performance for GISTs, the most common potentially malignant SELs (Supplementary Table 2). In six studies ($N = 381$), EUS showed sensitivity of 71%–95% and specificity of 33%–88% [23, 27, 31–34]. Two studies specifically on malignant GISTs reported sensitivities of 83.3% and 62.5%, specificities of 76.5% and 83.3%, and accuracies of 78.2% and 78.9% [32, 35].

Studies have also evaluated EUS accuracy by lesion type. Among studies with ≥5 cases per lesion type, accuracy ranged from 50% to 100% for NETs, 17% to 85.3% for leiomyomas, 7.7% to 92% for ectopic pancreas, 0% to 80% for lipomas, and 0% for schwannomas. Other results included 100% for inflammatory fibrous polyps, 62.5% for adenoid tumors, 11% for gastric/duplicate cysts, and 0% for vascular lesions. One prospective study ($n = 48$) reported EUS sensitivity and specificity of 92% and 100% for extrinsic compression [26].

While some SELs can show surface or color changes, most are indistinguishable endoscopically. EUS helps identify the origin layer (e.g., muscularis mucosa, submucosa, or propria) and provides information on lesion echogenicity and homogeneity (Table 1). Malignant GISTs are predicted with 80%–92% sensitivity when EUS reveals >3 cm size, heterogeneity, and irregular margins [34, 36].

Although not included in our analysis, previous studies have evaluated contrast-enhanced EUS. A meta-analysis reported its sensitivity of 0.87 (95% CI: 0.82–0.91), specificity of 0.82 (95% CI: 0.74–0.89), and positive likelihood ratio of 3.55 (95% CI: 2.39–5.27) for predicting GISTs [37]. It also showed 0.93 sensitivity and 0.81 specificity for differentiating low- and high-risk GISTs [37].

EUS elastography has been rarely studied for SELs. A pilot study showed GISTs were stiffer than other SELs based on stiffness and color scoring. In another study using strain ratio, sensitivity and specificity were 100% and 94% for distinguishing GISTs (strain ratio: 51.1) from leiomyomas (strain ratio: 6.0), but differentiation from schwannomas (strain ratio: 62.0) remained difficult [38].

In summary, EUS imaging alone (without tissue acquisition) is useful for characterizing SELs, although its sensitivity and specificity are not sufficient for all types. Many included studies were retrospective with small samples, yet over 1500 SELs were analyzed. Diagnostic EUS is very safe, with a complication rate of 0.001% [39]. Given its clinical utility and minimal risk, EUS is strongly recommended for diagnosing gastric SELs.

3.3 | KQ2: Is It Recommended to Follow-Up With Endoscopy for Gastric Subepithelial Lesions Smaller Than 1 cm?

Statement 2. *For gastric SELs less than 1 cm in size that are not suspected to be malignant, endoscopic follow-up without further investigation may be considered (level of evidence: expert consensus; strength of recommendation: conditional).*

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TABLE 1 | EUS characteristics of subepithelial tumors.

Subepithelial tumors	Layer of origin	EUS findings
Benign		
GIST-low risk	4th (rarely 2nd, 3rd)	Hypoechoic, homogenous, round, smooth margin, <3 cm
Leiomyoma	2nd, 4th	Hypoechoic, well-circumscribed
Ectopic pancreas	2nd, 3rd, 4th	Hypoechoic or mixed echogenicity (heterogeneous = acinous tissue, anechoic = ductal structures), indistinct margin
Schwannoma	4th	Hypoechoic
Lipoma	3rd	Intensely hyperechoic, homogeneous, smooth margin
Granular cell tumor	2nd, 3rd	Hypoechoic, heterogeneous
Inflammatory fibroid polyp	2nd, 3rd	Hypo- to hyperechoic, homogeneous, indistinct margin
Duplication cyst	Any or extramural	Anechoic, three to five layer wall, round or oval, absent Doppler signal
Lymphangioma	3rd	Anechoic with internal septa
Varices	3rd	Anechoic, serpiginous, Doppler positive
Malignant potential		
GIST-high risk	4th (rarely 2nd or 3rd)	Hypoechoic, heterogeneous, irregular extraluminal margin, cystic spaces, echogenic foci, >3 cm,
Neuroendocrine tumor	2nd, 3rd	Mildly hypoechoic, homogeneous, oval or round, smooth margin
Lymphoma	2nd, 3rd, 4th	Hypoechoic
Metastasis	Any or all	Hypoechoic, heterogeneous
Glomus tumor	3rd, 4th	Hypoechoic

Abbreviations: EUS, endoscopic ultrasonography; GIST, gastrointestinal stromal tumor.

Our literature search found no study directly comparing follow-up by endoscopy alone versus after EUS. Fifteen observational studies describing the natural course and endoscopic follow-up of gastric SELs were identified (Supplementary Figure 2) [40–54]. Study quality was assessed using ROBANS 2.0 (Supplementary Table 3).

Eight studies evaluated tumor growth and GIST proportion during follow-up of gastric SELs ≤3–4 cm after EUS [42–44, 48–52]. Tumor enlargement occurred in 10%–28% of cases; overall, 22% increased in size. Among resected lesions, 51% were GISTs, with 13% classified as intermediate or high risk. In tumors <1 cm, only 17% showed size change.

Two studies followed gastric SELs <3 cm by endoscopy alone [45, 47]. With mean follow-up of 24–59 months, only 4.0%–6.4% of lesions <1 cm increased in size; among these, 1.5% were intermediate- or high-risk GISTs. Larger initial size was associated with more rapid and frequent growth. In two other studies, all SELs ≤2 cm were resected, and only 0.3% of ≤1 cm lesions were intermediate- or high-risk GISTs [53, 54].

In gastric SELs <1 cm with rolling sign and no high-risk features on EUS or biopsy (if performed), follow-up showed low growth rate (~5%) and slow enlargement. As the proportion of intermediate- or high-risk GISTs is very low, endoscopic follow-up alone is unlikely to impact prognosis (Supplementary Table 4).

3.4 | KQ3: Is Biopsy Recommended for Lesions Larger Than 2 cm Suspected to Be GISTs on Endoscopic Ultrasonography?

Statement 3. *Among the lesions suspected of being GISTs, if there are high-risk findings or if pathological diagnosis is required for treatment decision, a tissue biopsy may be considered (level of evidence: expert consensus; strength of recommendation: conditional).*

High-risk findings included size >3–5 cm, heterogeneous echotexture, irregular margins, and echogenic

foci.

The diagnostic accuracy of gastric SELs by EUS alone is limited (50%–64%) [7, 30]. Features like heterogeneity, large size (>3–5 cm), irregular margins, or internal changes may suggest GISTs [34, 55, 56], but interobserver variability limits reliability. Biopsy can enhance diagnostic accuracy.

A review of 16 studies on EUS-guided biopsy for gastric SELs (Supplementary Figure 3) [57–72] showed a diagnostic rate of 66.3% (95% CI: 62.3–69.7) with FNA and 76.2% (95% CI: 70.1–81.6) with FNB. Given these rates exceed those of EUS alone, histologic diagnosis is recommended when pathology informs

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treatment decisions, such as for chemotherapy or surgery of cardia SELs (Supplementary Table 5).

3.5 | KQ4: Are Endoscopic Ultrasonography–Guided Fine-Needle Biopsy or Mucosal Incision–Assisted Biopsy Recommended for the Histological Diagnosis of SEL?

Statement 4. *EUS-FNB and MIAB are equally recommended for tissue acquisition from SEL, and MIAB is preferred if the size of the SEL is less than 2 cm (level of evidence: moderate; strength of recommendation: conditional).*

Standard forceps biopsy is often inadequate for SELs due to limited mucosal access. Bite-on-bite biopsies using jumbo forceps can improve yield, especially for submucosal (third layer) lesions [73, 74]. However, effectiveness is limited for muscularis propria lesions and may cause bleeding.

EUS-FNA and FNB are widely used for SELs, with diagnostic accuracy ranging from 46% to 93% [8, 75]. A meta-analysis comparing both methods showed FNB had higher accuracy and required fewer passes [76]. Adequate sample rates were 94.9% (95% CI: 92.3%–97.5%) for FNB and 80.6% (95% CI: 71.4%–89.7%) for FNA. MIAB (unroofing technique) involves mucosal incision and surface biopsy. In a meta-analysis of seven studies, its diagnostic yield was 89% (95% CI: 82.7%–93.5%) with a bleeding rate of 5.03% (95% CI: 0.4%–12.9%) [77]. Our meta-analysis of five studies comparing MIAB with EUS-FNA/FNB (Supplementary Figures 4, 5) [78–82] found diagnostic rates of 91% (95% CI: 86.0%–95.0%) for MIAB vs. 76.7% (95% CI: 69.7%–83.0%) for EUS-FNA/FNB, favoring MIAB (risk ratio 1.13, 95% CI: 1.04–1.24).

A subgroup analysis of three studies reported diagnostic rates by lesion size [78–80]. For lesions ≥2 cm, MIAB and EUS had similar yields: 91.2% (95% CI: 81.9%–97.4%) vs. 92.5% (95% CI: 83.5%–98.1%). For lesions <2 cm, MIAB showed a higher rate of 90.1% (95% CI: 81.0%–96.4%) compared to 56.0% (95% CI: 43.3%–68.3%) for EUS, with a risk ratio of 1.59 (95% CI: 1.25–2.01; Supplementary Table 6).

3.6 | KQ5: When Should Follow-Up Examinations Be Conducted for Subepithelial Lesions Greater Than 1 cm?

Statement 5-1. *For SELs measuring 1–2 cm identified through endoscopy, if the diagnosis on endoscopic ultrasound is unclear, a follow-up endoscopy should be performed after 6 months, and if the size remains <2 cm, a follow-up examination should be conducted after 12 months (level of evidence: expert consensus; strength of recommendation: conditional).*

Statement 5-2. *For SELs measuring 2 cm or larger identified through endoscopy, if there are no high-risk findings on endoscopic ultrasound, a follow-up endoscopy should be performed after 6 months, and if there is no significant size increase, another follow-up examination should be conducted after 12 months (level of evidence: expert consensus; strength of recommendation: conditional).*

Significant size increase is defined as an increase of 25% or more in the maximum diameter, based on natural history studies of gastric SELs. Song et al. reported that among 954 upper gastrointestinal SELs followed for a mean of 47.3 months, only 34 (3.6%) demonstrated ≥25% diameter increase [4]. This threshold represents clinically meaningful growth that exceeds typical measurement variability. Growth kinetics vary significantly by initial lesion size: lesions <10 mm show annual growth of 1.31–1.68 mm, those measuring 10–20 mm grow 2.09–3.83 mm per year, while lesions >20 mm demonstrate 2.28–7.13 mm annual growth [45]. Studies confirm that growth rates correlate with initial size, with larger lesions showing more rapid progression [45, 49]. The 25% criterion provides an objective measure to distinguish true tumor progression from measurement error while guiding clinical decision-making regarding surveillance intervals and intervention timing.

SELs such as GISTs and NETs may show malignant behavior, requiring resection. Differentiating benign tumors (e.g., lipomas, heterotopic pancreas, granular cell tumors, schwannomas, leiomyomas) from potentially malignant tumors is critical. While initial detection often occurs during screening endoscopy with visual size estimation, endoscopic ultrasound should be performed when SELs appear to be 1 cm or larger for accurate size measurement, as visual estimation may be inaccurate, particularly for lesions with extraluminal components.

No specific prospective study on follow-up for gastric SELs ≥10 mm was found, but 15 studies reported their natural course and endoscopic follow-up (Supplementary Figure 6; Supplementary Table 7). For GISTs, tumor doubling time was 24 months in low-risk, 17.1 in intermediate, and 3.9 in high-risk groups [40]. Other studies showed annual growth rates of 1.57–1.67 mm (<10 mm), 1.68–3.83 mm (10–20 mm), and 3.72–7.13 mm (>20 mm), with faster growth in larger lesions (Table 2) [45, 49].

EUS aids in differentiating SELs, with sensitivity for GISTs of 62.5%–83.3%, specificity 76.5%–83.3%, and accuracy 78.2%–78.9%, although definitive diagnosis is not always possible. If GIST is suspected but unclear, biopsy is preferred; otherwise, endoscopic follow-up may be needed. For SELs <20 mm, even if identified as GISTs, high-risk potential is low (0%–2.5%) [53]. If EUS findings are inconclusive, follow-up at 6 months is recommended to assess size, and if stable, re-evaluation after 12 months can be considered [10].

For SELs >20 mm found during initial endoscopy, biopsy may be considered if GIST differentiation is needed. If high-risk GIST features are absent on EUS, international guidelines suggest follow-up endoscopy after 6 months to assess growth, and if stable, another exam at 12 months may follow [10]. Clearly benign lesions (lipomas, heterotopic pancreas, granular cell tumors, schwannomas, leiomyomas, glomus tumors) on EUS do not require regular follow-up, regardless of size [10].

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TABLE 2 | Growth rates (mm/year) of subepithelial tumors according to their initial size.

	<1 cm	≥1 cm to >2 cm	≥2 cm	*p*
Kim et al. (2011) *n* = 84	1.68	2.64	3.72	0.003
Song et al. (2015) *n* = 34	1.31 ± 1.38	2.09 ± 1.47	2.28 ± 1.90	0.059
Kim et al. (2022) *n* = 138	1.57 ± 1.23	3.83 ± 4.24	7.13 ± 9.71	<0.001

3.7 | KQ6: Is Endoscopic Resection More Effective Than Follow-Up for Proven or Suspected GISTs Less Than 2 cm?

Statement 6. *Endoscopic resection is recommended for proven or suspected gastric GISTs less than 2 cm to establish definitive diagnosis and risk stratification. Close follow-up may be considered as an alternative after multidisciplinary discussion (level of evidence: very low; strength of recommendation: conditional).*

Management recommendations differ significantly based on diagnostic certainty. For proven GISTs <2 cm (histologically confirmed), endoscopic or surgical resection is recommended as the preferred approach to establish definitive risk stratification, as even small GISTs may harbor intermediate or high-risk features (2.4% in our analysis). Surveillance may be considered only after multidisciplinary discussion in selected patients with significant comorbidities or limited life expectancy. For SELs suspected but not proven to be GISTs, tissue acquisition should be attempted first (Statement 4). If GIST is confirmed, proceed with resection. If tissue diagnosis remains inconclusive despite adequate sampling, management should be individualized based on EUS features, patient factors, and shared decision-making. For undiagnosed SELs <2 cm without high-risk features, surveillance according to Statement 5-1 is appropriate, as the majority will be benign lesions not requiring intervention.

Size and mitotic index are key factors in determining GIST malignancy. According to the 2008 modified NIH criteria, gastric GISTs <2 cm with ≤5 mitoses are very low risk, while those with >5 are high risk [83]. Thus, even small GISTs require risk stratification through pathology.

Tissue acquisition techniques have improved, but EUS-FNA/B diagnostic yield remains size-dependent, at ~70% for 1–2 cm lesions [84, 85]. One study reported 100% accuracy with onsite pathology, although mitotic index correlation with surgical specimens was unclear [86]. EUS-FNA and bite-on-bite biopsy cannot reliably assess mitotic rate due to tumor heterogeneity [87], and biopsy-confirmed GISTs may still carry malignancy risk despite low-risk classification.

No RCTs have compared follow-up and resection for gastric GISTs <2 cm. A prospective study of 972 SETs <2 cm resected endoscopically found 42.3% were GISTs [53]. Of these, 97.6% were very low or low risk, but 2.4% were intermediate (1.9%) or high risk (0.5%). In a retrospective study, only 10.5% of 66 gastric SETs <2 cm were malignant GISTs [88]. While malignancy was suspected by EUS in 22 of 26 cases, most were benign. Three malignancies were missed by EUS. EUS sensitivity, specificity, and accuracy were 50%, 62%, and 60%. Additionally, 73% of FNAs were noncontributive. Thus, EUS and FNA/B are unreliable for predicting malignancy, and endoscopic resection should be considered for definitive diagnosis. Even for <2 cm GISTs, resection requires multidisciplinary discussion.

3.8 | KQ7: Is Endoscopic Resection More Effective Than Surgery for Gastric GIST Larger Than 2 cm?

Statement 7. *Surgical resection is recommended for gastric GIST larger than 2 cm. However, endoscopic resection may be considered depending on the experience of the endoscopist (level of evidence: low; strength of recommendation: conditional).*

Laparoscopic resection is standard for GISTs, offering efficacy, safety, and short hospital stays. With improved endoscopic techniques, resection is now a viable option for smaller tumors. ESD and submucosal excavation are feasible for submucosal tumors, while EFTR is used for those in the muscularis propria.

We reviewed 2026 articles and included 13 retrospective studies comparing endoscopic resection and surgery for gastric GISTs >2 cm, focusing on efficacy, complications, and recurrence (Supplementary Figures 7, 8) [89–101]. Most surgeries were performed laparoscopically, except for one patient who underwent both open and laparoscopic surgeries. Regarding endoscopic resection, there were five articles on endoscopic resection [89–91, 93, 101], four articles on ESD [95, 96, 99, 100], and others on EFTR [92, 94, 97, 98]. In the meta-analyses, surgery was superior to endoscopic resection in terms of complete resection (OR: 8.31). 95% CI: 2.80–24.69, $I^2 = 39\%$; Supplementary Figure 9). However, recurrence (OR: 0.52; 95% CI: 0.21–1.31; $I^2 = 0\%$) and complications (OR: 0.91; 95% CI: 0.58–1.45; $I^2 = 0\%$) were similar between groups (Supplementary Figures 10, 11). Endoscopic resection took less time than surgery despite high heterogeneity (mean difference: −39.32 min; 95% CI: −60.67 to −17.96; $I^2 = 95\%$; Supplementary Figure 12). Thus, both approaches appear feasible for gastric GISTs >2 cm.

In endoscopic resection, lesion relation to the muscularis propria is key. ESD is suitable when GISTs are narrowly connected (subtype 1) or broadly attached at an obtuse angle (subtype 2) to the muscularis propria and protrude into the lumen. For lesions within the wall (subtype 3) or protruding toward the serosa (subtype 4), EFTR or surgery is recommended [102].

In addition, because most GISTs invade the muscularis propria, a high level of skill is important for the success of the

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procedure. R0 resection is not easy; there is a risk of perforation, and many cases are located in the fundus and cardia [103]. Therefore, a medical environment should be established where smooth treatment can be achieved in cases where endoscopic resection is initiated but collaboration with surgery is required. Treatment of gastric type 1 NETs <1 cm is controversial and also for "very small" gastric type 1 NETs. "Very small" or "small than 5 mm". There are patients with multiple gastric type 1 NETs smaller than 1 cm; how to manage in this clinical scenario?

3.9 | KQ8: What Is the Optimal Treatment Approach for Gastric NETs <2 cm Based on Type and Tumor Characteristics?

Statement 8. *Endoscopic resection or surgery can be considered for gastric neuroendocrine tumors less than 2 cm, depending on the NET type (type 1, 2, or 3), size, invasion depth, and tumor grade (level of evidence: very low; strength of recommendation: conditional).*

Gastric NETs are classified into three types: type 1 (70%–80%) with chronic atrophic gastritis and hypergastrinemia; type 2 (5%–10%) with Zollinger–Ellison syndrome; and type 3 (10%–15%) with normal gastrin and no associated disease [104]. Treatment options include endoscopic resection or surgery, depending on size, grade, and depth. The management approach for gastric NETs <2 cm varies significantly by type:

- Type 1 (<1 cm): Surveillance is the preferred approach, with excellent prognosis and virtually no risk of metastasis. Surgical resection is not indicated.
- Type 1 (1–2 cm): Endoscopic resection may be considered based on grade and invasion depth.
- Types 2 and 3: More aggressive management with endoscopic resection or surgery based on individual factors.

We reviewed six retrospective studies on gastric NETs <2 cm, focusing on outcomes like lymph node metastasis, recurrence, and death (Supplementary Figures 13, 14) [105–110].

No prospective studies have compared surgery and endoscopic treatment for gastric NETs, and most focus on oncologic outcomes. For type 1 NETs <1 cm, studies consistently show excellent prognosis with surveillance alone, with no reported lymph node metastases or disease-specific mortality, making surgical resection unnecessary in virtually all cases. However, outcomes vary for 1–2 cm lesions. In a study of 123 patients, lymph node metastasis was 0%, 8.3%, and 100% depending on invasion depth, and 0% in grades 1–2 vs. 50% in grade 3 [110]. In a Taiwanese study of 187 patients with type 1 gastric NETs, no lymph node or distant organ metastasis occurred in lesions <1 cm [106]. Yet, for 1–2 cm grade 1 NETs with muscularis propria invasion, metastasis was reported. Among four grade 2 NETs (1–2 cm), half invaded mucosa/submucosa, and half invaded the muscularis propria. Thus, while <1 cm lesions show similar outcomes across treatments, 1–2 cm NETs require caution based on depth and grade.

No RCTs have compared endoscopic resection and surgery for type 3 gastric NETs. In a multicenter retrospective study ($n = 176$), lymph node metastases occurred in 8.4%, but no recurrence was noted in 53 patients with G1 submucosal lesions <1 cm [111]. Korean retrospective studies have also reported no recurrence in G1 lesions confined to the submucosal layer of less than 1.5 cm [112, 113].

In summary, for type 1 gastric NETs <1 cm, endoscopic resection is preferred if submucosal; for 1–2 cm lesions, treatment depends on depth and grade. Type 3 NETs <2 cm require individualized decisions based on lesion size, invasion depth, and grade.

3.10 | KQ9: Is Follow-Up Observation Possible for Gastric Type 1 Neuroendocrine Tumors Smaller Than 1 cm?

Statement 9. *We suggest endoscopic resection for type 1 NETs measuring <1 cm. However, regular endoscopic surveillance may also be considered for very small lesions (level of evidence: very low; strength of recommendation: conditional).*

Gastric NETs account for approximately 7% of all digestive NETs [114] and are subdivided into three main types [115]. Type 1 gastric NETs have a low risk of metastasis, which is directly correlated with tumor size [110]. Endoscopic treatment is often performed based on the type, size, and grade of the tumor [10].

To assess the feasibility of follow-up for gastric NETs <1 cm, we identified 1017 studies. Of 843 initially screened, five original articles (since 2019) and five review articles (since 2017) were selected by title/abstract. Full texts were reviewed, and three original articles from 2019, four from reviews, and one via manual search, were included for final quality assessment (Supplementary Figures 15, 16; Supplementary Table 8).

Seven studies assessed death or disease progression without treatment, and one analyzed lymphovascular invasion by tumor size after endoscopic resection. Most were retrospective; one was prospective. In untreated patients ($n = 8$–87), no NET-related deaths occurred. In 11 patients with type 1 gastric NETs followed for a median of 54 months (range 9–136), four showed increased lesion numbers, but no lesions >1 cm or metastases were observed [116]. In a Japanese multicenter study ($n = 82$), including endoscopic surveillance ($n = 25$), endoscopic resection ($n = 41$), and surgery ($n = 16$), no untreated patients developed metastasis, progression, or died. RFS was 97.6%, and disease-specific survival 100% [109]. In a single-center study of 26 patients, eight were monitored without treatment (2–13 mm); one died, but none from NETs [117]. Among 97 gastric NET patients, 3 underwent surgery, 45 received curative endoscopic resection, 13 had observation only, and 36 received somatostatin analogs. All remained alive and metastasis-free at follow-up [118].

A Korean retrospective study identified 104 type 1 gastric NETs among 223 cases diagnosed from 1996 to 2011 [119]. Of these, 67 patients received endoscopic treatment, and 27 were observed

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without intervention. Complete resection was achieved in 53 patients (79.1%) and recurrence occurred in 14 (20.9%). Among those observed, 19 (70.4%) had stable disease and 8 (29.6%) showed progression. Mean tumor size did not differ by progression status, but four patients had tumors >10 mm, and tumor grade was not reported. Mean follow-up was 49 months (range 31–210), with no deaths in either group.

In a recent retrospective study, 87 of 115 patients with grade 1 gastric NETs (75 with tumors ≤1 cm) underwent endoscopic surveillance without initial treatment [120]. Over a median 62-month follow-up, 91% ($n = 79$) showed no clinically significant changes in tumor size or grade. Among ≤1 cm tumors ($n = 75$), no size increase occurred. Three patients progressed from G1 to G2 but received no further treatment due to comorbidities: two regressed to G1, and one remained G2. Among 1–2 cm tumors ($n = 12$), three had >0.5 cm growth. Overall, G1 NETs <1 cm showed no meaningful progression.

A recent prospective study followed 127 gastric NETs (G1, $n = 80$) with endoscopy [105]. Tumors <1 cm were resected with forceps or cold snare; larger ones by EMR or ESD. Among 127 lesions: 87.4% were <0.5 cm, 8.7% were 0.6–1 cm, 3.1% were 1.1–2 cm, and 0.8% were >2 cm. Of the G1 NETs <0.5 cm, 15 patients (18.7%) were safely observed without resection. In a study of 155 cases (165 lesions) of G1 NETs, 24.8% had lymphovascular invasion [121]. Even in G1 tumors, the rate was 22.8%, with 3.4% for <0.5 cm and 8.7% for 0.5–1 cm. To keep invasion ≤10%, tumor size needed to be ≤0.8 cm; for ≤5% invasion, ≤0.6 cm. A 0.6-cm cutoff yielded 79% sensitivity and 63% specificity.

The management of type 1 gastric NETs <1 cm remains controversial internationally. While some guidelines increasingly favor surveillance, our data showing 3.4%–8.7% lymphovascular invasion rates even in small lesions cannot be overlooked. The optimal approach may vary based on healthcare system resources and accessibility. In Korea's context with excellent endoscopic access and technical expertise, both resection and surveillance are valid options, with the choice individualized based on patient factors and preferences.

Based on the aforementioned evidence, in terms of lesion progression, in the case of very small grade 1 NETs measuring less than 0.5 cm, follow-up without resection may be an option. However, lymphovascular invasion occurs in 3.4% of patients with tumors less than 0.5 cm; therefore, endoscopic observation without complete resection can be considered only in cases where regular endoscopic examination is possible. There was very little evidence regarding survival rate, disease progression, and lymphovascular invasion (Supplementary Tables 9–11).

For patients with multiple type 1 gastric NETs <1 cm, management should be individualized. Options include: (1) selective resection of the largest lesions combined with surveillance of smaller ones, (2) complete resection of all visible lesions if technically feasible, or (3) surveillance alone if lesions are all <5 mm with regular endoscopic monitoring. The decision should consider the total number of lesions, patient age, comorbidities, and ability to comply with surveillance protocols. Evidence for managing multiple small type 1 NETs remains limited and represents an area requiring future research.

In summary, for gastric grade 1 neuroendocrine tumors (NETs) smaller than 0.5 cm, active surveillance without resection may be considered, although the condition itself may be of concern. Both the anticipated benefits and harms of this approach are minimal, the supporting evidence is of very low certainty, and there is considerable uncertainty regarding patient values and preferences. Therefore, no clear superiority can be determined between resection and surveillance. In the context of Korea, where biennial national cancer screening and high accessibility to healthcare services are available, both acceptability and feasibility of surveillance are considered generally high. Taking these factors into account, a conditional recommendation is made in favor of surveillance over resection in such cases. In the voting of related professional societies, 88.4% (38/43) agreed with the recommendation; however, at the public hearing, there were concerns about the follow-up observations of gastric NETs smaller than 0.5 cm. In some cases, small gastric NETs are almost completely removed or degenerated by biopsy and are not visible when endoscopy is performed again for resection. Progression of small, grade I, and type I gastric NET is extremely rare. Considering the conditions in Korea, where access to gastroscopy is very high, small, grade I and type I gastric NETs can be observed without the need for resection. However, small grade I and type I gastric NETs can show an aggressive course, although this is very rare. In Korea, criminal prosecutions for medical negligence are 750 times higher than those in the UK (750 cases per year in Korea and 1–2 cases per year in the UK). Legal prosecution is possible even in unusual circumstances. Due to the high risk of exposure to legal risks, it was recommended to revise the size to "very small" rather than specifying it. In the final recommendation, "less than 0.5 cm" was revised to "very small," which generally refers to lesions ≤5 mm, though this threshold requires clinical discretion based on individual patient factors.

3.11 | KQ10: Which Endoscopic Resection Technique Should Be Used to Resect Subepithelial Tumors?

Statement 10. *Endoscopic resection methods for gastric SELs include endoscopic submucosal tunnel resection, EFTR, and ESD, depending on the experience of the endoscopist and the circumstances of the institution (level of evidence: low; strength of recommendation: conditional).*

Advances in endoscopic instruments and techniques now allow endoscopic resection to be considered as an alternative to surgery for gastric SELs, depending on clinical context. Thirty-six studies reported outcomes of endoscopic resection, although most were retrospective, with only seven directly comparing procedures. The selection and quality assessment process is shown in Supplementary Figure 17. In one study comparing ESD and EFTR, en bloc resection rates were 96.2% and 95%, respectively. Another comparing submucosal tunnel resection and EFTR showed rates of 93.3%–95% and 96.4%–96.8% [122–124].

For gastric SELs in the muscularis propria, ESD showed en bloc resection rates of 90.2%–100% and complete resection rates of 74.2%–100% [125–135]. EFTR achieved 92.8%–100% and

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97.3%–100%, respectively, while submucosal tunnel resection yielded 84.7%–100% en bloc and 96.8%–100% complete resection rates [122–124, 136–146]. A meta-analysis of nine ESD studies ($n = 288$) reported a pooled complete resection rate of 86.2% (95% CI: 78.9–91.3); for muscularis propria–origin tumors, the rate was 84.4% (95% CI: 78.7–88.8). Thus, EFTR and submucosal tunnel resection may be more effective than ESD for tumors in the muscularis propria. However, as long-term recurrence rates are similar, choice of procedure can depend on lesion characteristics and operator preference. In tumors within the submucosal layer, mostly gastric NETs, four studies reported complete resection rates of 69%–100% for EMR and 66.6%–92.8% for ESD [119, 147, 148].

Considering the above findings, when SELs are located in the muscularis propria of the stomach, the efficacy of EFTR and endoscopic submucosal tunnel resection is high, considering the en bloc and complete resection rates of these procedures. However, because few institutions have much experience with the above two procedures, ESD can also be considered an option in terms of oncological results. ESD is superior to EMR for gastric SELs in the submucosal layer.

3.12 | KQ11: What Is the Follow-Up Strategy After Endoscopic Resection of Subepithelial Lesions?

Statement 11. The follow-up strategy after endoscopic resection of SELs should be determined based on the type of SELs and whether complete resection was achieved (level of evidence: expert consensus; strength of recommendation: conditional).

1. Completely resected benign SELs are not recommended for follow-up examinations.
2. Completely resected GISTs and NETs are recommended for regular endoscopic and radiological follow-up examinations.
3. In cases of incomplete resection, follow-up observation, additional endoscopic resection, or surgical resection is considered depending on the type of resection.

The KQ addresses the follow-up strategy after endoscopic resection of SELs. The PICO framework was as follows: patient, those who underwent endoscopic resection for SELs; intervention, regular follow-up examinations performed after endoscopic resection; comparator, no regular follow-up examinations; and outcome, benefits and risks, including recurrence-free survival and costs. The number of articles retrieved from the systematic literature review is shown in Supplementary Table 12.

One article titled "How should patients with completely resected gastrointestinal stromal tumors (GIST) be followed-up?" analyzed 33 patients post-resection to assess recurrence [149]. Although limited and indirect, the study suggests endoscopic follow-up every 6 months for 2 years, then annually for 3 years. However, the small sample size limits generalizability. The 2022 ESGE guidelines state that SEL follow-up depends on lesion type and completeness of resection. No follow-up is needed for completely resected benign SELs, except type I gastric NETs, which require endoscopy every 1–2 years. According to the US NCCN guidelines, type I gastric NETs should be followed with endoscopy every 6–12 months for the first 3 years, then annually. Type 2 and 3 gastric NETs warrant annual surveillance, while G3 or >20 mm NETs require endoscopy every 4–6 months during year one, then annually [10, 150].

For GISTs, the ESGE guidelines recommend only general imaging examinations, such as CT, because local recurrence is rare. However, owing to the limited research on the natural course after endoscopic resection, endoscopic examinations are performed every 6–12 months for the first 3 years after resection. In cases of incomplete GIST resection, reoperation or re-endoscopic procedures are necessary. If this is not feasible, the tumor should be considered locally advanced, and the treatment plan should be determined through multidisciplinary consultation [10, 151, 152].

Funding

The authors have nothing to report.

Ethics Statement

Given the nature of this study as a systematic review and meta-analysis of previously published research, and the absence of direct involvement with human subjects or data collection, Institutional Review Board (IRB) approval was not required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Transparency

All data support the published claims and comply with field standards.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** PRISMA flow diagram for KQ1. **Figure S2:** PRISMA flow diagram for KQ2. **Figure S3:** PRISMA flow diagram for KQ3. **Figure S4:** PRISMA flow diagram for KQ4. **Figure S5:** Quality assessment of included studies for KQ4. **Figure S6:** PRISMA flow diagram for KQ5. **Figure S7:** PRISMA flow diagram for KQ7. **Figure S8:** Quality assessment of included studies for KQ7. **Figure S9:** Forest plot of studies comparing incomplete resection in 13 observational studies. **Figure S10:** Forest plot of studies comparing tumor recurrence in 13 observational studies. **Figure S11:** Forest plot of studies comparing postoperative complication in 13 observational studies. **Figure S12:** Forest plot of studies comparing operation time in 13 observational studies. **Figure S13:** PRISMA flow diagram for KQ8. **Figure S14:** Quality assessment of studies for KQ8. **Figure S15:** PRISMA flow diagram for KQ9. **Figure S16:** Risk of bias for KQ9. **Figure S17:** Quality assessment of included studies for KQ10. **Table S1:** Quality assessment of included studies by QUADAS-2 for KQ1. **Table S2:** Summary of findings for KQ1. **Table S3:** Quality assessment of included studies for KQ2. **Table S4:** Summary of findings for KQ2. **Table S5:** Quality assessment of included studies in KQ3. **Table S6:** Summary of findings for KQ4. **Table S7:** Quality assessment of included studies for KQ5. **Table S8:** Quality assessment of included studies for KQ9. **Table S9:** Summary of findings regarding endoscopic follow-up compared to resection for carcinoid tumor less than 10 mm. **Table S10:** Summary of findings regarding endoscopic follow-up compared to resection for carcinoid tumor less than 10 mm. **Table S11:** Summary of judgment regarding endoscopic follow-up compared to resection for carcinoid tumor less than 10 mm. **Table S12:** Quality assessment of included studies for KQ11.

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