Current Guidelines in the Management of Upper GI SET

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Introduction

Subepithelial tumors that occur in the gastrointestinal tract include all lesions with smooth prominentia in the inner cavity of gastrointestinal tract and no change in the mucosal surface on endoscopy. They were previously called submucosal tumors and are frequently detected in patients with cancer screening examination. The term “subepithelial tumor” includes lesions in the mucosal layer that grow under the epithelium. Subepithelial tumors are classified into non-neoplastic and neoplastic lesions. Most lesions are asymptomatic and clinically insignificant. However, carcinoid tumors, lymphomas, and gastrointestinal stromal tumors (GISTs) are malignant or have the potential to become malignant. Even with developed endoscopic facilities and abundant research, subepithelial tumors are still very difficult to diagnose with noninvasive methods, such as endoscopy or endoscopic ultrasonography (EUS), before surgery. There are various methods available for histological diagnosis of the tumor, including a bite-on-bite biopsy, EUS guided fine-needle aspiration (EUS-FNA), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and submucosal tunneling with endoscopic resection (STER). To find and treat malignant lesions at an early stage, appropriate diagnostic approaches are necessary, depending on the characteristics of the lesions.

Clinical Characteristics and Follow-up Results of Subepithelial Lesions

Subepithelial lesions are classified into non-neoplastic lesions including inflammation, cysts, and an ectopic pancreas, and neoplastic lesions, such as GISTs, carcinoid tumors, leiomyomas, lymphomas, schwannomas, and lymphangiomas. Inflammation due to parasitic infestation by Anisakis and poorly differentiated adenocarcinomas in the stomach rarely present as subepithelial lesions.

Subepithelial tumors are frequently found in asymptomatic patients in Japan and Korea where cancer screening tests routinely include endoscopy. In follow-up studies of asymptomatic upper gastrointestinal tract subepithelial lesions, the lesions increased in size in less than 10% of patients. Among patients who had health screening tests, Lim et al. reported that 795 (0.76%) had subepithelial lesions. They conducted a follow-up study of 252 patients for an average of 84 months using endoscopy. The size of lesions increased in only eight (3.2%) of the patients. Gill et al. reported a follow-up study of 51 asymptomatic patients with subepithelial lesions <3 cm in the upper gastrointestinal tract for 29.7 months, on average, using EUS. The lesions changed in size or echogenicity showed in only seven (13.7%) of the patients. Among tumors that originated from the fourth layer, the lesions increased in size in five (12%) patients. Kim et al. evaluated 948 patients in Korea with 989 gastric subepithelial tumors <30 mm in size using endoscopy or EUS. The lesions changed in size, echogenicity, and form in 84 (8.5%) of the patients, and 21 showed changes in echogenicity. Among 25 patients who underwent resection through surgery or endoscopy, 19 patients were diagnosed with a GIST (Fig. 1).
Gastrointestinal Stromal Tumors

1. Clinical manifestation and prognosis

Most subepithelial tumors can be classified as malignant or benign at the time of the diagnosis. Although GISTs have the potential to become malignant, small asymptomatic lesions appear as benign tumors. GISTs are the most common type of subepithelial tumor in the stomach. Kawanowa et al. analyzed resected stomachs. Fifty GISTs were found in 35 patients, with 90% of the tumors located in the upper stomach. Considering the frequency of GISTs observed in the clinic, only a small number of microscopic GISTs seem to show changes, such as an increase in size.\(^4\) Agaimy et al. reported that microscopic GISTs were not common in intestinal resections.\(^5\) Therefore, the detection frequency of GISTs appears to depend on their location in the gastrointestinal tract.\(^5\)

In contrast to the frequency of gastric GIST in the gastrointestinal system, they are uncommon in the duodenum and very rare in the esophagus. The prognosis of patients with GISTs in the stomach is relatively good compared with GISTs in other organs.\(^5\)\(^7\) Along with the location of the tumor, its size and mitotic count are major factors that determine the malignant potential of a GIST.\(^6\) Miettinen et al. reported the characteristics of 1,765 cases of stomach GISTs.\(^6\) Only 2.7% developed before the age of 21, and the most common symptom was gastrointestinal bleeding. In their study, the size of the tumors and their mitotic counts were important factors in the long-term prognosis. When a tumor was <10

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**Fig. 1.** Gastric GIST with rapid growing. (A) Endoscopy didn’t detect any mass in the stomach. (B) 4 years later, endoscopy showed round smooth elevated mass in gastric angle. (C) Endoscopic submucosal resection was performed. Tumor size was 1.7cm. (D, E, F) Microscopic finding. GIST with spindle cell type had 7 mitoses/50 HPFs. H & E stain (X 200, D) was done, and immunohistochemical stains were for positive for c-kit (X 200, E) and CD34 (X 200, F).
cm or the mitotic count was <5/50 HPFs, only 2-3% were metastasized. However, in tumors >10 cm and in those with a mitotic count >5/50 HPFs, 86% were metastasized. All GISTs that occurred in the intestines had more than a moderate possibility of metastasis when they were >5 cm or had >5 mitoses/50 HPFs. In tumors <5 cm with a mitotic count <5/50 HPFs, the intestinal GISTs had a low possibility of metastasis.

Other than the size of the tumor and the mitotic count, mucosal disruption, necrosis, high cellularity, and tumor rupture are additional pathological factors that affect GIST malignancy. Trupiano et al. divided 77 GIST patients into an adverse outcome group and a nonadverse outcome group. They suggested that the following were associated with malignancy: a tumor larger than 7 cm, high cellularity, mucosal invasion, a high nuclear grade, more than 5 mitoses/50 HPFs, a mixed cell type, the existence of a myxoid background, and the absence of stromal hyalinization. In their study, the sensitivity was 100%, and the specificity was 92%, showing a high predictive value.

Nilsson et al. analyzed 288 GIST patients based on a risk classification system proposed in 2002. There were only two (1.2%) tumor-related deaths among the patients classified as having a very low risk, a low risk, or an intermediate risk. In contrast, among those classified as having high-risk and malignant tumors, there were 63% and 83% of tumor-related deaths, respectively.

2. Treatment approach

An National Comprehensive Cancer Network (NCCN) Report in 2010 suggested different treatments for gastrointestinal tract GISTs with malignant potential, depending on their location, size, and mitotic counts. According to the report, if the GIST was >2 cm or <2 cm with symptoms, it should be removed. It noted that GISTs <2 cm and found by accident should first undergo EUS-FNA or an abdomino/pelvis computed tomography with contrast enhancement (CECT). If the EUS revealed a high-risk tumor (irregular border, cystic space, ulceration, echogenic foci, and heterogeneity), it should be surgically removed. If there was no high risk, the GIST should be followed up at 6-12 months intervals. In 2014, the European Society for Medical Oncology (ESMO) group proposed that histologically diagnosed small GISTs should be removed. They based this proposal on previous studies showing that tumors <2 cm with <5 mitoses/50 HPFs are classified as very low risk, although they can metastasize in very rare cases.

3. Endoscopy and EUS

According to an earlier study, gastric GISTs located in the gastroesophageal junction or fundus or those that exhibit coagulation necrosis, ulceration, or mucosal invasion have a poor prognosis, whereas those located in the antrum have a good prognosis. Another study reported that GISTs with irregular borders or tumorous ulcers on endoscopy have the potential to become malignant.

The accuracy of EUS in diagnosing subepithelial lesions is relatively low (46-48%). According to Hwang et al., masses present in the third and fourth layers are more difficult to diagnose. EUS is the most accurate test to distinguish the layer where a lesion is located. Its internal echo pattern is also very useful for deciding the course of treatment. High-risk lesions on EUS are those with irregular borders and internal heterogeneity, including anechoic area (necrosis) and echogenic foci (bleeding), heterogeneous enhancement, and regional lymph node enlargement.

**Diagnostic approach to tumors located in the mucosal and submucosal layer**

Most lesions classified as subepithelial are located in the mucosal and submucosal layers and are asymptomatic. However, malignant adenocarcinomas, lymphomas, or tumors with metastasis can result in symptoms. Patients with anisakis infestation in the stomach present with upper abdominal pain in both the acute and chronic phases.
Subepithelial lesions can be diagnosed by endoscope and EUS, although the accuracy of the diagnosis depends on the skill of the endoscopist. In some lesions, EMR or EUS-FNA may be helpful in the diagnosis. According to a recommendation by the American Society of Gastrointestinal Endoscopy (ASGE) in 2013, symptomatic lesions or lesions that increase in size should be resected using EMR or ESD. For asymptomatic lesions or those that do not change in size, lipomas, vascular lesions, or cysts can be diagnosed only by using EUS and other type of lesions should be evaluated histologically after the following: EUS-FNA, a bite-on-bite biopsy, an EUS core biopsy, the unroofing technique, a single incision needle-knife (SINK) biopsy, submucosal endoscopy with core biopsy, or a jumbo biopsy. If not enough tissues are acquired, EMR, ESD, or a gastrofiberscopic follow-up should be performed.

In 2011, the guideline of European Society of Gastrointestinal Endoscopy (ESGE) suggested that a bite-on-bite biopsy should first be conducted, followed by an endoscopic resection. Patients with suspected lymphomas, neuroendocrine tumors, or extrinsic tumors on EUS should be managed with EUS-guided FNA or a biopsy.

**Approach to tumors located in the muscularis propria layer**

GISTs, leiomyomas, and schwannomas are located in the fourth layer on EUS. Occasionally, an ectopic pancreas may invade the third and fourth layer. GISTs are most common in the stomach, and leiomyomas are frequent in the esophagus. In terms of the diagnostic approach, it is very important to distinguish a GIST from other types of tumors, precisely judge the malignant potential of the tumor, and decide how to treat it. The accuracy of the diagnosis was reported to be less than 50% when using only EUS. Invasive tests, such as EUS-FNA, were reported to have a diagnostic yield of over 90%. However, it is difficult to measure and interpret the level of mitoses in a GIST using FNA or various biopsy techniques because the cellularity and the mitotic count of GISTs is different according to the site within the tumor. The fixation time and the type of fixative can also affect measurements of mitoses.

1. **Tumors less than 2 cm**

Miettinen et al. reported the long-term prognosis of GISTs. Tumors <2 cm were not metastasized if the number of mitoses was less than 5/50 HPFs. However, GISTs with a mitotic count greater than 6/50 HPFs showed a high level of metastasis in all gastrointestinal tract tumors, except the stomach. Japan Gastroenterological Endoscopy Society (JGES) in 2013 recommended the use of EUS, EUS-FNA, CT with contrast enhancement (CT-CE), and surgery for gastric subepithelial tumors <2 cm suggestive of malignancy (an irregular border or a tumorous ulcer) on endoscopy. It recommended that lesions not considered malignant should be followed up every year or two using endoscopy or EUS. In cases of asymptomatic subepithelial lesions <2 cm in the gastrointestinal tract that showed no changes in size, the ASGE suggested that a histological diagnosis should be attempted using various methods. If this approach failed, it suggested doing an endoscopic follow-up. The ESMO and the ESGE suggested performing EUS three months after the detection of subepithelial tumors <2 cm in the esophagus, stomach, and duodenum, followed by a yearly follow-up thereafter. If the lesions increased in size or became symptomatic, they should be removed.

2. **Tumors larger than 2 cm**

Although GISTs between 2 and 5 cm with mitoses less than 5/50 HPFs were reported to have a low possibility (less than 10%) of metastasis, the risk of metastasis increased to 16-73% when the mitotic count increased. The ASGE suggested STER or curative resection via surgery when the tumors between 2 and 4 cm is symptomatic, or increase in size. According to the ESGE, laparoscopic wedge resection was the best treatment method. As the diagnostic accuracy and evaluation of mitoses are limited with EUS-FNA and biopsies, the ESGE recommended these only for GISTs with a high
risk in surgery, tumors located in the cardia or esophagus, or unresectable GISTs. The JGES also recommended surgical resection for gastric subepithelial lesions between 2 and 5 cm. In 2008, the Japan Society of Clinical Oncology (JSCO) suggested that tumors greater than 5 cm were an indication for surgery. It recommended EUS, EUS-FNA, or CECT for gastric lesions of 2-5 cm. In addition, it stated that if a biopsy result indicated that the lesion was not a GIST, it should choose a treatment method according to the types of disease. If endoscopy and CECT (necrosis, hemorrhage, irregularity of the margin, abundant blood flow) did not suggest malignancy, it advised that the lesion could be operated upon using endoscopic surgery or periodically observed.

Conclusion

Subepithelial lesions include various neoplastic and non-neoplastic tumors. Most of these are benign. Malignant tumors can be distinguished with endoscopy and EUS. Although GISTs have the potential to become malignant, Small (<2 cm) asymptomatic tumors usually have benign clinical course. GIST is the most common subepithelial tumor to occur in the stomach. Although various methods are employed to diagnose GISTs, the risk of GIST metastasis cannot be accurately predicted before lesions are completely resected.

Recently, new endoscopic diagnostic methods and treatment techniques have been developed that allow the diagnosis and resection of lesions located in the muscularis propria, without any complications. These endoscopic methods have different guidelines depending on regions where they are performed as the surgeons have different levels of experience. The role of endoscopy has expanded to include not only the diagnosis of subepithelial lesions but also their treatment.

References