ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Current Guidelines in the Diagnosis and Management of Gastric Subepithelial Tumors

Elleuch Nour*, Soumaya Mrabet, Aya Hammami, Hanen Jaziri, Aida Ben Slama, Ajmi Salem, Brahim Ahlem, Ksiaa Mehdi and Jmaa Ali

Department of Gastroenterology, Sahloul Hospital Sousse, University of Sousse, Tunisia

***Corresponding Author:** Elleuch Nour, Department of Gastroenterology, Sahloul Hospital Sousse, University of Sousse, Tunisia.

Received: April 19, 2020; **Published:** August 18, 2020

Abstract

Gastric subepithelial tumors (GSETs) are frequently asymptomatic and found by endoscopic examinations as protuberant lesions or bumps covered with intact mucosa. They are classified in epithelial and non-epithelial tumors (benign or malignant lesions). Among the mesenchymal tumors, gastrointestinal stromal tumors (GISTs) are the most frequent. The diagnostic strategy is based on endoscopic, radiological and cytological examinations. Endoscopic ultrasonography (EUS) is the key exam for eliminating extraluminal compressions, for presumptive diagnosis and clinical management of GSETs. Cytological or biopsy specimens, which can be performed during EUS, are indicated when the diagnosis cannot be specified by EUS. Therapeutic approach to GSETs depends on their histology first, their size secondly and finally on the presence or not of specific symptoms. The management may be very different according to the lesion, from abstention to endoscopic or surgical resection requiring a precise pretreatment assessment.

Keywords: *Subepithelial Tumors (SETs); Gastric Subepithelial Tumors (GSETs); Endoscopic Ultrasonography (EUS)*

Introduction

Subepithelial tumors (SETs) were previously called submucosal tumors [1]. These terms are clinically used for protuberant lesions or bumps covered with intact mucosa [2]. The term subepithelial tumor is preferred to the term submucosal tumor, which should be reserved for those that originate from the submucosal layer. Gastric subepithelial tumors (GSETs) arise in the muscularis mucosae, submucosa or muscularis propria of the gastric wall [3].

This localization is rare and found in 0.3% of middle-aged adults equally in men and women, half of which are considered to be neoplastic [4].

In the present up to date, we will focus on the diagnostic approach to GSETs and we will discuss the therapeutic options including emerging techniques.

Clinical features of GSETs

GSETs are a common incidental finding occurring on routine esogastroduodenoscopy (EGD) and radiographic examinations [4]. The detection rate of GSETs on EGD is approximately 0.8 to 2% [5]. Specific symptoms or complications are rare. In fact, the majority of patients with GSETs do not have symptoms, probably as a result of the intact mucosa, especially when they are small. The most common

symptoms include gastrointestinal bleeding, subsequent iron-deficiency anemia, and non-specific abdominal pain. Obstructive symptoms are less frequent, usually caused by a large tumor located near the cardia or pylorus. Palpable abdominal mass and weight loss may often be associated with advanced and malignant GSETs [4].

Methods of diagnosis of GSETs

For some SETs, such as a lipomas, duplication cysts and ectopic pancreas, endoscopic and endoscopic ultrasonography (EUS) appearances are considered diagnostic and tissue sampling is not required. However, hypoechoic and heterogeneous lesions from the submucosal and muscularis propria layers such as gastro-intestinal stromal tumors (GIST), leiomyomas, and carcinoid tumors have a wide differential diagnosis, and tissue sampling or removal is recommended to diagnose and determine the malignant potential of these lesions. Immunohistochemical staining is mandatory to further characterize these lesions [6].

Esogastroduodenoscopy (EGD)

The detection rate of suspected GSETs with EGD has previously been reported to be approximately 0.4% [7]. Currently with the development of digestive endoscopy techniques, this rate has increased to 0.8 to 2% [5].

On EGD, GSETs is a protuberant lesion covered with intact mucosa. The site of predilection is the proximal stomach. Gastro-intestinal stromal tumor (GIST) which is the most frequent tumor in the stomach, is commonly seen in the border of fundus and body of the stomach. Leiomyoma is frequently found in the esophagus and in the upper stomach around the esophagogastric junction. It may be difficult to arrive at the correct histological diagnosis with only a standard endoscopic biopsy, because the surface of GSETs is covered with normal epithelium and tumors usually are located in deep layers [8]. Performing bite on bite biopsy can improve diagnostic rate. Also, mucosal cutting biopsy (MCB) can be required to reach a positive diagnosis [9]. MCB consists on mucosal incision made by a needle-knife after an injection of saline. MCB may be chosen as an alternative diagnostic modality in tumors with intraluminal growth [8]. This technique has recently been employed, and some studies have already reported its usefulness. Yoshiko N and al demonstrated that a definitive diagnosis was obtained by MCB in 78% of cases, and the main factor found to improve the diagnostic rate was a clear exposure of the tumor [3].

Tumors with low malignant potential may appear endoscopically similar to those with a much higher risk for malignant transformation and biopsies often fail to provide diagnostic tissues. Thus, further imaging and sampling techniques often are used to characterize these lesions [6].

Endoscopic ultrasonography (EUS)

Currently, endoscopic ultrasonography (EUS) is the most sensitive imaging modality for the evaluation of GSETs. Diagnostic EUS has the ability to differentiate intramural tumors from extraluminal compressions and eliminate differential diagnosis of intramural lesion such as cysts and vessels. Owing to its high spatial resolution, EUS is able to provide informations about the layer of origin, size, internal echogenicity and echotexture of the tumor [7].

Table 1 summarize the characteristics of GSETs in EUS.

EUS alone is not able to definitely differentiate benign lesions from malignant ones. Nevertheless, certain risk criteria established on EUS such as size > 3 cm, inhomogeneous echo pattern, irregular margins and presence of lymph nodes, may suggest malignancy. The most reliable of these criteria is probably the size. To reach a positive diagnosis, EUS-guided fine-needle aspiration (EUS-FNA) is required. EUS-FNA is a reliable, useful and suitable method for the histological evaluation of GSETs. The successful diagnostic rate for GSETs by a EUS-FNA combined with cytology has been reported to be relatively high (83%) [10]. The Japanese GIST therapeutic guidelines recommend that EUS-guided fine-needle aspiration biopsy (EUS-FNAB) examinations should be used to diagnose gastric SETs 2 - 5 cm in diameter, as well as those < 2 cm in diameter that are growing or exhibit malignant findings, such as ulcer formation or an irregular surface [3].

Subepithelial tumor	Most common site of occurrence	EUS layer	EUS appearance
Leiomyomas	Oesophagus, cardia	The second or forth echo-poor layer	An echo-poor pattern, homogeneous hypoechoic, well demarcated
GISTs	Commonly seen in the border of fundus and body of stomach	The fourth echo-poor layer (which corresponds to the muscularis propria	An echo-poor pattern, more or less homogeneous and more or less well demarcated.
Aberrant pancreas	Gastric antrum proximal to the pylorus	2, 3,4	Heterogenous hypechoic, poorly defined outline, may include cystics components
Lipoma	Gastric antrum	3	Diffuse hyperchoic
Duplication cysts	Anywhere	Any or extramural	Anechoic, 3-5 layer wall, round or oval, absent Doppler signal

Table 1: *The characteristics of GSMT in EUS.*

The disadvantages are the cost of EUS-FNA systems and the need for experienced pathologists and cytology technicians [8]. So that, only a limited number of patients undergoes this procedure, even in hospitals specializing in gastroenterology.

Elastography is a type of virtual biopsy that attempts to assess differences in elasticity between normal and tumor tissue: soft tissues are shown in red and hard tissues in blue. In patients with GSETs, EUS-elastography can enhance diagnostic accuracy. However, a limitation exists concerning GISTs. In fact, we can predict the presence of GIST by elastography, but not the malignant potential which depends on the size and the number of mitoses per 50 high-power fields [11].

Abdomino-pelvic computed tomography (APCT) and magnetic resonance imaging (MRI)

The identification of large GSETs can be achieved by other imaging modalities such CT and MRI. There is a theoretical advantage of these two exams over EUS in staging, therapeutic planning and follow-up [12].

Abdomino-pelvic computed tomography (APCT) allows to characterize subepithelial tumors based on CT attenuation values and evaluation of lymph node status. This exam can also assess local extension, invasion to adjacent organs, or possible metastasis of the tumor. However, APCT is unable to determine the layer of origin, which is an important factor in presumptive diagnosis. Sang Yoon Kim demonstrated in a study including 53 patients that the overall accuracy of EUS and APCT was 64.2% and 50.9%, respectively. In particular, the accuracy of EUS vs. APCT for the diagnosis of GIST, leiomyomas, and ectopic pancreas was 83.9% vs. 74.2%, 37.5% vs. 0.0%, and 57.1% vs. 14.3%, respectively. So, APCT and MRI remains useful modalities for malignant and potentially malignant GSETs [7].

Recently, positron emission tomography (PET) seems to be promising in the diagnosis, staging, evaluation of response and even in assessment of GSET recurrence [13].

To summarize, GSETs can be diagnosed by endoscopy and EUS, although the accuracy of the diagnosis depends on the skill of the endoscopist. In some lesions, EUS-FNA may be helpful in the diagnosis. In 2017, the guideline of the European Society of Gastrointestinal Endoscopy (ESGE) suggested performing bite on bite biopsy as the first diagnostic procedure for subepithelial tumors. If this does not yield a diagnostic specimen, EUS-guided sampling is suggested in asymptomatc hypoechoic SET >=2 cm, if a targeted therapy of a suspected GIST is being considered or if a carcinoma, neuroendocrine tumor, lymphoma, or intramural metastasis is suspected [5].

Classification

GSETs include a diverse array of benign, potentially malignant, and malignant lesions. The classification of GSETs is based on endoscopic findings, microscopic and immunohistochemical characteristics [14].

They are classified in epithelial and non-epithelial or mesenchymal tumors [4]. According to the World Health Organization (WHO), mesenchymal tumors are divided into four major categories, including myogenic tumors (leiomyomas or leiomyosarcomas), neurogenic tumors (Schwannomas, granular cell tumors and neurofibromas), fibroblastic tumors (desmoid, inflammatory myofibroblastic tumors) and GISTs [14]. Table 2 summarize this classification.

Non epithelial tumors	Epithelial tumors	Non tumoral Lesions
Mesenchymal tumors GIST Leiomyoma Schwannoma Granular cell tumor Inflammatory fibroid tumor Lipoma Vascular tumor (glomus tumor, hemangioma...) Lymphatic tumor (lymphangioma Lymphoma	Neuroendocrine tumor Carcinoma Metastatic carcinoma	Aberrant pancreas Duplication

Table 2: *GSETs categories.*

GISTs are the most common type of SET in the stomach and have no specific endoscopic or EUS findings, and diagnosis is difficult to achieve by histopathological examination using hematoxylin and eosin staining alone. Immunohistochemical analysis such as that involving KIT, CD34 or DOG1 measurement is essential for a definitive diagnosis [15].

Therapeutic modalities

Therapeutic approach of GSETs depends on their histology first, their size secondly and finally on the presence or not of specific symptoms [4]. In fact, asymptomatic benign lesions such as lipomas, vascular lesions, cysts, pancreatic rests, and leiomyomas do not require any intervention or follow-up. The American Society for gastrointestinal endoscopy (ASGE) 2017 suggest that lesions with malignant potential should be resected either endoscopically or surgically, based on patient preference, lesion type, size, location; and available expertise in endoscopic resection techniques or surgery [6].

Although treatment strategy should be based on pathological diagnosis, most GSETs including GIST have been surgically removed without preoperative histological diagnosis in clinical practice because of difficulties in preoperative tissue collecting. Surgical treatment is also indicated for GSETs with specific symptoms such as bleeding [4]. Standard treatment is macroscopic complete resection by either open or laparoscopic surgery. Laparoscopic surgery is suggested to be less invasive and to have similar oncological outcomes to open surgery, but this approach is not recommended for resection of large tumors [16].

Japan Gastroenterological Endoscopy Society (JGES) recommended the surgery approach for GSETs < 2 cm suggestive of malignancy with an irregular border or a tumorous ulcer on endoscopy. They recommend that lesions not considered malignant should be followed up every year using endoscopy or EUS. The JGES recommends surgical resection for GSETs between 2 and 5 cm [4]. The European Society for Medical Oncology (ESMO) and the European Society of Gastrointestinal Endoscopy (ESGE) suggest performing EUS 3 months after the detection of GSMT < 2 cm, followed by a yearly follow-up thereafter. If the lesions increase in size or became symptomatic, they should be removed [16].

Endoscopic resection techniques include endoscopic submucosal resection (ESMR), endoscopic submucosal dissection (ESD), submucosal tunneling with endoscopic resection (STER) and endoscopic full thickness resection (EFTR) [6]. However, several factors underlie the difficulties associated with endoscopic treatment. First, determining the possibility of malignancy for GSETs is difficult before resec-

tion. Endoscopic treatments alone do not guarantee complete resection and prevention of cancer recurrence. Lastly, the effectiveness of endoscopic treatment is highly affected by the location of the GSETs with a high perforation risk [17].

Particular situation: Treatment approach for GISTs

GISTs, the most common GSETs are potentially malignant, even when they are small. Multidisciplinary treatment planning is needed (involving pathologists, radiologists, surgeons, and medical oncologists, as well as gastroenterologists, nuclear medicine specialists, etc) [16]. The National Comprehensive Cancer Network guidelines indicate that GISTs with symptoms should be removed independently of size [18]. In 2018, the European Society of medical oncology (ESMO) proposed that the standard approach to patients with gastric nodules < 2 cm is endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumour increases in size or becomes symptomatic. In a histologically proven small GIST, standard treatment is excision regardless of tumor size. The standard approach to tumours > 2 cm in size is biopsy/excision, because they are associated with a higher risk of progression if confirmed as GIST. The standard treatment of localised GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes. Imatinib is the standard treatment of locally advanced inoperable and metastatic disease [19].

Therefore, asymptomatic GSETs smaller than 2 cm usually have a benign course, and it is recommended that they be managed by periodic surveillance using endoscopy or EUS. GIST proven by biopsy should be removed completely regardless of tumor size. GSETs with lesion-specific symptoms or those with malignant features on endoscopy or high-risk features on EUS have a high probability of a clinically malignant condition. Biopsy or resection of these tumors is needed for accurate determination of the long-term prognosis.

Therapeutic strategies of GSETs were summarized in figure 1.

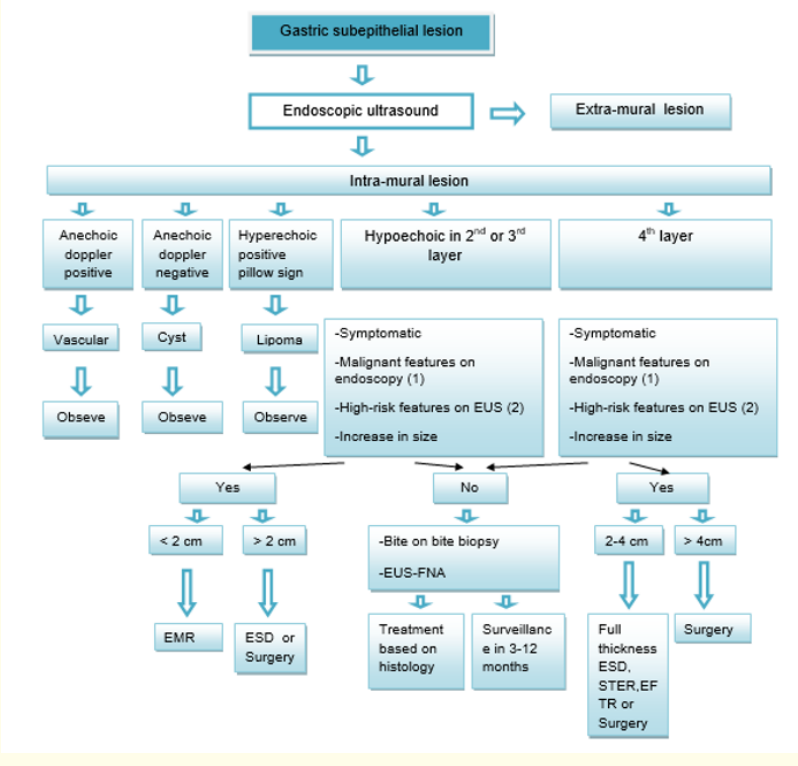

Figure 1: *Diagnostic and therapeutic strategies for GSETs.*

(1): Irregular border, or tumorous ulcer, (2): Anechoic area, echogenic foci, irregular border, or regional lymph node swelling, EUS: Endoscopic Ultrasonography; EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Submucosal Dissection; STER: Submucosal Tunneling with Endoscopic Resection; EFTR: Endoscopic Full Thickness Resection.

Conclusion

Gastric subepithelial tumors are relatively common features encountered during endoscopic examinations. The difficulty is to discriminate malignant lesions from benign ones and so that to identify lesions requiring therapy and those with a wait-and-see approach. EUS is a reliable investigative procedure for evaluation of GSETs. Symptomatic GSETs and histologically proven-malignant tumors should undergo endoscopic or surgical resection. Tumors > 4 cm, with malignant or high-risk features, or increasing in size are encouraged to undergo treatment even if asymptomatic and small. Recently, the role of endoscopy has expanded to include not only the diagnosis of subepithelial lesions but also their treatment.

Bibliography

1. Jin Woong C and the Korean ESD Study Group. "Current guidelines in the management of upper gastrointestinal subepithelial tumors". *Clinical Endoscopy* 49 (2016): 235-240.

2. Wiech T., *et al.* "Histopathological classification of nonneoplastic and neoplastic gastrointestinal submucosal lesions". *Endoscopy* 37 (2005): 630-634.

3. Yoshiko N., *et al.* "Reasons for diagnostic failure in forty-five consecutive mucosal cutting biopsy examinations of gastric subepithelial tumors". *Clinical Endoscopy* (2020).

4. Nishida T., *et al.* "Submucosal tumors: Comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors". *Digestive Endoscopy* 25 (2013): 479-489.

5. Dumonceau JM., *et al.* "Indications, results and clinical impact of endoscopic ultrasound guided sampling in Gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE)" (2017).

6. L Faulx A., *et al.* "The role of endoscopy in subepithelial lesions of the GI tract". *Gastrointestinal Endoscopy* (2017).

7. Sang Yoon Kim., *et al.* "Comparison of the Diagnostic Ability of Endoscopic Ultrasonography and Abdominopelvic Computed Tomography in the Diagnosis of Gastric Subepithelial Tumors". *Clinical Endoscopy* 52 (2019): 565-573.

8. Ikehara H., *et al.* "Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy vs mucosal cutting biopsy". *World Journal of Gastrointestinal Endoscopy* 7.14 (2015): 1142-1149.

9. Kataoka M., *et al.* "Mucosal cutting biopsy technique for histological diagnosis of suspected gastrointestinal stromal tumors of the stomach". *Digestive Endoscopy* 25 (2013): 274-280.

10. Rong L., *et al.* "Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions". *Digestive Endoscopy* 24 (2012): 358-363.

11. Azuma M., *et al.* "Diagnostic potential of endoscopic ultrasonography-elastography for gastric submucosal tumors". *Digestive Endoscopy* 27.1 (2015): 23.

12. Lau S., *et al.* "Imaging of gastrointestinal stromal tumour (GIST)". *Clinical Radiology* 59 (2004): 487-498.

13. Ponsaing LG., *et al.* "Diagnostic procedures for submucosal tumors in the gastrointestinal tract". *World Journal of Gastroenterology* 13 (2007): 3301-3310.

14. Wiech T., *et al.* "Histopathological classification of nonneoplastic and neoplastic gastrointestinal submucosal lesions". *Endoscopy* 37 (2005): 630-634.

15. Kazuya Akahoshi., *et al.* "Current clinical management of gastrointestinal stromal tumor". *World Journal of Gastroenterology* 24.26 (2018): 2806-2817.

16. ESMO/European Sarcoma Network Working Group. "Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology* 25.3 (2014): iii21-iii26.

17. Su Young Kim and Kyoung Oh Kim. "Management of gastric subepithelial tumors: The role of endoscopy". *World Journal of Gastrointestinal Endoscopy* 8.11 (2016): 418-424.

18. Jin Woong Cho and the Korean ESD Study Group. "Current Guidelines in the Management of Upper Gastrointestinal Subepithelial Tumors". *Clinical Endoscopy* 49.3 (2016): 235-240.

19. PG Casali., *et al.* "Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Annals of Oncology* 29 (2018): 68-78.

Volume 7 Issue 9 September 2020
©All rights reserved by Elleuch Nour.*, et al.*