

SUMMARY OF SPEAKERS' PRESENTATIONS

What to do with the incidental asymptomatic small gastric subepithelial lesions. Facts? Recommendations?

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Since upper endoscopy is widely available, clinicians more often encounter the bulges arising beneath the epithelium, with variable clinical significance ranging from insignificant to malignant lesions. Endoscopic biopsies can unlikely determine the diagnosis because these lesions lie deep in the GI wall. For the subepithelial lesions (SELs) larger than 10 mm, evaluation with EUS is recommended to ascertain the size, layer of origin, features of echogenicity, and high-risk features for malignancy suspicion (1).

Evaluation of the small gastric subepithelial lesions

In most cases, EUS findings only allow a presumptive diagnosis and determine the need for further explorations like tissue sampling, surgery, or follow-up. Muscularis propria (MP) (fourth layer) hypoechoic lesions are mostly GISTs if they are localized in the stomach, but EUS alone is not sufficient to differentiate GIST from other causes of hypoechoic MP masses like schwannoma, leiomyoma, lymphoma, etc. therefore, a tissue diagnosis with EUS guided-fine needle aspiration (EUS-FNA) is generally performed.

At present, although EUS-FNA is considered the procedure of choice for preoperative diagnosis of GIST by immunohistochemical analysis of the sample for c-KIT (2), it provides inadequate material in up to 33.3% of the cases. Particularly, smaller tumors are technically more difficult to obtain adequate histological samples compared to larger ones (3). So, the diagnosis of small GISTs may be only presumptive based on the EUS appearance but also performing EUS-FNA and management decision may be challenging. Nevertheless, GIST appeared to be the most common diagnosis among the MP-SELs in many studies evaluating the post-operative results. In one study, post-operative histological examination revealed GIST in 16 of 19 (84.2%) resected gastric MP-SELs ≤ 3 cm in size (the others were 2

schwannomas and 1 leiomyoma) (4). Even in the case of a GIST diagnosis accomplished by EUS-FNA, evaluation of the malignant potential of the tumor based on the mitotic index may not be possible due to the lack of as sufficient material as required for prompt investigation. Thus EUS-FNA may not change the management strategy at least in a significant subset of patients with asymptomatic small MP-SELs.

The National Institutes of Health (NIH) consensus (5) classified GISTs into very low, low-, intermediate-, and high-risk categories by using the size and mitotic count of the lesions. Furthermore, Miettinen and Lasota(6) indicated that GISTs ≤ 20 mm with a mitotic index of $\leq 5/50$ HPF have no metastasis risk, thus they defined these lesions as benign, although NIH has avoided such a category. Nevertheless, obtaining sufficient material from a small SEL in an attempt to scrutinize its malignant potential by assessing the mitotic count may be technically difficult.

How to follow up the small muscularis propria subepithelial lesions

The frequency of follow-up duration of small SELs suggestive of GIST is controversial in different guidelines. The American Gastroenterological Association (AGA) recommends surveillance for <30 mm lesions without concerning the endosonographic features. (7) The US National Comprehensive Cancer Network (NCCN) avoids making a clear statement for the small gastric GISTs (<20 mm) because of the insufficient data, but recommends resection of the small lesions with high-risk EUS features, and endoscopic surveillance at 6- to 12-month intervals for the lesions without high-risk features. (8) European Society for Medical Oncology (ESMO) guidelines suggest a short-term first control (e.g. at 3 months) continuing with a longer interval follow-up schedule in case of no growth, if follow-up strategy is chosen for small lesions. (9) Japanese guidelines recommend that lesions <20 mm in size and without ulceration or surface depression can be managed with endoscopic follow-up once or twice a year. (10) There are no large scale investigations providing evidence for the effectiveness of these follow-up schedules. The study published by our group has shown that small hypoechoic SELs of <2 cm originating from MP in stomach suggestive of GIST lesions with EUS survive disease free for a mean duration of 4 years although most patients in our series had much longer surveillance. (11). Therefore we support the notion of conservative management of small hypoechoic SELs originating from MP of gastric wall. Our results suggest that following up of those small asymptomatic MP-SELs detected incidentally during upper gastrointestinal endoscopy without any high risk echogenic features for malignancy not less than 4 years is sufficient. We believe, the guidelines regarding the follow-up recommendations of small hypoechoic MP SELs of stomach suggestive of GISTs should be revised as they currently recommend EUS follow-ups every 3 to 12 months after the initial examination. (12)

In conclusion, drawing definite conclusions for small gastric GISTs may be limited by the insufficient sample size of studies, mostly due to the fact that GISTs are rare tumors. Available data support the notion of a conservative management strategy, rather than a surgical approach, for small gastric MP-SELs, but in the light of the uncertainties, final decision for these small lesions must be individualized after options are thoroughly discussed with the patient. More accurate non-invasive characterization with the newer imaging techniques that allow a more targeted puncture, improvements in design of needles providing larger and safer tissue acquisition, and identification of the molecular and genetic aspects of malignant transformation profiles at the early stage for the small gastric MP-SELs may provide superior risk estimation and refinement of the management strategies in the future.

References

1. Hwang JH, Kimmey MB. The Incidental Upper Gastrointestinal Subepithelial Mass. *Gastroenterology*. 2004;126(1):301-7.
2. Akahoshi K, Oya M. Gastrointestinal stromal tumor of the stomach: How to manage? *World J Gastrointest Endosc*. 2010;2(8):271-7.
3. Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. *World J Gastroenterol* 2007; 13(14): 2077-2082.
4. Kim MY, Jung HY, Choi KD, Song HJ, Lee JH, Kim do H, et al. Natural history of asymptomatic small gastric subepithelial tumors. *J Clin Gastroenterol*. 2011;45(4):330-6.
5. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; 33:459-465.
6. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23:70– 83.
7. Hwang JH, Rulyak SD, Kimmey MB; American Gastroenterological Association Institute. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology*. 2006;130(7):2217-28.
8. George D. Demetri, Margaret von Mehren, Cristina R. Antonescu, Ronald P. DeMatteo, Kristen N. Ganjoo, Robert G. Maki, et al. NCCN Task Force Report: Update on the Management of Patients with Gastrointestinal Stromal Tumors. *JNCCN* 2010; 8[Suppl 2]:S1–\$40.].
9. The ESMO / European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2012; 23 (Supplement 7): vii49–vii55, 2012.
10. Nishida T, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, Otani Y, Shimada Y, Takahashi F, Kubota T. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008; 13: 416-430.
11. Yegin EG, Kani T, Banzragch M, Kalayci C, Bicakci E, Duman DG. *Survival in patients with hypochoic muscularis propria lesions suggestive of gastrointestinal stromal tumors in gastric wall*. *Acta Gastroenterol Belg*. 2015;78(1):12-7.
12. Yegin EG, Duman D. Small EUS-suspected gastrointestinal stromal tumors of the stomach: an overview for the current state of management. *EUS Journal* 2015(article in press)