國立臺灣大學醫學院臨床醫學研究所
碩士論文

Graduate Institute of Clinical Medicine

College of Medicine

National Taiwan University

Master Thesis

諧波造影增強內視鏡超音波是否可有效鑑別上消化道上皮下腫瘤?一項回溯性研究

Could CEH-EUS increase the diagnostic accuracy of subepithelial tumor in upper GI tract? A retrospective study

林姿伶
Tzu-Ling Lin

指導教授：王秀伯 國立臺灣大學醫學院教授
Advisor: Hsiu-Po Wang
Professor of National Taiwan University
College of Medicine

中華民國110年7月
July 2021

doi:10.6342/NTU202102982

誌謝

上消化道上皮下腫瘤雖不罕見，然而因為內視鏡超音波檢查的技術門檻較高、顯影劑的取得及使用在上皮下腫瘤尚未普及、病人需要開刀且願意開刀的比例不高、適逢 COVID-19 疫情等因素，合適個案的資料蒐集並不容易。在此非常感謝指導教授：王秀伯醫師；學長：韓明倫醫師、陳介章醫師；學弟：戎伯岩醫師，無私且熱情的協助。這個研究是為了解決一直困擾著臨床醫師的問題，雖然這還不是盡善盡美的研究，不過仍然希望目前的發現可以提供臨床醫師診療上的一點建議。

doi:10.6342/NTU202102982

中文摘要

目的：評估諧波造影增強內視鏡超音波在上消化道上皮下腫瘤診斷中的診斷準確性。

方法：在這個單一醫學中心、回溯性研究中，我們收集了 136 名患者的數據（這些患者共有 137 個病灶）。這些患者接受的上消化道上皮下腫瘤檢查，都含有諧波造影增強內視鏡超音波的評估。我們將最終病理報告為胃腸道基質細胞瘤、以及平滑肌瘤的病人，他們諧波造影增強內視鏡超音波的評估中、對比劑增強效果進行了分析。

結果：這些病人的最終病理診斷共有 35 個胃腸道基質細胞瘤以及 22 個平滑肌瘤。我們發現對比度的增強有助於區分胃腸道基質細胞瘤和平滑肌瘤。（ 全組：敏感度 = 0.8，p 值 < 0.001；95%信賴區間為 0.631~0.916。小腫瘤組：敏感度 = 0.54，p 值 = 0.041；95%信賴區間為 0.251~0.808）

結論：諧波造影增強內視鏡超音波有助於診斷上消化道的上皮下腫瘤，即使在小腫瘤組中也是如此。(≦ 20 mm) 如果可行，切除上消化道上皮下腫瘤的術前評估可能需要包括諧波造影增強內視鏡超音波，即使是小於 2 公分的小腫瘤。不過因為這只是單一醫學中心的回溯性研究，如果有可能的話，應該進行多醫學中心的前瞻性研究來進一步確認這個結論。

關鍵詞：超音波顯影劑、內視鏡超音波、諧波造影增強內視鏡超音波、上消化道上皮下腫瘤、胃腸道基質細胞瘤、平滑肌瘤、黏膜下腫瘤

doi:10.6342/NTU202102982

English Summary

Aims: To evaluate the diagnostic accuracy of CEH-EUS in upper GI tract SETs.

Methods: We retrieved data for 136 patients with 137 lesions that underwent CEH-EUS study for upper GI tract SETs. Enhancement of contrast, final pathology, and other clinical information were reviewed retrospectively.

Results: 35 GISTs and 22 leiomyomas were pathologically diagnosed. Contrast enhancement helps in differentiating GISTs and leiomyomas. (All-size group: SE = 0.8, P < 0.001; CI 95% 0.631~0.916. Small-size group: SE = 0.54, P = 0.041; CI 95% 0.251~0.808)

Conclusions: CEH-EUS helps in diagnosing SETs in upper GI tract, even in a small-size group. (≦ 20 mm) Evaluations before small tumor resection might include CEH-EUS if feasible.

Key words: EUS, CEH-EUS, subepithelial tumor, submucosal tumor, GIST, leiomyoma, upper GI tract

doi:10.6342/NTU202102982

目　錄

doi:10.6342/NTU202102982

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) represent the largest group of subepithelial tumors (SETs) of the stomach, duodenum and small intestine but occur only very seldom in the esophagus and large intestine. In contrast to leiomyomas, lipomas and most other SETs, GISTs are now considered as malignant, and all GISTs are eligible for cancer staging.[1,2] Therefore, after detection of a subepithelial lesion in the upper gastrointestinal (GI) tract, correct characterization is crucial to start an assessment whether surgery or local resection would be an appropriate approach for the patient.

Endoscopic Ultrasound (EUS) is a diagnostic method with high sensitivity for the detection of subepithelial tumors (SETs); however, it is usually difficult to achieve a differential diagnosis between benign lesions and malignant SETs with conventional EUS.[3] Therefore, we require tissue sampling, with the risk of bleeding, especially for a suspicious GIST. Nevertheless, the sensitivity is low due to sometimes insufficient tissue sampling. Power Doppler EUS is also a useful technique for the assessment of intra-tumor vessels in SETs, but it has limitations, such as motion artifacts and less sensitivity to the slow flow within intra-tumor vessels.

Contrast for ultrasonography is now available for medical use. The aim of this study was to evaluate the effectiveness of contrast and if the contrast could help in diagnosing SETs in the upper GI tract.

doi:10.6342/NTU202102982

MATERIALS AND METHODS

Study population

The medical records of 136 patients with 137 upper GI tract SETs who underwent contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) between December 2017 and December 2020 were retrieved from a consecutively collected database at National Taiwan University Hospital (NTUH) in the R.O.C. An upper GI tract SET that was diagnosed by endoscopy would be referred to the EUS room for further evaluation. The choice of contrast injection depended on the on-site doctor. Images that were not qualified or those with suspected leaked contrast were excluded from this study. Pathology reports were collected thereafter. (Figure 1. Table 1.) The echogenicity and contrast enhancement was decided from images required in CEH-EUS studies, and confirmed after a meeting composed of five doctors. For the reason of specificity, only GISTs and leiomyomas were included. Thus, clinical data for a total of 56 patients with 57 lesions were enrolled for analysis, including tumor size (in EUS), location, EUS echogenicity features, contrast enhancement and pathology. This retrospective study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital, National Taiwan University, R.O.C.

EUS procedures

Under conscious sedation, the patients received a regular EUS study first (linear) and were changed to an echoendoscope that was developed specifically for CEH-EUS if contrast injection was considered (GF-UCT260, Olympus Medical Systems Co. Ltd., Tokyo, Japan or EG-580UR, Fujifilm Medical Systems Co. Ltd., Tokyo, Japan). The

doi:10.6342/NTU202102982

choice of echoendoscope depended on availability. Sonazoid (Daiichi-Sankyo, Tokyo, Japan) was used as the contrast agent. The transmitting frequency and mechanical index were 4.7 MHz and 0.2, respectively, with titration.

After evaluation, tissue sampling was attempted with digging biopsy, polypectomy, ESD, FNB or surgical resection. For the suspected benign small gastric SETs, at least an annular EUS checkup was suggested.

Diagnostic definitions

Pathology results were classified as diagnostic or non-diagnostic. Patients' data with a non-diagnostic pathology result would not be analyzed until further evaluation revealed a diagnostic pathology result.

A diagnostic pathology result was defined when sufficient tissue was obtained to allow for the pathologists at NTUH to establish a formal report with or without immunohistochemistry, including stains for c-kit (CD117), CD34, and smooth muscle actin.

A non-diagnostic pathology result was defined as follows:

1. Insufficient tissue for architectural details or immunohistochemistry
2. Probably not a true SET tissue, such as superficial gastritis/esophagitis/duodenitis or mucosal tag

A diagnosis of GIST was made when microscopy revealed spindle or epithelioid cells that were positive for c-kit with or without positive CD34 immunohistochemistry.

A leiomyoma was diagnosed by smooth muscle or spindle cells that were positive for actin and negative for c-kit.

doi:10.6342/NTU202102982

Statistical analysis

Analyses were conducted using Stata version 13.1 (StataCorp, College Station, Texas 77845 USA) and MedCalc® (MedCalc Software Ltd, Ostend 8400, Belgium). Descriptive statistics were used to characterize the study subjects. Continuous variables were expressed as means ± SD and compared using a Student t-test. The Fisher's exact test was used to compare categorical variables. All statistical calculations were 2-sided, and a p-value less than 0.05 indicated statistical significance.

RESULTS

Of the 136 CEH-EUS patients with 137 lesions, 85 diagnostic pathology reports were available, with 35 GISTs and 22 leiomyomas in 56 patients. The clinical features of patients that were diagnosed with GISTs and leiomyomas are shown in Table 2a and Table 2b. The mean age of the 56 patients was 59.2 years, and 62.5% were female. The mean tumor size was 25.3 mm, and 29 tumors (50.9%) were equal or less than 20 mm in diameter. There was no difference in tumor diameter between the GIST and leiomyoma groups (28.8 ± 19.0 mm and 19.8 ± 14.0 mm, respectively; p = 0.059). The mean age of the GIST group was significantly higher than that in the leiomyoma group (64.8 ± 11.8 years and 50.5 ± 15.3 years, p = 0.0003). Genders in both groups showed no significant difference (p = 0.161).

For the EUS, all SETs in both groups revealed hypoechoic echogenicity and most of them grew from the 4th layer. The EUS features of both groups are shown in Table 3.

Contrast enhancement was found significantly more frequently hyperenhanced in tumors that were diagnosed as GISTs than as leiomyomas (SE = 0.8, P < 0.001) (Table

doi:10.6342/NTU202102982

4).

SETs that were smaller or equal to 20 mm were further categorized into small-size groups. Contrast enhancement was also found more frequently hyperenhanced in small SETs that were diagnosed as GISTs than as leiomyomas (SE = 0.54, p = 0.041) (Table 5). There was no significant tumor size difference between the small GIST group and the small leiomyoma group (14.6 ± 4.3 mm and 13.6 ± 4.6 mm, respectively; p = 0.56). (Table 6a and 6b)

DISCUSSION

This single-centered, retrospective study demonstrated the effectiveness of CEH-EUS in differentiating GISTs from leiomyomas, even in small-size groups. Age differed in both groups, which might not suggest the contrast enhancement pattern (GIST: 64.8 ± 11.8 years; leiomyoma: 50.5 ± 15.3 years, respectively; p = 0.0003).

The term subepithelial tumor (SET) is clinically used for an elevated lesion, which is covered with intact mucosa. SETs are equally found in men and women, especially after the fifth decade of life. Half of the gastric SETs found in middle-aged adults during a health examination are considered to be neoplastic.[4]

SETs are most commonly found in the stomach, followed by the esophagus, duodenum and large intestine. A leiomyoma is the most frequent tumor in the esophagus and in the upper stomach around the esophago-gastric junction, while the gastric GIST is commonly found in the proximal stomach.[5]

Around 10% to 20% of gastric SETs are of malignant potential, while GISTs are the most common tumors.[6] A study in Taiwan demonstrated about 20% tumor growth rate

doi:10.6342/NTU202102982

in initial small-size group (<2cm). [7]

Location is not a reliable indicator for differentiating GISTs from leiomyomas. The tissue of most SETs could not be easily approached by a luminal endoscopic forceps biopsy, and an advanced diagnostic resection might be considered due to the risk of malignancy. However, the procedure might induce risks of bleeding or perforation.

In cases without adequate tissue for a pathology examination, primary tumor size and clinical features were taken into consideration with annular follow-up and/or some other image modality check.[8]

For a symptomatic SET, those that were larger than 2 cm, or tumors with malignant clinical features, the decision of surgery was acceptable, due to the risk of malignancy, especially GISTs, which may progress when larger than 2cm.[9]

Emerging "non-surgical" techniques of tumor resection with flexible endoscopy for small SETs include endoscopic submucosal dissection (ESD), endoscopic full-thickness resection (EFTR) and natural orifice transluminal endoscopic surgery (NOTES). Nevertheless, after these advanced endoscopic resections, some of those SETs were still leiomyomas, which might not need to be resected due to the risk of bleeding and perforation.[10]

As for the asymptomatic SETs that were less than 2 cm and were clinically benign looking, annular check-up was suggested first, but the risk of progress still persisted. Because the decision of so-called benign and malignant GISTs is considered to be very difficult, not only by clinical investigations or by pathology examinations, the European Society for Medical Oncology (ESMO) and the Japanese GIST guidelines both suggest surgical resection when an SET is diagnosed as a GIST even if less than 2 cm.[11,12] The current NCCN guideline also suggests of aggressive resection for the SETs that known

doi:10.6342/NTU202102982

to be or clinically suspicious to be GIST. Except for those very small gastric GISTs that were less than 2cm, periodic endoscopic or radiographic surveillance might be considered. [13] If no tissue can be gathered from a small SET, we cannot exclude the possibility of a GIST, especially for the small SETs, whose sizes are very close to 2 cm. The wait-and-see approach may lead to the progress of the GIST.

Modalities for SET survey have been developed with a different pooled diagnostic yield. Among them, EUS-FNA (fine needle aspiration), contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have good performance (84.0%, 73.6%, 91.7%, respectively, for GIST). [14] EUS-FNB (fine needle biopsy) is even superior to EUS-FNA for diagnostic yield of suspected GIST lesions. (89% vs 37%, with median lesion size in each group: 21 mm vs 25 mm, p = 0.25) [15] However, some limitations still persist, for example, the risk of bleeding, failed sampling, and sometimes insufficient tissue for immunocytochemistry (ICC) stain in the EUS-FNA/FNB procedure; renal toxicity and radiation from the contrast enhanced CT scan; and the risk of nephrogenic fibrosing dermopathy of the MRI contrast. MRI is also considered only as a helpful adjunct to CT, especially large SETs, while the multi-planar capability of magnetic resonance can help the determination of organ of origin, and the relationship to other organs. MRI could also describe the major blood vessels. But contrast enhanced MRI offers no additional information compared to contrast enhanced CT about the internal features of SETs, at least, GISTs [16,17] For the small-size GISTs, especially those that were less than 2 cm, contrast enhanced CT and MRI have limited role in detection and differentiation. For example, contrast enhanced CT failed to demonstrate any neovascularization in study by Fukuta et al [18], and its sensitivity to detect the blood vessels was 0% in small lesions (<3 cm) and 42% only in large lesions

doi:10.6342/NTU202102982

(>3 cm) in the study by Sakamoto et al. [19] In the contrast enhanced MRI studies, there were very limited cases in demonstrating the enhancement pattern of small GISTs that were less than 2cm. [20] CT and MRI modality cannot be performed on site, neither. EUS is still a useful imaging technique to diagnose small (<2 cm), incidentally detected subepithelial GISTs. EUS could also describe the gut wall layers and allow for further tissue acquirement assistance. [21] However, the EUS study that basing on only subtle differences in the shape, size, layers, echogenicity and homogenesity has limited role in differentiating tumors that with similar appearance, such as GIST and leiomyoma. Additional assistance is required, such as digital image analysis or the diagnosis of malignant GIST might not be sure when the size is less than 35mm [22,23]

Contrast for ultrasonography has been developed to provide more detailed information. As for applications to SETs, higher vascularity and contrast enhancement was found in GISTs.[24] Contrast enhanced EUS is now considered to be a non-invasive modality with valuable assessment of perfusion patterns of GISTs and subepithelial tumors. Its sensitivity is higher than EUS–FNA, contrast enhanced CT and Doppler EUS for detecting the neo-vascularity. [25] However, due to limited cases and variable tumor size included, the efficacy in detecting and differentiating the SETs, especially the small ones (<2cm) remains uncertain. The sensitivity and specificity of CEH-EUS in detecting GISTs from subepithelial tumors ranged from 53.8% to 100%.[26,27,28]

For more specified condition, we compared the performance of the contrast in the two most common SETs: GISTs and leiomyomas in the upper GI tract. The goal was to help decide either to require resection or just a wait-and-see approach for these SETs, especially the ones that were smaller than but very close to 20 mm. For elderly and older patients and patients with multiple morbidities, bleeding, or other risks for surgery or

doi:10.6342/NTU202102982

endoscopic resection, we believe CEH-EUS can provide more information for patients and doctors to make the best decision.

A multi-centered prospective study might be conducted to verify the conclusion.

doi:10.6342/NTU202102982

Figure 1

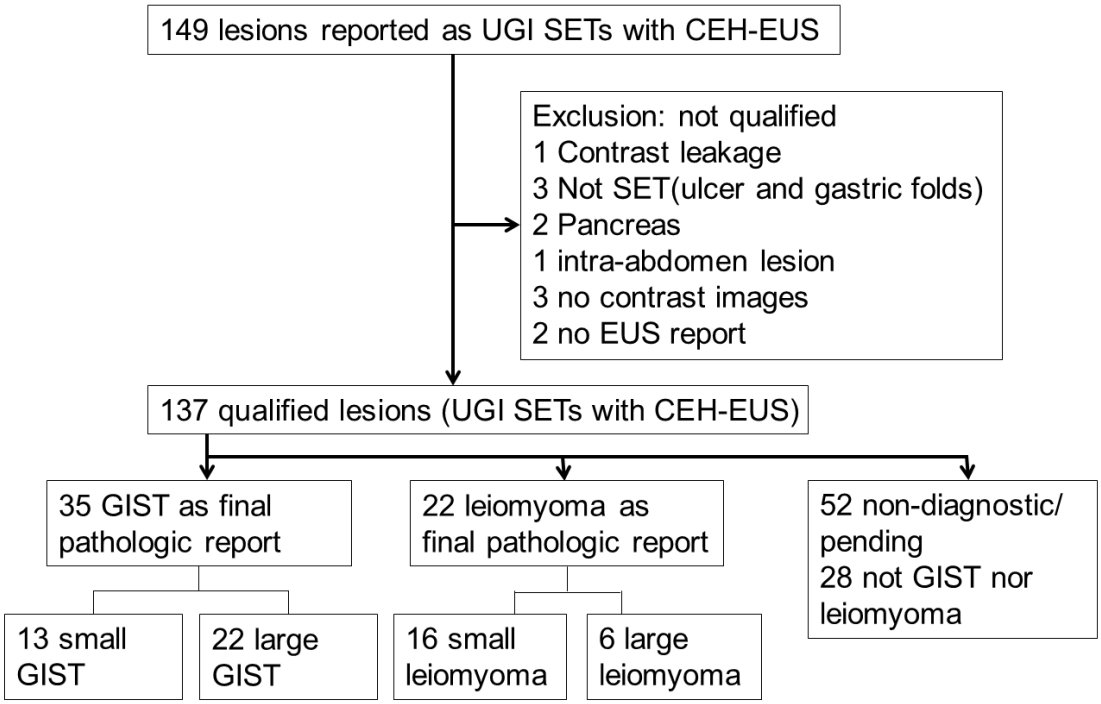

Table 1 the pathology excluded (not GIST nor leiomyoma)

Pathology	**Lesion number**
NET	3
abberrant pancreas	6
adenocarcinoma	5
adenoma	1
carcinoma	2
gastritis cystica polyposa	1
glomus tumor	1
granular cell tumor	1
lipoma	4
lymphoma	1
malignant melanoma	1
schwannoma	1
squamous cell carcinoma	1

doi:10.6342/NTU202102982

Table 2a

The clinical features of patients diagnosed with GISTs and leiomyomas

Case (GIST and Leiomyoma)	57(56 patients)
Age (at first contrast) y/o	59.2 ± 14.9 (25-88) (56 patients)
Gender	
Female	35
Male	21
Size (mm)	25.3 ± 17.7 (5-90) (57 lesions)
Organ	
Duodenum	6
Esophagus	8
Stomach	43

Table 2b

	GIST	**Leiomyoma**	
Case	35 (34 patients)	22	
Age (at first contrast) y/o	64.8 ± 11.8	50.5 ± 15.3	**P = 0.0003**
Gender			
Female/Male	24/10	11/11	**P=0.161**
Size (mm)	28.8 ± 19.0	19.8 ± 14.0	**P = 0.059**
Organ			
Duodenum	5	1	
Esophagus	1	7	
Stomach	29	14	

doi:10.6342/NTU202102982

Table 3 EUS features of the GIST and leiomyoma groups

EUS findings	**GIST**	**Leiomyoma**	**Total**
Layers			
1st	0	0	0
2nd	0	3	3
3rd	0	0	0
4th	35	19	54
Echogenicity			
Hypoechoic	35	22	57
Hyperechoic	0	0	0

Table 4 Contrast enhancement in the GIST and leiomyoma groups

Contrast enhancement	**GIST**	**Leiomyoma**
Hyperenhanced	28	5
Hypoenhanced	7	17

P<0.001

Statistic	**Value**	**95% CI**
Sensitivity	80.00%	63.06% to 91.56%
Specificity	77.27%	54.63% to 92.18%
Positive Likelihood Ratio	3.52	1.60 to 7.74
Negative Likelihood Ratio	0.26	0.13 to 0.52

doi:10.6342/NTU202102982

Table 5 Contrast enhancement in the small GIST and small leiomyoma groups

Contrast enhancement	**GIST**	**Leiomyoma**
Hyperenhanced	7	2
Hypoenhanced	6	14

P=0.041

Statistic	**Value**	**95% CI**
Sensitivity	53.85%	25.13% to 80.78%
Specificity	87.50%	61.65% to 98.45%
Positive Likelihood Ratio	4.31	1.07 to 17.31
Negative Likelihood Ratio	0.53	0.28 to 0.98

doi:10.6342/NTU202102982

Table 6a The clinical features of patients diagnosed with small GISTs and leiomyomas

Case (GIST and Leiomyoma)	29
Age (at first contrast) y/o	57.0±13.1 (27-85)
Gender	
Female	15
Male	14
Size (mm)	14.1±4.4 (5-20)
Organ	
Duodenum	1
Esophagus	6
Stomach	22

Table 6b

	GIST	**Leiomyoma**	
Case	13	16	
Age (at first contrast) y/o	63.2±9.2	51.9±13.7	**P=0.0168**
Gender			
Female/Male	9/4	6/10	**P=0.139**
Size (mm)	14.6±4.3	13.6±4.6	**P=0.56**
Organ			
Duodenum	1	0	
Esophagus	0	6	
Stomach	12	10	

doi:10.6342/NTU202102982

REFERENCES

1.Raut, Chandrajit, Dematteo, Ronald. Evidence-Guided Surgical Management of GIST: Beyond a Simple Case of Benign and Malignant. (March 2008) Ann. Surg. Oncol. 15(5): 1542-1543

2.AJCC (8th edition)

3.Hwang JH, Saunders MD, Rulyak SJ, et al. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. Gastrointest Endosc 2005; 62: 202-8

4.Hedenbro JL, Ekelund M, Wetterberg P. Endoscopic diagnosis of submucosal gastric lesions. The results after routine endoscopy. Surg. Endosc. 1991; 5: 20–3.

5.Miettinen M, Sarlomo-Rikala M, Sobin LH. Mesenchymal tumors of muscularis mucosae of colon and rectum are benign leiomyomas that should be separated from gastrointestinal stromal tumors–a clinicopathologic and immunohistochemical study of eighty-eight cases. Mod. Pathol. 2001; 14: 950–6

6.Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy 2005;37:635-645. 16010608.

7.Yu-Jen Fang, Tsu-Yao Cheng, Meng-Shun Sun, Chang-Shyue Yang, Jiann-Hwa Chen, Wei-Chih Liao, Hsiu-Po Wang. Suggested cutoff tumor size for management of small EUS-suspected gastric gastrointestinal stromal tumors. J Formos Med Assoc 2012 Feb 111, (2) 88-93

8.Nishida T, Hirota S, Yanagisawa A et al. Clinical practice guideline for gastrointestinal stromal tumor (GIST) in Japan. Int. J. Clin. Oncol. 2008; 13: 416–30

9.Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor. Arch Pathol Lab Med. 2010 Feb;134(2):165-70.

10.Su Young Kim and Kyoung-Oh Kim. Endoscopic Treatment of Subepithelial Tumors. Clin Endosc 2018;51:19-27.

11.Nishida T, Hirota S, Yanagisawa A et al. Clinical practice guideline for gastrointestinal stromal tumor (GIST) in Japan. Int. J. Clin. Oncol. 2008; 13: 416–30.

12.ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2012; 23 (Suppl 7): vii49–55.

13.NCCN guideline for GIST management. 2021.Version 1

14.Scarpa M, Bertin M, Ruffolo C, et al. A systematic review on the clinical diagnosis of gastrointestinalstromal tumors. J Surg Oncol 2008; 98: 384-92

15.Arvind J. Trindade, Petros C. Benias,Mohammed Alshelleh, Ahmad N. Bazarbashi,Benjamin Tharian, Sumant Inamdar, Neil Sharma, Christina Zelt, Praneet Korrapati, Mohamed Barakat, Divyesh V. Sejpal, and Marvin Ryou. Fine-needle biopsy is superior to fine-needle aspiration of suspected gastrointestinal stromal tumors: a large multicenter study. Endosc Int Open. 2019 Jul; 7(7): E931–E936.

16.Laura Graves Ponsaing, Katalin Kiss, Annika Loft, Lise Ingemann Jensen, and Mark Berner Hansen. Diagnostic procedures for submucosal tumors in the gastrointestinal tract. World J Gastroenterol. 2007 Jun 28; 13(24): 3301–3310.

17.Lau S, Tam KF, Kam CK, Lui CY, Siu CW, Lam HS, Mak KL. Imaging of gastrointestinal stromal

doi:10.6342/NTU202102982

tumour (GIST) Clin Radiol. 2004;59:487–498.
18.Fukuta N, Kitano M, Maekawa K, Chikugo T, Kudo M. Estimation of the malignant potential of gastrointestinal stromal tumors: the value of contrast-enhanced coded phase-inversion harmonics US. J Gastroenterol. 2005;40:247–255.
19.Sakamoto H, Kitano M, Matsui S, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos) Gastrointest Endosc. 2011;73:227–237.
20.Mi Hye Yu, Jeong Min Lee, Jee Hyun Baek, Joon Koo Han, Byung-Ihn Choi. MRI Features of Gastrointestinal Stromal Tumors. AJR:203, November 2014
21.Kochhar R, Manoharan P, Leahy M, Taylor MB: Imaging in gastrointestinal stromal tumours: current status and future directions. Clin Radiol 65: 584-592, 2010.
22.Kim GH, Kim KB, Lee SH, et al. Digital image analysis of endoscopic ultrasonography is helpful in diagnosing gastric mesenchymal tumors. BMC Gastroenterol. 2014;14:7.
23.Kim GH, Park DY, Kim S, et al. Is it possible to differentiate gastric GISTs from gastric leiomyomas by EUS? World J Gastroenterol. 2009;15:3376–3381.
24.Kannengiesser et al, Scand J Gastroenterol. 2012 Dec;47(12):1515-20
25.Ankit Chhoda1, Deepanshu Jain, Venkateswar R Surabhi, Shashideep Singhal. Contrast Enhanced Harmonic endoscopic Ultrasound: A Novel Approach for Diagnosis and Management of Gastrointestinal Stromal Tumors. Clin Endosc 2018;51:215-221
26.Ignee A, Jenssen C, Hocke M, et al. Contrast-enhanced (endoscopic) ultrasound and endoscopic ultrasound elastography in gastrointestinal stromal tumors. Endosc Ultrasound. 2017;6:55–60.
27. Kannengiesser K, Mahlke R, Petersen F, et al. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. Scand J Gastroenterol. 2012;47:1515–1520.
28.Park HY, Jeon SW, Lee HS, et al. Can contrast-enhanced harmonic endosonography predict malignancy risk in gastrointestinal subepithelial tumors? Endosc Ultrasound. 2016;5:384–389.

doi:10.6342/NTU202102982