Histological diagnosis of gastric submucosal tumors: A pilot study of endoscopic ultrasonography-guided fine-needle aspiration biopsy vs mucosal cutting biopsy

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Abstract

AIM: To compare the usefulness of endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) in the histological diagnosis of gastric submucosal tumor (SMT).

METHODS: We prospectively compared the diagnostic yield, feasibility, and safety of EUS-FNAB and those of MCB based on endoscopic submucosal dissection. The cases of 20 consecutive patients with gastric SMT $\geq$ 1 cm in diameter, who underwent both EUS-FNAB and MCB were investigated.

RESULTS: The histological diagnoses were gastrointestinal stromal tumors ($n = 7$), leiomyoma ($n =$
INTRODUCTION

Gastric submucosal tumors (SMTs) including gastrointestinal stromal tumors (GISTs), leiomyomas, schwannomas, aberrant pancreas and more are frequently identified during routine upper endoscopies. Although endoscopic ultrasonography (EUS) is a useful modality for diagnosing gastric SMTs\(^1\), it is not always possible to differentiate a GIST from a leiomyoma or schwannoma by EUS, especially when the tumor originated from the muscularis propria layer. GISTs are rare neoplasms that account for only 0.1%-3% of all gastrointestinal (GI) malignancies\(^2\)-\(^4\), whereas they represent approximately 80% of GI mesenchymal tumors\(^5\). As GISTs are potentially malignant, histological diagnosis by an EUS-fine-needle aspiration biopsy (FNAB) is recommended\(^6\),\(^7\). It is thus very important to discriminate these lesions from benign SMTs originating from the muscularis propria, such as leiomyomas and schwannomas. However, it may be difficult to arrive at the correct histological diagnosis with only a standard endoscopic biopsy, because the surface of an SMT is covered with normal epithelium.

EUS-FNAB is a reliable, useful and suitable method for the histological evaluation of SMTs\(^8\)-\(^10\). Although EUS-FNAB is used widely, only a limited number of cases are subjected to this method, even in hospitals specializing in gastroenterology. In addition, EUS-FNAB systems including an echoendoscope and its observing system are very expensive and require not only experienced pathologists but also cytology technicians capable of handling and processing biopsy specimens\(^7\). The successful diagnostic rate for SMT by an EUS-FNAB combined with cytology has been reported to be relatively high (83%), but the success rate for histology is not satisfactory (50%)\(^11\)-\(^13\). An alternative modality for the histological diagnosis of SMTs is thus needed.

Endoscopic submucosal dissection (ESD) was developed in Japan in the 2000s\(^14\) and has since been widely adopted for the treatment of superficial gastric neoplasms. By applying this method, Lee et al\(^15\) described cases in which an ESD-associated technique rather than EUS-FNAB was useful for the tissue sampling of SMTs. The applications of several similar methods for the histological diagnosis of gastrointestinal (GI) SMTs were also reported: mucosal cutting biopsy (MCB), a mucosal incision-assisted biopsy technique, and an “unroofing” biopsy based on endoscopic mucosal resection (EMR)\(^16\)-\(^20\). A comparison of the histological diagnostic yield of SMTs between EUS-FNAB without its combination with cytology and MCB has not been published, to our knowledge. The aim of the present study was to prospectively compare the diagnostic yield of gastric SMTs and the feasibility, safety and complications between EUS-FNAB and MCB by performing both diagnostic modalities simultaneously for the same SMT patients.

MATERIALS AND METHODS

Patients

Between May 2012 and February 2015 in our depart-

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6), schwannoma \((n = 2)\), aberrant pancreas \((n = 2)\), and one case each of glomus tumor, metastatic hepatocellular carcinoma, and no-diagnosis. The tumors’ mean size was 23.6 mm. Histological diagnosis was made in 65.0% of the EUS-FNABs and 60.0% of the MCBs, a nonsignificant difference. There were no significant differences in the diagnostic yield concerning the tumor location or tumor size between the two methods. However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth by the MCB method \((P = 0.01)\). All four SMTs with extraluminal growth were diagnosed only by EUS-FNAB \((P = 0.03)\). No complications were found in either method.

CONCLUSION: MCB may be chosen as an alternative diagnostic modality in tumors showing the intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

Key words: Submucosal tumor; Endoscopic ultrasonography-guided fine-needle aspiration biopsy; Gastrointestinal stromal tumor; Mucosal cutting biopsy; Endoscopic submucosal dissection

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Core tip: We prospectively compared the diagnostic yield and the safety between endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) without cytology and mucosal cutting biopsy (MCB) based on endoscopic submucosal dissection. Although no significant difference in histological diagnosis was found between EUS-FNAB and MCB, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All submucosal tumors (SMTs) with extraluminal growth were diagnosed only by EUS-FNAB. No complications were found in either method. Therefore, MCB may be chosen as an alternative diagnostic modality in tumors showing intraluminal growth, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.
ment, both EUS-FNAB and MCB were prospectively performed for 20 consecutive patients with gastric SMTs ≥ 1 cm in diameter which were diagnosed by EUS (UM2000, UM-2R and 3R; Olympus Optical Corp., Tokyo) prior to the EUS-FNAB and MCB procedures. If the EUS finding of SMT showed mainly inward or outward growth from the gastric wall, the lesion was judged as intraluminal or extraluminal growth, respectively. Since hyperechoic lesions on EUS that originate from the submucosal layer are generally diagnosed as lipoma, these lesions were excluded from the study. All patients were admitted on the day of EUS-FNAB and MCB, and were usually discharged the day after the procedures. Thus the hospital stay for the patients without any clinical complications was generally 1 d, based on the clinical protocol at our hospital.

Written informed consent was obtained from all patients prior to the study, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 1710).

Operators of the EUS-FNAB and MCB procedures
Operator skill may affect the diagnostic yield and the complications of these procedures. In Japan, endoscopists receive board certification from the Japan Gastroenterological Endoscopy (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy and after passing an examination administered by the JGES. Accordingly, the EUS-FNAB and MCB procedures in the present study were performed by expert endoscopists with board certification from the JGES. The same endoscopist performed the EUS-FNAB and MCB in a given patient.

EUS-FNAB procedure
The EUS-FNAB procedure was performed first with the patient under conscious sedation by midazolam with or without pethidine. The EUS-FNAB procedure was performed by expert endoscopists. Fundamentally, a convex linear-array echoendoscope (GF-UCT260; Olympus Optical) connected to an observing system (UM-ME1; Olympus Optical) was used in this procedure. A 22-gauge needle (EchoTip ProCore High Definition Ultrasound Biopsy Needle; Cook Japan, Tokyo) was used to obtain specimens for the histological analysis. After properly targeting the mass, the endoscopist punctured the lesion with the needle. Thereafter, the inner needle was pulled out, and the endoscopist moved the needle back and forth 20 times while applying suction using the connected 10-mL syringe. The EUS-FNAB was performed by making 1 to 4 passes, at the discretion of the endoscopist. That is, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped.

The obtained material was immediately and directly stained. Cytology was not performed as an on-site cytologist was not available in this procedure, and a cell block for confirmatory IHC was also not prepared.

Mucosal cutting biopsy
Immediately following the EUS-FNAB in each patient, an MCB was performed. The MCB technique was as follows: first, saline was injected into the submucosa and then mucosal cutting was performed using a needle-knife (KD-1L-1; Olympus Optical). Under direct vision of the SMT, several biopsy specimens were taken using conventional biopsy forceps (Radial Jaw™ 4: Boston Scientific, Natick, MA). One to six biopsy samples were taken at the discretion of the operators. As in the EUS-FNAB procedure, when the endoscopist judged that grossly visible material was obtained, the procedure was stopped. Thereafter, the mucosal incision was closed with hemoclips (EZ Clip™; Olympus Optical) to prevent post-procedure bleeding (Figure 1) and to reduce the risk of ulceration that may cause peritoneal dissemination.

The patient’s oral intake was allowed starting the morning after the day of the procedure, and then the patient was discharged. A proton pump inhibitor was administered for 2 wk after the procedure.

IHC staining of the samples obtained by both methods was performed using the following antibodies: c-kit, CD34, S100 protein, and desmin. Patients diagnosed with a GIST were offered surgical resection.

Analysis parameters
We evaluated the diagnostic yield and post-procedure bleeding and other complications between the EUS-FNAB and MCB methods, and we tried to determine the causes of nondiagnostic cases.

Statistical analysis
The data were assessed by Welch’s t test between two groups, and the chi-square test or Fisher’s exact test was used to examine differences between two proportions. Statistical significance was defined as a P value < 0.05. Statistical analyses were performed with GraphPad Prism5 software (GraphPad Software, La Jolla, CA).

RESULTS
Patient characteristics and clinicopathological data of SMTs
Table 1 provides the characteristics of the 20 patients and a summary of the targeted SMTs. All patients underwent EUS prior to the EUS-FNAB and MCB procedures and were diagnosed as having a gastric SMT originating from the submucosal (third layer) or the muscularis propria layer (fourth layer). The mean age of the patients was 61.8 ± 12.5 years (range 39-77 years), and women accounted for 50.0% of the patients. The tumors had a mean size of 23.6 mm (range 10-57). Among the 20 cases, four showed extraluminal growth on EUS. The histological diagnoses were GIST
for the glomus tumor, and at the greater curvature of the antrum in the nondiagnostic case. All seven GIST cases diagnosed by EUS-FNAB or MCB were surgically resected and confirmed histologically as GISTs.

Diagnostic yields of EUS-FNAB and MCB
The median values 3.0 [interquartile range (IQR): 2.0, 4.0] for the EUS-FNAB samples and 3.0 (IQR: 1.5, 4.5) for the MCB samples were obtained per patient. All 15 cases of GIST, leiomyoma and schwannoma were diagnosed by IHC. The rates of histological definitive diagnosis were 65.0% (13 of 20) by EUS-FNAB and 60.0% (12 of 20) by MCB, a nonsignificant difference. The concordance rate of the histological diagnosis between the two methods was 100%. There were also no significant differences in the diagnostic yield regarding tumor location or tumor size between the EUS-FNAB and MCB methods (Table 2). However, diagnostic specimens were significantly more frequently obtained in lesions with intraluminal growth than in those with extraluminal growth in the MCB method ($P = 0.01$). All four of the SMTs that showed extraluminal growth, including three GISTs and the single HCC, were correctly diagnosed only by EUS-FNAB (Figure 2), and not by MCB ($P = 0.03$). Seventeen of the SMTs (85.0%) were histologically diagnosed by both methods.

Complications in both procedures
Two cases showed mild bleeding during the MCB procedure, but both were successfully managed by...
hemoclips. The mean number of hemoclips for closing the incised mucosa was 3.4 (range: 1-6 clips). No post-procedural hemorrhage, fever, or peritonitis was seen following either procedure.

**DISCUSSION**

To date, there are many reports on the methods of tissue acquisition from SMTs: EMR, MCB and EUS-FNAB. Histological diagnosis by a standard biopsy or EMR may be confined to SMTs that arise from the muscularis mucosa or submucosa, which corresponds to second- or third-layer lesions on EUS. In contrast, it may be impossible to make a histologic diagnosis of the lesions located in the muscularis propria by these methods. Therefore, EUS-FNAB was suggested to play an important role in histological diagnoses such as gastric SMTs, although the results can be quite variable. However, although the use of EUS-FNAB is quite prevalent, only a limited number of patients undergo this procedure - even in hospitals specializing in gastroenterology - because an expensive dedicated endoscopic system is needed to conduct an EUS-FNAB. For example, the price of the needle for EUS-FNAB is approximately $300 United States dollars (USD), and the total prices of devices such as the needle knife, injection needle and EZ Clip™ for MCB are also approximately $100 USD, and thus the cost may be

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**Figure 2** Endoscopic ultrasonography-guided fine-needle aspiration biopsy of a gastrointestinal stromal tumor with extraluminal growth. A: EUS-FNAB of a hypoechoic lesion in the muscularis propria layer showing extraluminal growth; B: Histological finding showing spindle cells in the EUS-FNAB specimen (HE); C: Immunohistochemical staining is positive for c-kit. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy.

**Table 2** Diagnostic yields obtained with endoscopic ultrasonography-guided fine-needle aspiration biopsy and mucosal cutting biopsy

|                      | EUS-FNAB |            |            | MCB |            |            |
|----------------------|----------|------------|------------|-----|------------|------------|
|                      | Diagnosed (%) | Not diagnosed (%) | $P$ value | Diagnosed (%) | Not diagnosed (%) | $P$ value |
| **Histological diagnosis** | (n = 13) | (n = 7) | 0.33 | (n = 12) | (n = 8) | > 0.99 |
| **Location 1** | Upper | 7 (63.6) | 4 (36.4) | 0.33 | 8 (72.7) | 3 (27.3) | 0.28 |
| | Middle | 6 (75.0) | 2 (25.0) | 0.00 | 4 (50.0) | 4 (50.0) | 0.28 |
| | Lower | 0 (0) | 1 (100) | 0.00 | 0 (0) | 1 (100) | 0.00 |
| **Location 2** | Lesser curvature | 4 (66.7) | 2 (33.3) | 0.81 | 3 (50.0) | 3 (50.0) | 0.27 |
| | Greater curvature | 2 (50.0) | 2 (50.0) | 0.00 | 1 (25.0) | 3 (75.0) | 0.00 |
| | Anterior wall | 4 (80.0) | 1 (20.0) | 0.00 | 4 (80.0) | 1 (20.0) | 0.00 |
| | Posterior wall | 3 (60.0) | 2 (40.0) | 0.00 | 4 (80.0) | 1 (20.0) | 0.00 |
| **Tumor size** | $\leq$ 20 mm | 7 (58.3) | 5 (41.7) | 0.64 | 9 (75.0) | 3 (25.0) | 0.17 |
| | > 20 mm | 6 (75.0) | 2 (25.0) | 0.00 | 3 (37.5) | 5 (62.5) | 0.00 |
| **Growth pattern** | Intraluminal | 9 (56.3) | 7 (43.8) | 0.10 | 12 (75.0) | 4 (25.0) | 0.01 |
| | Exclaluminal | 4 (100) | 0 (0) | 0.00 | 0 (0) | 4 (100) | 0.00 |
| **Median number of samples to the diagnosis (IQR)** | 3.0 (2.5, 3.5) | 3.0 (3.0, 3.0) | 0.93 | 5.0 (3.0, 6.0) | 2.5 (1.0, 5.75) | 0.17 |

$^a$P values were calculated using Fisher’s exact test; $^b$P = 0.67 between EUS-FNAB and MCB in tumor size $\leq$ 20 mm; Fisher’s exact test; $^c$P = 0.31 between EUS-FNAB and MCB in tumor size $> 20$ mm; Fisher’s exact test; $^d$P = 0.46 between EUS-FNAB and MCB in intraluminal growth pattern; Fisher’s exact test; $^e$P = 0.03 between EUS-FNAB and MCB in extraluminal growth pattern. EUS-FNAB: Endoscopic ultrasonography-guided fine-needle aspiration biopsy; IQR: Interquartile range; MCB: Mucosal cutting biopsy.
addition, all four extraluminal-growth tumors could the diagnostic procedures (\( \alpha = 0.05 \) (two-sided).). In those studies, the diagnostic yield of the EUS-FNAB method in the present study was relatively lower compared to previous reports\(^{17}\), One of the reasons might be an effect of the difference in the FNA needle size used for the EUS-FNABs. The larger-bore 19-gauge needle may actually show a higher diagnostic yield compared to the 22-gauge needle used in the present study\(^{24,31}\), but the exact difference in diagnostic yield between 19- and 22-gauge FNA needles remains unclear\(^{24,30}\). We did not adequately assess procedural factors such as the needle gauge and the number of needle passes in the present study. More passes or the use of a larger-bore needle would provide more tissue. However, Sepe et al\(^{23}\) reported that the number of passes did not significantly affect the diagnostic capability of EUS-FNAB. In their study, as standard practice, this decision regarding the number of passes was made at the discretion of the individual endosonographer and was based on a real-time assessment of presumed tissue adequacy, as in our study, and our finding is in agreement with their result\(^{23}\).

No major complications were caused by either the EUS-FNAB or MCB method in the present study, although mild bleeding occurred in two cases during the MCB; both were successfully managed by hemoclips. Perforation did not occur in any of the 20 patients during MCB, but extra care should be taken to prevent perforation in cases with extraluminal growth\(^{17}\). A laparoscopic and endoscopic cooperative surgery (LECS) is now being performed for the treatment of gastrointestinal SMTs\(^{32,33}\). However, the MCB method is unlikely to preclude LECS for the treatment of SMTs.

The present study had some potential limitations. First, the sample size of this study was small and drawn from a single institution. When the diagnostic yield is assumed to be approximately 70% for the EUS-FNAB without cytology method and approximately 90% for the MCB method, 62 patients with SMT are needed in each group in order to have a power of 80% to detect a difference at the level significance of \( \alpha = 0.05 \) (two-sided). Second, there is the issue of EUS-FNAB- and MCB-related dissemination as a late complication, but this has not been reported to date. It is important to close the mucosal incisions appropriately with endoclips after tissue sampling to prevent post-procedure complications in MCB\(^{17}\). Third, if the diagnostic yield of the combination of EUS-FNAB and MCB is assessed, the histological diagnosis by the two methods should be compared to that of a surgically resected whole specimen as a “golden standard.”

In conclusion, although EUS-FNAB is the widely used gold standard for the histological and cytological diagnoses of gastric SMTs, MCB may be chosen as an alternative diagnostic modality in tumors showing the
intraluminal growth pattern. A randomized controlled trial to compare the capability of MCB with that of EUS-FNAB is needed.

**COMMENTS**

**Background**

As gastric submucosal tumors (SMTs) comprise both benign and malignant lesions, histological diagnosis is needed. Endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) is a useful method for the histological evaluation of SMTs. However, EUS-FNAB systems are very expensive and require experienced pathologists and cytology technicians, and thus this procedure may be unavailable in hospitals not specializing in gastroenterology.

**Research frontiers**

Although the diagnostic yields of EUS-FNAB and mucosal cutting biopsy (MCB) have been reported, there are no studies comparing the diagnostic capabilities of EUS-FNAB and MCB based on endoscopic submucosal resection in the same patients. The authors prospectively compared the diagnostic yield, feasibility, and safety of these two methods.

**Innovations and breakthroughs**

In this prospective study, no significant difference in histological diagnosis was found between EUS-FNAB and MCB regardless of tumor location and tumor size. However, diagnostic specimens were significantly more frequently obtained in the lesions with intraluminal growth compared to those with extraluminal growth by the MCB method. All SMTs with extraluminal growth were diagnosed only by EUS-FNAB, not by MCB. No complications were produced by either method.

**Applications**

MCB may be chosen as an alternative diagnostic modality in tumors showing an intraluminal growth pattern regardless of tumor size, whereas EUS-FNAB should be performed for SMTs with extraluminal growth.

**Terminology**

EUS-FNAB. This method is a needle biopsy procedure considered to be a reliable and accurate method for the evaluation of SMTs in the gastrointestinal tract; gastrointestinal stromal tumor (GIST): GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract.

**Peer-review**

The authors present an interesting result regarding the efficacy of MCB in the histological diagnosis of SMTs. This procedure will be accepted widely even in hospitals not specializing in gastroenterology.

**REFERENCES**

1. Rösch T, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, Ulm K. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. Scand J Gastroenterol 2002; 37: 856-862 [PMID: 12190103 DOI: 10.1080/0300289768521]

2. Crosby JA, Cattan CN, Davis A, Couture J, O’Sullivan B, Kandel R, Swallow CJ. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Ann Surg Oncol 2011; 8: 50-59 [PMID: 2126225 DOI: 10.1007/s10434-001-0050-4]

3. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-58 [PMID: 10636102 DOI: 10.1097/00000458-200001000-00008]

4. Nishida T, Hirosa S. Biological and clinical review of stromal tumors in the gastrointestinal tract. Histol Histopathol 2000; 15: 1293-1301 [PMID: 11005253]

5. Miettinen M, Lasota J. Gastrointestinal stromal tumors—definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001; 438: 1-12 [PMID: 11204280 DOI: 10.1007/s004280000338]

6. Miettinen M, Soinin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005; 29: 52-68 [PMID: 15613856 DOI: 10.1097/01.pas.0000146010.92933.de]

7. Japan Society of Clinical Oncology, Japanese Gastric Cancer Association, Japanese Study Group on GIST. GIST Therapeutic Guidelines. Tokyo: Kankara Co., Ltd, 2008

8. Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, Hayakawa T. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc 2002; 55: 37-43 [PMID: 11756912 DOI: 10.1067/mge.2002.120323]

9. Matsui M, Goto H, Niwa Y, Arisawa T, Hirooka Y, Hayakawa T. Preliminary results of fine needle aspiration biopsy histology in upper gastrointestinal submucosal tumors. Endoscopy 1998; 30: 755-755 [PMID: 9937253 DOI: 10.1055/s-2007-1001416]

10. Philipper M, Hoberbach S, Gabbit HE, Heikaus S, Böcking A, Pomjanski N, Neuhaus H, Frielin T, Schumacher B. Prospective comparison of endoscopic ultrason-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. Endoscopy 2010; 42: 300-305 [PMID: 20306384 DOI: 10.1055/s-0029-1244006]

11. Meeky MA, Yamako K, Sawaki A, Mizuno N, Hara K, Nafeh MA, Osman AM, Koshikai T, Yatabe Y, Bhatia V. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. Gastrointest Endosc 2010; 71: 913-919 [PMID: 20226456 DOI: 10.1016/j.gie.2009.11.044]

12. Wiersema MJ, Vilhm P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and comparison assessment. Gastroenterology 1997; 112: 1087-1095 [PMID: 9097990 DOI: 10.1055/s-2001-8085370](710164-1]

13. Wiech T, Walch A, Werner M. Histopathological classification of nonneoplastic and neoplastic gastrointestinal submucosal lesions. Endoscopy 2005; 37: 630-634 [PMID: 16010607 DOI: 10.1055/s-2005-870127]

14. Okuhwa M, Hosokawa K, Boku N, Ohta A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001; 33: 221-226 [PMID: 11293753 DOI: 10.1055/s-2001-12805]

15. Lee HL, Kwon OW, Lee KN, Jun DW, Eun KS, Lee KY, Jeon YC, Han DS, Yoon BC, Choi HS, Hahn JS, Park SS. Endoscopic histologic diagnosis of gastric GI submucosal tumors via the endoscopic submucosal dissection technique. Gastrointest Endosc 2011; 74: 693-695 [PMID: 21762901 DOI: 10.1016/j.gie.2011.04.037]

16. Kataoka M, Kawai T, Yagi K, Sugimoto H, Yamamoto K, Hayama Y, Nonaka M, Aoki T, Fukuzawa M, Fukuzawa M, Itoi T, Moriyasu F. Mucosal cutting biopsy technique for reliable tissue diagnosis of upper GI subepithelial tumors. Dig Endosc 2013; 25: 274-280 [PMID: 23366082 DOI: 10.1111/j.1443-1661.2012.01384]

17. Ibara H, Matsuhashuku H, Honda K, Hata Y, Sumida Y, Akiho K, Misawa T, Toyoshima S, Chijiwa Y, Nakamura K, Takayangi R. Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors. World J Gastrointest Endosc 2013; 5: 191-196 [PMID: 23596545 DOI: 10.4253/wjge.v5.i4.191]

18. Kobara H, Mori H, Fujiwara S, Nishiyama N, Kobayashi M, Kamata H, Masaki T. Bloc biopsy by using submucosal endoscopy with a mucosal flap method for gastric subepithelial tumor tissue sampling (with video). Gastrointest Endosc 2013; 77: 141-145 [PMID: 23021164 DOI: 10.1016/j.gie.2012.08.008]

19. Lee CK, Chung IK, Lee SH, Lee TH, Park SH, Kim HS, Kim SJ, Cho HD. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). Gastrointest Endosc 2010; 71: 188-194 [PMID: 19879567]
diagnostic accuracy, complication assessment, and impact on management. *Endoscopy* 2005; 37: 984-989 [PMID: 16189771 DOI: 10.1055/s-2005-870272]

27 **Erickson RA**, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastroint Endosc* 2000; 51: 184-190 [PMID: 10650262 DOI: 10.1016/S0016-5107(00)70416-0]

28 **Komanduri S**, Keefer L, Jakate S. Diagnostic yield of a novel jumbo biopsy “unroofing” technique for tissue acquisition of gastric submucosal masses. *Endoscopy* 2011; 43: 849-855 [PMID: 21833902 DOI: 10.1055/s-0030-1256650]

29 **Buscaglia JM**, Nagula S, Jayaraman V, Robbins DH, Vadada D, Gross SA, DiMaio CJ, Pais S, Patel K, Sejpal DV, Kim MK. Diagnostic yield and safety of jumbo biopsy forceps in patients with subepithelial lesions of the upper and lower GI tract. *Gastroint Endosc* 2012; 75: 1147-1152 [PMID: 22425270 DOI: 10.1016/j.gie.2012.01.032]

30 **Eckardt AJ**, Adler A, Gomes EM, Jenssen C, Siebert C, Gottschalk U, Koch M, Röcken C, Rösch T. Endosonographic large-bore biopsy of gastric subepithelial tumors: a prospective multicenter study. *Eur J Gastroenterol Hepatol* 2012; 24: 1135-1144 [PMID: 22797706 DOI: 10.1097/MEG.0b013e328356eae2]

31 **Larghi A**, Verna EC, Ricci R, Seerden TC, Galasso D, Carnuccio A, Uchida N, Rindi G, Costamagna G. EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. *Gastroint Endosc* 2011; 74: 504-510 [PMID: 21872709 DOI: 10.1016/j.gie.2011.05.014]

32 **Hiki N**, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Miki A, Ohyama S, Seto Y. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008; 22: 1729-1735 [PMID: 18074180 DOI: 10.1007/s00464-007-9696-8]

33 **Kang WM**, Yu JC, Ma ZQ, Zhao ZR, Meng QB, Ye X. Laparoscopic-endoscopic cooperative surgery for gastric submucosal tumors. *World J Gastroenterol* 2013; 19: 5720-5726 [PMID: 24039367 DOI: 10.3748/wjg.v19.i34.5720]
