




Endoscopic ultrasound classification for prediction of endoscopic submucosal dissection resectability: PREDICT classification ▶

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ABSTRACT

Background and study aims The safety of endoscopic submucosal dissection (ESD) has been reported, and the risk of lymph node metastasis is low for colorectal cancer if depth of invasion is the only non-curative factor on histological evaluation. ESD is increasingly performed even if submucosal (SM) invasion is suspected. However, reports about endoscopic findings for the criteria to predict ESD resectability remain limited. Endoscopic ultrasound (EUS) can directly visualize the tomographic image of the gastrointestinal wall and may help predict ESD resectability. Therefore, we investigated the possibility of predicting ESD resectability using EUS.

Patients and methods We compared the association between EUS findings and pathological results for gastric or colorectal lesions with suspected SM invasion using white light endoscopy between June 2020 and January 2023. EUS findings were grouped based on the status of the underlying the tumor, as follows: Type I, submucosal layer was observed with reproducibility; Type II, submucosal layer not fully visible; and Type III, submucosal layer disrupted and muscularis propria (MP) layer thickened.

Results Forty-one gastric cancer and 22 colorectal cancer cases were analyzed. The proportions of pathological VM0 (no tumor exposed on any vertical margin) for ESD-resected specimens were 89% and 33% for Type I and II, respectively, ($P \leq 0.01$). The proportions of cancer involving MP or deeper were significantly higher for Type II/III than for Type I (41% vs 0%, $P \leq 0.01$).

Conclusions EUS may have an important role in predicting ESD resectability of gastric and colorectal cancers suspected of having SM invasion.

Introduction

Colorectal and gastric cancers are gastrointestinal cancers with high incidence and poor prognosis. Colorectal cancer has the third highest incidence and second highest mortality rate worldwide, whereas gastric cancer has the fifth highest incidence and fourth highest mortality rate [1]. Cancer invasion depth is strongly correlated with lymph node metastasis and patient prognosis [2, 3, 4, 5, 6]; therefore, preoperative prediction of invasion depth (T staging) is essential for deciding on an appropriate treatment strategy. Surgery with lymph node dissection is the standard treatment for clinically diagnosed submucosal (SM) cancer.

In recent years, a high en bloc resection rate and safety of endoscopic submucosal dissection (ESD) have been reported for superficial gastrointestinal cancer [7, 8], and studies have shown that risk of lymph node metastasis in colorectal cancer is low only if the depth of invasion is a noncurative factor in histological evaluation [9]. ESD is the most accurate tumor staging modality to investigate the invasion depth using pathological examination of the resected specimen because en bloc resection rate is high. The European Society of Gastrointestinal Endoscopy guidelines also state that ESD does not preclude the possibility of subsequent surgery and should be considered the most definitive tumor staging modality [10]. In addition, endoscopic diagnostic accuracy of cancer invasion depth is reportedly 63% to 93% and 70% to 80% for gastric [11, 12, 13, 14] and colorectal cancers, respectively [15, 16]. Considering the insufficient diagnostic performance, using ESD to confirm cancer invasion depth by pathological evaluation would be a reasonable strategy for gastrointestinal cancers with suspected SM invasion. Therefore, applications of ESD are increasing in clinical practice even for lesions with suspected SM invasion.

Although ESD is increasingly being performed for SM-invasive cancer, whether ESD can be safely applied with vertical margin (VM)0 has not been adequately investigated. Recent progressive development of minimally invasive endoscopic techniques including ESD warrants development of a set of new diagnostic criteria to predict ESD resectability. Risk of associated adverse events (AEs), including perforation or incision into the cancerous lesion, increases if the tumor has invaded the muscularis propria (MP) or deeper (\geq MP) layers. SM-invasive cancer can be considered as a relative indication and cancer involving MP is currently considered a contraindication for ESD. Therefore, predicting whether ESD can be safely performed with histologically negative VM before treatment is important.

Endoscopic ultrasound (EUS) directly visualizes tomographic images of the gastrointestinal tract wall. EUS generally depicts normal gastric and colorectal walls as a five-layered structure. The gastrointestinal mucosa is visualized as a combination of the first hyperechoic and second hypoechoic layers, whereas submucosa corresponds to the third hyperechoic layer. The MP and serosa, including the subserosa, are visualized as the fourth hypoechoic layer and fifth hyperechoic layer, respectively [17]. Thickening of the MP layer observed on EUS is suggestive of MP-

invasive cancer, even if cancer involving MP is not suspected on white light endoscopy (WLE) for duodenal cancer [18].

Therefore, we aimed to investigate whether EUS can be used as a modality to select lesions for which ESD can be safely performed with VM0 or to exclude MP-invasive cancer, which is a contraindication to ESD. Reports about the applicability of EUS to predict resectability of ESD remain limited. Therefore, we conducted this study to investigate the possibility of predicting ESD resectability using EUS compared with histological results.

Patients and methods

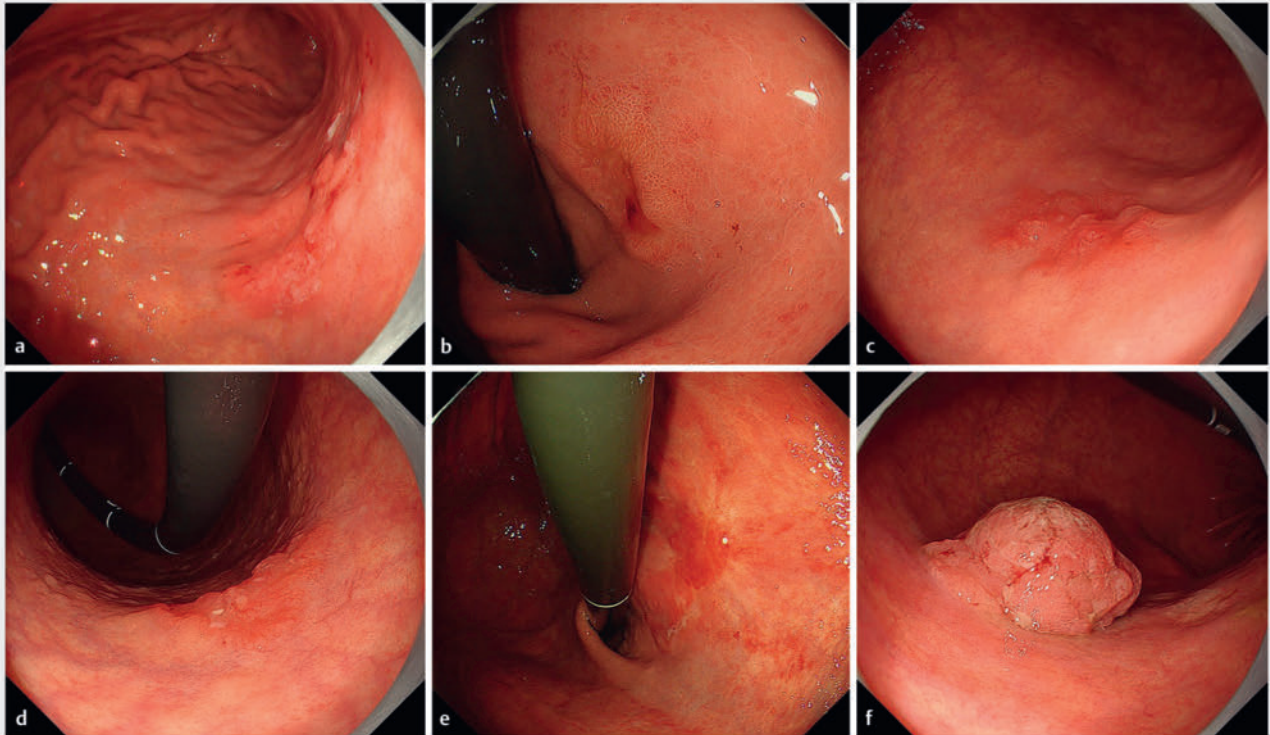
Study participants

This retrospective observational study was performed at an endoscopy unit in a Japanese referral university hospital using a prospectively maintained database. Patients with gastric or colorectal cancers with suspected SM invasion based on WLE findings who underwent EUS prior to receiving therapy between June 2020 and January 2023 were included in this study. Lesions with endoscopic findings of an ulcer scar (mucosal folds or rugae converging at one point), an active ulcer, history of surgery, or poor EUS images were excluded. This study was conducted in accordance with the 2008 revision of the Declaration of Helsinki. The study protocol was approved by the institutional review board of the host hospital (20180163, 20190139).

Diagnostic endoscopy

WLE and magnifying endoscopy, as well as chromoendoscopy with indigo carmine staining, were performed on patients. Diagnostic endoscopy was performed using a magnifying endoscope (GIF-H260Z, 290Zor 1200EZ, PCF-H290Z; Olympus Medical Systems Co., Tokyo, Japan or EG-L600ZW7, EC-L600ZP7; FUJIFILM, Tokyo, Japan). Patients were sedated with midazolam, flunitrazepam, or pethidine, and their cardiorespiratory function was monitored during the procedures. Scopolamine butylbromide or glucagon was administered intravenously to reduce gastrointestinal movement, as appropriate. The location, macroscopic type (elevated, flat, depressed, or mixed type), and lesion size were evaluated. Magnifying or chromoendoscopy with indigo carmine staining was performed to investigate the lesion range, as appropriate. For colorectal lesions, magnifying endoscopic observation was followed by Japan NBI Expert Team (JNET) classification to investigate invasion depth [19]. Pit pattern diagnosis was not performed for colorectal lesions because of the potential cancer risk associated with crystal violet dye.

After diagnosis using WLE, magnifying endoscopy, and chromoendoscopy, EUS was performed for lesions with suspected SM invasion. EUS was performed by endoscopists who were trained in more than 20 cases. EUS was predominantly performed using 20-, 15- or 12-MHz mini-probes (UM-DP20–25R, UM-DP12–25R, OLYMPUS, Tokyo, Japan or P2226–20, P2726–15, FUJIFILM, Tokyo, Japan) or Radial EUS (GF-UE260-AL5, GF-UE290, OLYMPUS, Tokyo, Japan), and scanning was performed using the water- or gel-filling method. Patients were followed up after the completion of endoscopic examinations and were assessed for AEs. Cancer invasion depth was comprehensively diagnosed with WLE, magnifying endoscopy, and EUS.



► **Fig. 1** Representative images of findings characteristic of submucosal invasion in stomach lesions. **a** Irregular surface. **b** Submucosal tumor (SMT)-like elevation. **c** Nodule in the depressed area. **d** Nonextension sign. **e** Substantial redness. **f** Large nodules.

Diagnosis based on WLE findings

The following findings were recognized as signs of SM invasion of gastric lesions based on previous studies [11, 12]: irregular surface, submucosal tumor (SMT)-like elevation, a nodule in the depressed area, nonextension sign, deep depression, substantial redness, large nodule, thickened folds, and fusion of convergent fold (► **Fig. 1**). The following findings were recognized as signs of SM invasion for colorectal lesions based on previous studies [20, 21, 22]: deep depression, demarcated depressed area, protuberance within the depression, expanding appearance, fold convergence, erosion, or white plaque (► **Fig. 2**).

Diagnosis based on EUS findings

EUS findings were classified into three subcategories according to the status of tissue below the tumor echogenic area: type I, the submucosal layer was observed with reproducibility; type II, the submucosal layer was not fully visible; and type III, the submucosal layer was disrupted and the MP layer was thickened (► **Fig. 3**, ► **Video 1**). We coined the term “PREDICT: Predicting Resectability of ESD by EUS Diagnosis of Invasion of Cancer by Tomographic image” for this classification. Resectability was defined as endoscopic total removal of the lesion with a negative VM. The diagnoses were retrospectively performed using a prospectively maintained database. All the lesions with suspected SM invasion on WLE observation during the study period generally underwent EUS. EUS was not performed for some le-

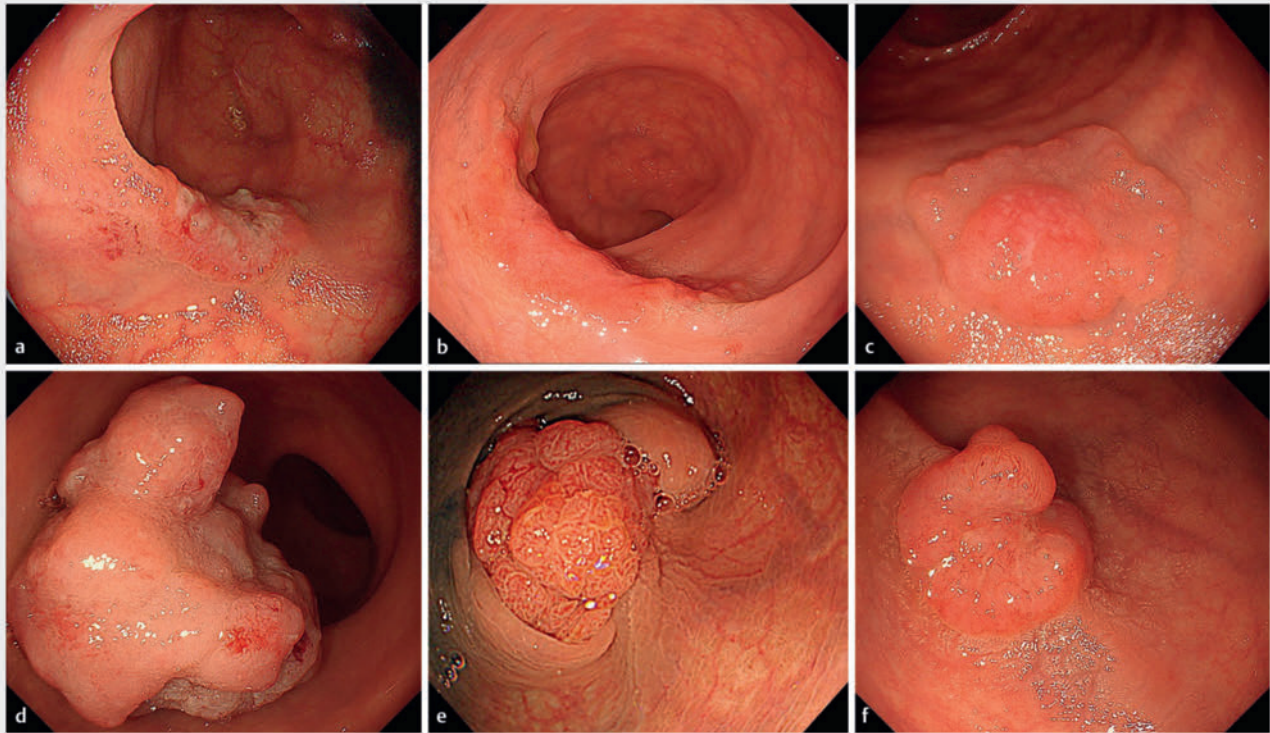
sions with suspected SM invasion owing to the limited endoscopic instruments available for EUS and the difficulty of performing unscheduled EUS.

Treatment strategy based on EUS findings

Treatment with endoscopic resection or surgery was selected based on results of WLE, pathological assessment, EUS, and computed tomography (CT) as well as the condition and choice of the patient. Type I was treated with ESD, type III with surgery, and type II with either ESD or surgery based on the condition and choice of the patient and clinician judgement.

Pathological evaluation

Resected specimens were extended on the mounting board using pins and fixed in 10% formalin for 24 hours. Sections were cut at 2-mm intervals for endoscopically resected tissues and 5-mm intervals for postsurgical specimens and assessed by experienced pathologists. Histopathological type, size, invasion depth, lymphatic and vascular involvement, and cancer involvement in the horizontal and VMs were further assessed. R0 resection was defined as en bloc resection with negative horizontal and vertical margins. The VM was also investigated: VM0 was defined as no tumor exposed on any VM, VM1 as tumor present on any VM, and vertical margin unclear (VMX) as inability to assess existence of a residual tumor on VM. Cancer invasion depth was classified as follows: M, mucosal cancer; SM, cancer in the SM layer; MP, cancer invades MP; SS, cancer in-



► **Fig. 2** Representative images of findings characteristic of submucosal invasion in colorectal lesions. **a** Deep depression. **b** Demarcated depressed area. **c** Protuberance within the depression. **d** Expanding appearance. **e** Fold convergency. **f** Erosion or white plaque.

vades subserosa; and SE, cancer perforates serosa or invades adjacent structures. Pathological curative resections and additional surgery indications for gastric and colorectal cancers were judged according to the Japanese gastric or colorectal ESD/EMR guidelines [9, 23].

Measured outcomes

Pathological invasion depth in endoscopically and surgically resected specimens was used as the reference standard. EUS findings were compared with histopathological invasion depth and VM status in ESD as a gold standard. We collected the following data for each patient: 1) patient information, including age and sex; 2) lesion information, including location, maximum size, and macroscopic type; 3) endoscopic diagnosis of cancer invasion depth; 4) therapy (ESD or surgery); 5) pathological results; 6) pathological curative or noncurative resection; 7) VM status in ESD lesions; 8) additional therapy and clinical course for noncurative resection cases; and 9) AEs. For ESD resectability, we investigated only ESD cases and excluded lesions from patients who underwent surgery to assess VM status. To assess usefulness and reproducibility of the diagnosis among multiple endoscopists, interobserver agreements of each EUS classification were assessed for all lesions in this study. The agreements targeted three endoscopists: A (N. M.), B (M. K.), and C (T. M.). A and B are endoscopists who are experts with EUS, whereas C is a nonexpert endoscopist who recently started learning EUS. Interobserver agreement was assessed using the extracted EUS

images with one to five JPEG-format images per lesion, which were evaluated by all three endoscopists.

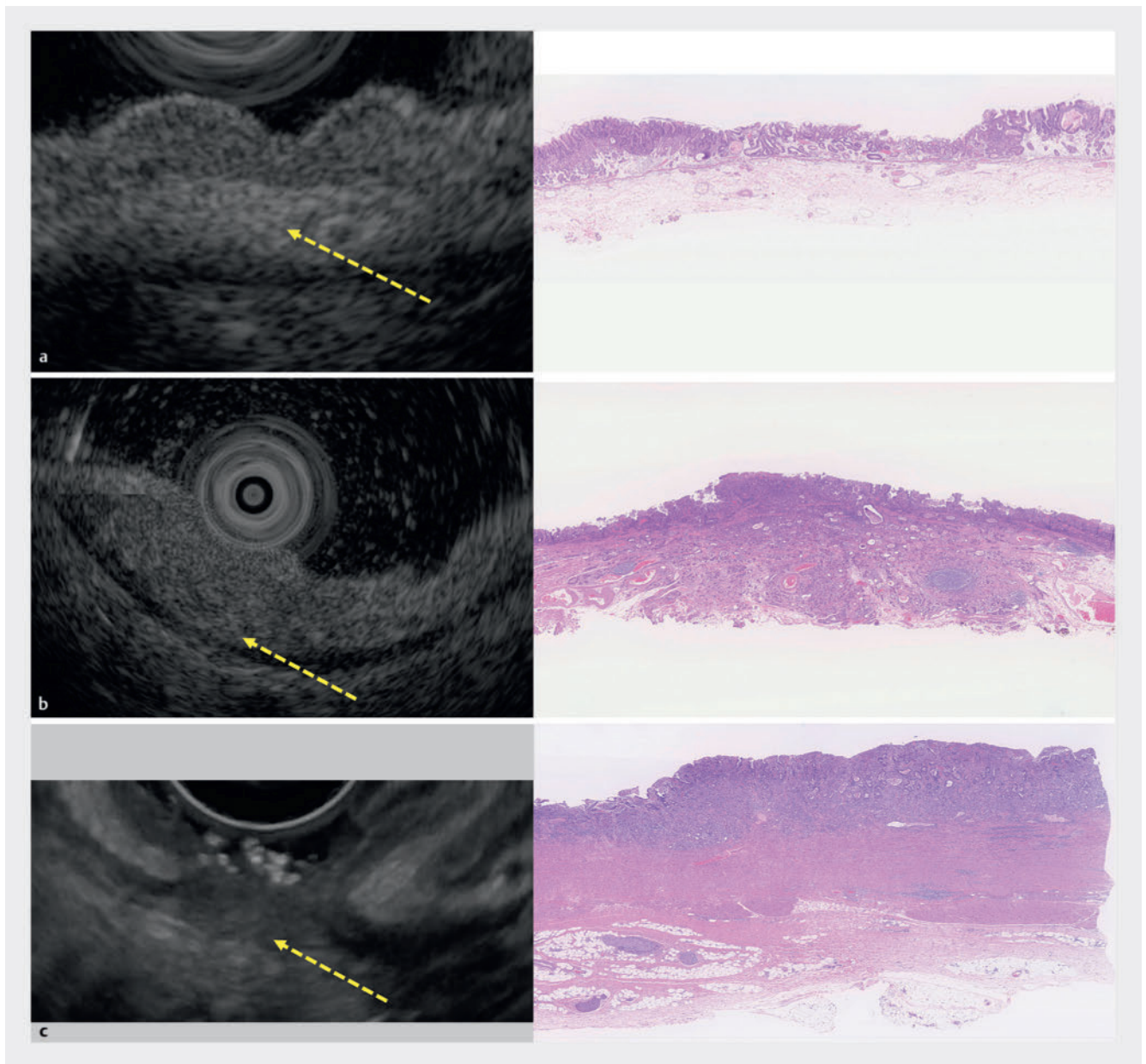
Statistical analysis

All continuous and categorical variables are reported as median (range) and frequency (percentage), respectively. Fisher's exact and Mann–Whitney U test was used to compare clinical variables. $P < 0.05$ was considered statistically significant. Cohen's κ coefficient was calculated to assess interobserver agreement among the three endoscopists. Agreement was regarded as excellent for $\kappa \geq 0.8$, good for $0.6 \leq \kappa < 0.8$, moderate for $0.4 \leq \kappa < 0.6$, and fair for $\kappa < 0.4$. All analyses were performed on a personal computer using JMP (version 14.0; SAS Institute Inc., Cary, North Carolina, United States).

Results

Baseline characteristics

Overall, 41 gastric and 22 colorectal lesions were identified from the database during the study period. Baseline characteristics of the evaluated patients and lesions are presented in ► **Table 1**. Median age of the patients was 74 years. The most common macroscopic type was depressed (41%), and the median endoscopic lesion diameter was 25 mm. ESD and surgery were performed on 24 (38%) and 17 (27%) gastric lesions and 10 (16%) and 12 (19%) colorectal lesions, respectively. EUS with miniature probe was performed on 50 lesions (79%) and



► **Fig. 3** Endoscopic ultrasound findings of PREDICT types. **a** PREDICT type I: The submucosal layer is observed below the tumor echoic area, with reproducibility (directional marker). **b** PREDICT type II: The submucosal layer is not fully visible below the tumor echoic area (directional marker). **c** PREDICT type III: The submucosal layer is destroyed, and the muscularis propria layer is thickened below the tumor echoic area (directional marker). PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image.

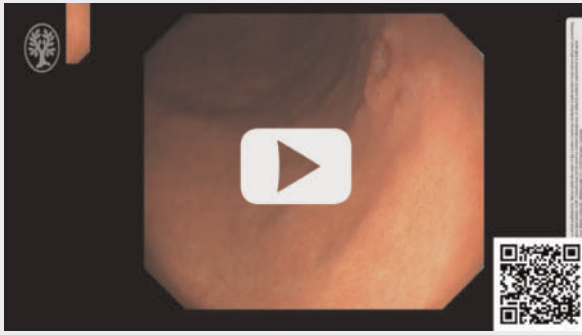
EUS with miniature probe followed by radial EUS in 13 (21%). For proximal colorectal lesions, EUS with miniature probe through endoscopic channels was performed. Pathological invasion depth was 30% in M, 52% in SM, and 18% in \geq MP lesions. Histopathological types included differentiated, mixed, and undifferentiated in 29 (46%), 26 (41%), and 7 (11%) lesions, respectively.

Details of treatment after endoscopic diagnosis

Overall, 36 (57%), 21 (33%), and 6 lesions (10%) were classified as PREDICT type I, II, and III, respectively, based on EUS findings. We also assessed interobserver agreements of EUS classification. The κ coefficients indicated good agreement in ► **Table 2**.

Details of ESD lesions by organ including lymphovascular invasion, invasion depth, and budding grade for colorectal lesions are presented in **Supplementary Table 1**. Neither intra-procedure nor delayed perforations were observed. In two patients

VIDEO



► **Video 1** Typical images of PREDICT types I, II, and III. **a** Type I: White light endoscopy shows submucosal tumor (SMT)-like elevation. EUS with miniature probe revealed that the submucosal layer is observed below the tumor echoic area, with reproducibility. Histological examination after ESD showed moderately differentiated adenocarcinoma, pT1a, pVM0. **b** Type II: White light endoscopy shows irregular surface. EUS with miniature probe reveals that the submucosal layer is not fully visible below the tumor echoic area. Biopsy shows moderately differentiated adenocarcinoma. Histological examination after ESD shows poorly differentiated adenocarcinoma, \geq pT1b, pVM1. **c** Type III: White light endoscopy shows substantial redness. EUS with miniature probe and radial echoendoscope show that the submucosal layer is destroyed and the muscularis propria layer is thickened below the tumor echoic area. Histological examination after surgical resection shows differentiated, predominantly mixed-type adenocarcinoma, pT2. EUS, endoscopic ultrasound; ESD, endoscopic submucosal dissection; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image; pVM0, pathological vertical margin negative; pVM1, pathological vertical margin positive.

► **Table 1** Baseline characteristics of patients and lesions.

Total number of patients/lesions	62/63
Male, n (%)	41 (66)
Age, years, median (range)	74 (33–89)
Organ, n (%)	
▪ Stomach/colon/rectum	41 (65)/7 (11)/15 (24)
Helicobacter pylori status for gastric cancer, n (%)	
▪ Current infection	4 (10)
▪ Past infection	14 (34)
▪ Noninfection	4 (10)
▪ Unclear	19 (46)

► **Table 1** (Continuation)

Location, n (%)	
Stomach	
▪ Upper third	22 (35)
▪ Middle third	14 (22)
▪ Lower third	5 (8)
Colon and rectum	
▪ Proximal colon (cecum-transverse colon)	3 (5)
▪ Distal colon (descending-sigmoid colon)	4 (6)
▪ Rectum	15 (24)
Macroscopic type, n (%)	
▪ Depressed	26 (41)
▪ Protruded	17 (27)
▪ Mixed (others)	19 (30)
▪ Type II	1 (2)
Endoscopic tumor size (mm), median (range)	25 (10–70)
EUS modality	
▪ Miniature probe	50 (79)
▪ Miniature probe + radial scanning	13 (21)
Initial treatment, n (%)	
Stomach	
▪ ESD/surgery	24 (38)/17 (27)
Colon and rectum	
▪ ESD/surgery	10 (16)/12 (19)
Histological type, n (%)	
▪ Differentiated type	29 (46)
▪ Undifferentiated type	7 (11)
▪ Mixed type	26 (41)
▪ Others	1 (2)
Pathological tumor invasion depth, n (%)	
▪ M/SM	19 (30)/33 (52)
▪ MP	7 (11)
▪ SS	3 (5)
▪ SE	1 (2)

EUS, endoscopic ultrasound; ESD, endoscopic submucosal dissection; M, mucosal cancer; SM, cancer in the submucosal layer; MP, cancer invades muscularis propria; SS, cancer invades subserosa; SE, cancer perforates serosa or invades adjacent structures.

with gastric lesions, delayed bleeding was observed; both were managed with endoscopic hemostasis. In one patient with gastric lesion aspiration, pneumonia occurred, which was treated conservatively with antibiotics.

Pathological VM status related to EUS findings and treatment outcomes in ESD cases

We analyzed the VM status of the 34 ESD specimens to assess the predictive value of EUS for ESD resectability. ESD was performed on 24 gastric and 10 colorectal lesions. The association between EUS findings and pathological VM status in ESD is presented in ► **Table 3**. The proportion of pathological VM0 was 89% (25/28 lesions) for PREDICT type I and 33% (2/6 lesions) for type II. The pathological VM0 resection and presence of the SM layer below the lesion showed a significant association ($P \leq 0.01$), regardless of 46% of pathological SM cancers in type I. The association between EUS findings and pathological VM status in ESD by gastric and colorectal lesions is presented in **Supplementary Table 2** and **Supplementary Table 3**.

Association between EUS findings and final pathological invasion depth

The association between EUS findings and pathological cancer invasion depth is presented in ► **Table 4** and ► **Table 5**. The proportion of lesions with invasion depth within M/SM was 100% in PREDICT type I, 67% in type II, and 33% in type III. Types II and III had a significantly higher proportion of lesions with invasion \geq MP than type I (0% vs. 41%, $P \leq 0.01$).

Cases of nonpathological VM0 among PREDICT type I are presented in ► **Table 6**. One gastric lesion had an undifferentiated histological type. Two gastric lesions were ≥ 30 mm in size. One patient with rectal pathological VMX resection underwent additional surgery. Pathological results revealed no residual cancer. The remaining two patients did not consent to additional surgery because of their age, comorbidities, or personal request. These patients experienced no recurrence (surveillance period range, 552–594 days).

Details of treatment related to EUS findings are presented in ► **Fig. 4**. Overall, 19 patients who underwent ESD (13 in PREDICT type I and 6 in type II) underwent noncurative resection, and 14 underwent additional surgery. One patient had residual cancer, and three had lymph node metastasis. Recurrence was not observed in five patients who did not accept additional surgery because of age, comorbidities, or personal choice (median surveillance period 372 days [range, 182–594 days]). No AEs related to the endoscopic examination were reported.

Discussion

We retrospectively investigated the possibility of predicting ESD resectability using EUS. Despite several reports about the effectiveness of EUS for gastrointestinal cancer, most of them focused solely on diagnosing cancer invasion depth (differentiating M and SM cancers) [24, 25, 26, 27, 28] and few studies have investigated the association between EUS findings and ESD resectability. Kamigaichi et al. investigated the distance from the tumor-invasive front to the muscle layer on EUS for

► **Table 2** κ coefficient of interobserver agreements of PREDICT classification.

	PREDICT classification diagnosis
Endoscopist A and B [95%CI]	0.71 [0.54–0.89]
Endoscopist A and C [95%CI]	0.68 [0.51–0.86]
Endoscopist B and C [95%CI]	0.65 [0.47–0.84]

CI, confidence interval; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image.

► **Table 3** ESD pathological vertical margin status based on EUS type.

		Margin status		P value
		pVM0, n (%)	pVMX or 1, n (%)	
PREDICT type I	ESD n = 28	25 (89)	3 (11)	< 0.01
PREDICT type II	ESD n = 6	2 (33)	4 (67)	

EUS, endoscopic ultrasound; ESD, endoscopic submucosal dissection; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image; pVM0, pathological vertical margin negative; pVMX, pathological vertical margin unclear; pVM1, pathological vertical margin positive.

► **Table 4** EUS-related pathological cancer invasion depth.

		Pathological cancer invasion depth	
		M and SM, n (%)	\geq MP, n (%)
PREDICT type I	n = 36	36 (100)	0 (0)
PREDICT type II	n = 21	14 (67)	7 (33)
PREDICT type III	n = 6	2 (33)	4 (67)

EUS, endoscopic ultrasound; M, mucosal cancer; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image; SM, cancer in the submucosal layer; MP, cancer invading muscularis propria.

► **Table 5** EUS-related pathological cancer invasion depth.

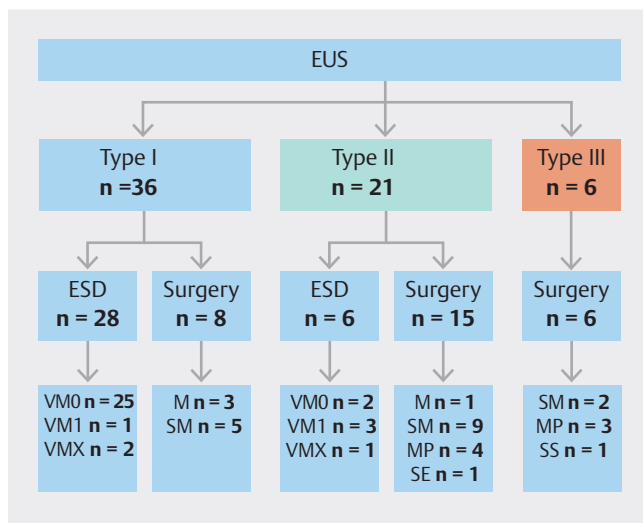
		Pathological cancer-invasion depth		P value
		M and SM, n (%)	\geq MP, n (%)	
PREDICT type I	n = 36	36 (100)	0 (0)	< 0.01
PREDICT type II & III	n = 27	16 (59)	11 (41)	

EUS, endoscopic ultrasound; M, mucosal cancer; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image; SM, cancer in the submucosal layer; MP, cancer invading muscularis propria.

► **Table 6** PREDICT type I cases with pVMX or pVM1 in ESD.

	Organ/location	Macroscopic findings	Tumor size (mm)	Histological type	Age (years)	pVM status	Additional treatment
Case 1	Stomach U	0-I	30	tub1>tub2	83	VM1	No (according to the request from the patient)
Case 2	Stomach M	0-I + IIc	40	tub2>tub1>-por>sig	79	VMX	No (according to the request from the patient)
Case 3	Rectum	0-IIa + Is	15	tub1>tub2	70	VMX	Surgery (no tumor residue)

ESD, endoscopic submucosal dissection; PREDICT, Predicting Resectability of Endoscopic submucosal dissection by endoscopic ultrasonography Diagnosis of Invasion of Cancer by Tomographic image; pVMX, pathological vertical margin unclear; pVM1, pathological vertical margin positive.



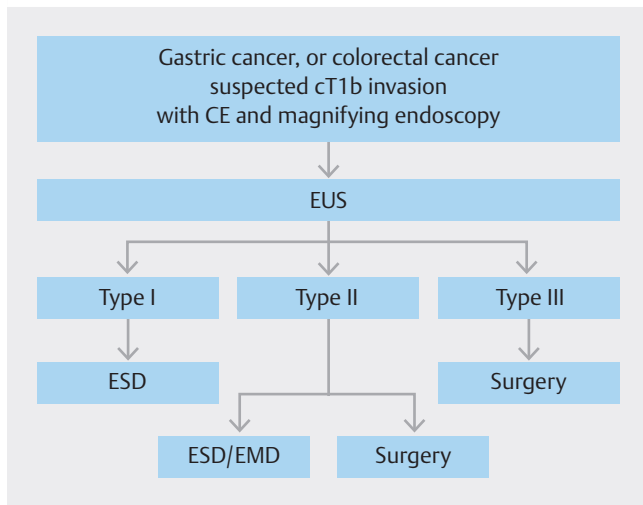
► **Fig. 4** Therapy and clinical course after EUS-based diagnostic endoscopy. EUS, endoscopic ultrasound; M, mucosal cancer; SM, cancer in the submucosal layer; MP, cancer invading the muscularis propria; SS, cancer invading subserosa; SE, cancer perforating the serosa or invading adjacent structures; pVM0, pathological vertical margin negative; pVMX, pathological vertical margin unclear; pVM1, pathological vertical margin positive.

JNET type 2B colorectal lesions and classified them as type I (tumor-free distance ≥ 1 mm) and type II (tumor-free distance < 1 mm). They concluded that the ratio of VM was $< 500 \mu\text{m}$ and VM1 was significantly higher in type II than in type I [29]. The study focused on assessing the resectability of ESD using EUS; however, real-time EUS diagnosis was limited because the distance from the invasive tumor front to the muscle layer was measured using special software by reviewing endoscopic images. The classification proposed in this study was based on real-time EUS diagnosis and can be understood more distinctively than those outlined in previous studies presenting methods to predict the resectability of ESD.

We classified EUS findings into three types by focusing on the status underlying the cancer (PREDICT classification). The proportion of pathological VM0 with ESD was significantly higher in type I than that in type II (89% vs. 33%, $P \leq 0.01$). The proportion of \geq MP cancers was significantly higher in PREDICT type II and III than in PREDICT type I (41% vs. 0%, $P \leq 0.01$).

In this study, we predicted the resectability of ESD including negative VM, not based on the diagnosis of cancer invasion depth, for the following reasons. First, as the European Society of Gastrointestinal Endoscopy guideline indicated [10], ESD is the most precise T staging modality to investigate invasion depth using pathological examination of the resected specimen because the en bloc resection rate is high. Furthermore, preoperative diagnostic accuracy for cancer invasion depth is unsatisfactory (approximately 70%), especially for clinical SM cancers. Recently, an investigation of the risk of lymph node metastasis using ESD-resected specimens was reported using the eCura system [30]. In colorectal cancer, risk of lymph node metastasis is low in cases in which the only noncurative factor is the depth of SM invasion, and diagnostic ESD is increasing [9]. The “resect and investigate additional therapy” strategy may become more common, owing to the high en bloc resection rate and safety of ESD. Therefore, the criteria to predict the resectability of ESD have considerable clinical benefits. Second, lesions with suspected \geq MP invasion currently are a contraindication to ESD because perforation or incision into the cancer can occur. Distinguishing clinical SM and \geq MP cancers is important. Even if clinical \geq MP invasion is not suspected on WLE, 40% of colorectal cancers are advanced disease that does not present with Borrmann-type features exist [22]. The WLE findings to distinguish between M/SM and \geq MP are not yet fully elucidated. In lesions classified as “type III,” 33% of SM invasion was reported. Histologically, these lesions revealed marked desmoplastic reaction and were difficult to resect endoscopically. Furthermore, CT conventionally has been used for TNM staging of gastric and colorectal cancers but has exhibited low diagnostic accuracy in T staging [31]. CT cannot discriminate the depth of tumor invasion between SM and MP, which is indispensable for selecting treatment modalities for gastric and colorectal cancers.

Based on the results of this study, we propose an initial treatment strategy for gastric or colorectal cancer lesions suspected of SM invasion (► **Fig. 5**). Currently, surgery with lymph node dissection is the standard treatment for clinical SM cancers. Furthermore, ESD can be indicated for T staging and palliative care for poor surgical candidates, including older patients or those with comorbidities. The PREDICT classification may help identify the initial treatment strategy. Lesions classified as “type I” are good candidates for T staging with ESD, as indica-



► **Fig. 5** Proposed strategy for preoperative evaluation of suspected T1b invasion cancer. CE, conventional endoscopy; EUS, endoscopic ultrasound; ESD, endoscopic submucosal dissection; EMD, endoscopic muscularis dissection.

ted by an endoscopic pathological VM0 resection rate of 89%. Lesions defined as “type II” are recommended for surgery but are borderline candidates for T staging with ESD, as indicated by an endoscopic pathological VM0 resection rate of 33%. Endoscopic muscularis dissection (EMD) [32] may be required to ensure adequate deep VM, if endoscopic resection is considered. Lesions classified as “type III” are recommended for surgery and contraindicated for ESD, as indicated by a \geq MP invasion rate of 67%.

However, this study has a few limitations. First, it was retrospective and conducted at a single university hospital. We could not perform EUS on all lesions with suspected SM invasion during the study period because the availability of endoscopic instruments for EUS was limited and unscheduled EUS was difficult for some lesions. Therefore, the possibility of selection bias exists. Prospective studies are required to validate the accuracy of this EUS classification in the future. Second, 80% of cases were performed by an experienced endoscopist familiar with gastrointestinal EUS with experience in \geq 2000 cases. However, the PREDICT classification is relatively simple. Therefore, we believe that this classification can be used even if the endoscopist is not an EUS expert. Third, we only included six type III lesions. Therefore, further investigation of advanced lesions is required. Fourth, κ coefficient was good, but not excellent. Although diagnosis based on EUS is evaluated with moving images and evaluation with still images has limitations, interobserver agreement of PREDICT classification was acceptable. PREDICT classification has a certain objectivity and may be generalizable. Fourth, lesions with ulcers were excluded from the present study because they were reported to have low diagnostic accuracy. Whether EUS can predict resectability of ESD for ulcer lesions requires further investigation. Fifth, in histological evaluation, endoscopic resection specimens are evaluated using 2-mm slices, whereas surgical resection specimens are evaluated using 5-mm slices, which may not estimate tumor in-

vasion depth in the same index. Despite these limitations, we believe our proposed PREDICT classification is simple and viable and will help identify the initial treatment strategy for gastric and colorectal cancers with suspected SM invasion.

Conclusions

In this study, we proposed a novel EUS classification (the PREDICT classification) focusing on resectability of ESD. This classification may play an important role in predicting ESD resectability and excluding cases in which ESD is contraindicated for gastric and colorectal cancers with suspected SM invasion.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209–249 doi:10.3322/caac.21660
- [2] Lin JX, Lin JP, Xie JW et al. Is the AJCC TNM staging system still appropriate for gastric cancer patients survival after 5 years? *Eur J Surg Oncol* 2019; 45: 1115–1120 doi:10.1016/j.ejso.2019.01.002
- [3] Ikoma N, Blum M, Chiang YJ et al. Survival rates in T1 and T2 gastric cancer: A Western report. *J Surg Oncol* 2016; 114: 602–606 doi:10.1002/jso.24382
- [4] Sekiguchi M, Oda I, Taniguchi H et al. Risk stratification and predictive risk-scoring model for lymph node metastasis in early gastric cancer. *J Gastroenterol* 2016; 51: 961–970 doi:10.1007/s00535-016-1180-6
- [5] Gotoda T, Yanagisawa A, Sasako M et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; 3: 219–225
- [6] Lee HH, Yoo HM, Song KY et al. Risk of limited lymph node dissection in patients with clinically early gastric cancer: indications of extended lymph node dissection for early gastric cancer. *Ann Surg Oncol* 2013; 20: 3534–3540
- [7] Suzuki H, Takizawa K, Hirasawa T et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: ‘real-world evidence’ in Japan. *Dig Endosc* 2019; 31: 30–39 doi:10.1111/den.13246
- [8] Shigita K, Oka S, Tanaka S et al. Long-term outcomes after endoscopic submucosal dissection for superficial colorectal tumors. *Gastrointest Endosc* 2017; 85: 546–553 doi:10.1016/j.gie.2016.07.044
- [9] Tanaka S, Kashida H, Saito Y et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; 27: 417–434 doi:10.1111/den.12456
- [10] Pimentel-Nunes P, Libânio D, Bastiaansen BAJ et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. *Endoscopy* 2022; 54: 591–622 doi:10.1055/a-1811-7025
- [11] Nagahama T, Yao K, Imamura K et al. Diagnostic performance of conventional endoscopy in the identification of submucosal invasion by

- early gastric cancer: the “non-extension sign” as a simple diagnostic marker. *Gastric Cancer* 2017; 20: 304–313
- [12] Choi J, Kim SG, Im JP et al. Endoscopic prediction of tumor invasion depth in early gastric cancer. *Gastrointest Endosc* 2011; 73: 917–927 doi:10.1016/j.gie.2010.11.053
- [13] Matsumoto Y, Yanai H, Tokiyama H et al. Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer. *J Gastroenterol* 2000; 35: 326–331 doi:10.1007/s005350050356
- [14] Mouri R, Yoshida S, Tanaka S et al. Usefulness of endoscopic ultrasonography in determining the depth of invasion and indication for endoscopic treatment of early gastric cancer. *J Clin Gastroenterol* 2009; 43: 318–322 doi:10.1097/MCG.0b013e3181775966
- [15] Tsuruta O, Kawano H, Tsuji Y et al. [Effectiveness of magnifying endoscopy and endoscopic ultrasonography in diagnosing invasion depth of early colorectal cancer.] (In Japanese). *Stomach Intestine* 2001; 36: 791–799
- [16] Tsuda S, Kikuchi Y, Yorioka M et al. The usefulness of conventional endoscopy, barium enema, endoscopic ultrasonography and magnifying endoscopy for the diagnosis of depth of invasion in colorectal cancer.] (In Japanese). *Stomach Intestine* 2001; 36: 769–782
- [17] Yanai H, Noguchi T, Mizumachi S et al. A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut* 1999; 44: 361–365 doi:10.1136/gut.44.3.361
- [18] Matsuura N, Kato M, Irino T et al. Gastrointestinal: Ten-millimeter advanced duodenal cancer with a gastric phenotype. *J Gastroenterol Hepatol* 2023; 38: 347
- [19] Sano Y, Tanaka S, Kudo SE et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; 28: 526–533 doi:10.1111/den.12644
- [20] Matsuda T, Fujii T, Saito Y et al. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am J Gastroenterol* 2008; 103: 2700–2706 doi:10.1111/j.1572-0241.2008.02190.x
- [21] Ikehara H, Saito Y, Matsuda T et al. Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy. *J Gastroenterol Hepatol* 2010; 25: 905–912 doi:10.1111/j.1440-1746.2010.06275.x
- [22] Koyama Y, Yamada M, Makiguchi ME et al. New scoring system to distinguish deep invasive submucosal and muscularis propria colorectal cancer during colonoscopy: a development and global multicenter external validation study (e-T2 Score). *Gastrointest Endosc* 2022; 96: 321–329.e2
- [23] Ono H, Yao K, Fujishiro M et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). *Dig Endosc* 2021; 33: 4–20 doi:10.1111/den.13883
- [24] Tsujii Y, Hayashi Y, Ishihara R et al. Diagnostic value of endoscopic ultrasonography for the depth of gastric cancer suspected of submucosal invasion: a multicenter prospective study. *Surg Endosc* 2023; 37: 3018–3028 doi:10.1007/s00464-022-09778-7
- [25] Tsujii Y, Kato M, Inoue T et al. Integrated diagnostic strategy for the invasion depth of early gastric cancer by conventional endoscopy and EUS. *Gastrointest Endosc* 2015; 82: 452–459 doi:10.1016/j.gie.2015.01.022
- [26] Kim J, Kim SG, Chung H et al. Clinical efficacy of endoscopic ultrasonography for decision of treatment strategy of gastric cancer. *Surg Endosc* 2018; 32: 3789–3797 doi:10.1007/s00464-018-6104-5
- [27] Choi J, Kim SG, Im JP et al. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. *Endoscopy* 2010; 42: 705–713 doi:10.1055/s-0030-1255617
- [28] Ishihara R, Mizusawa J, Kushima R et al. Assessment of the diagnostic performance of endoscopic ultrasonography after conventional endoscopy for the evaluation of esophageal squamous cell carcinoma invasion depth. *JAMA Netw Open* 2021; 4: e2125317 doi:10.1001/jamanetworkopen.2021.25317
- [29] Kamigaichi Y, Oka S, Tanino F et al. Novel endoscopic ultrasonography classification for assured vertical resection margin ($\geq 500 \mu\text{m}$) in colorectal endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2022; 37: 2289–2296 doi:10.1111/jgh.16008
- [30] Hatta W, Gotoda T, Oyama T et al. A scoring system to stratify curability after endoscopic submucosal dissection for early gastric cancer: “eCura system” *Am. J Gastroenterol* 2017; 112: 874–881 doi:10.1038/ajg.2017.95
- [31] Nie RC, Yuan SQ, Chen XJ et al. Endoscopic ultrasonography compared with multidetector computed tomography for the preoperative staging of gastric cancer: a meta-analysis. *World J Surg Oncol* 2017; 15: 113
- [32] Abe N, Takeuchi H, Ohki A et al. Comparison between endoscopic and laparoscopic removal of gastric submucosal tumor. *Dig Endosc* 2018; 30: 7–16