

Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer

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Abstract: Endoscopic ultrasonography (EUS) is considered to be useful for deciding the treatment course for early gastric cancer. To determine reliable indications suggesting submucosal tumor invasion, we retrospectively analyzed EUS images of the hyperechoic third layer, which corresponds to the submucosa. The subjects enrolled in this study were 75 patients, with 78 gastric cancers (diagnosed as mucosal cancer without ulcerous changes on endoscopy and as histologically differentiated adenocarcinoma on biopsy), who were also examined by EUS. We retrospectively classified EUS features of the third layer (submucosa) into five groups: (1) irregular narrowing, (2) budding sign, (3) multiple echo-free spots, (4) unclear, and (5) no changes. In endoscopically diagnosed gastric mucosal cancer, 16 of the 78 lesions were associated with histologic submucosal invasion. EUS features that were associated with a high incidence of histological submucosal tumor invasion were irregular narrowing (submucosal invasion, 60.0%) and the budding sign (85.7%), and 90.9% of lesions with either of these features had submucosal invasion of tumors when tumorous changes in the third layer exceeded 1 mm in depth. Endosonographic irregular narrowing and a budding sign of more than 1 mm in depth in the third layer are useful for the diagnosis of submucosal invasion in gastric cancers that are diagnosed as mucosal cancers without ulcerous change on endoscopy.

Key words: early gastric cancer, endoscopic ultrasonography

Introduction

In recent years, endoscopic treatment has been widely employed as a radical therapy for early gastric cancers.^{1,2} However, lesions with metastasis to lymph nodes or other organs are not indicated for endoscopic therapy because it is only a local therapy. Therefore, in accordance with previous reports,^{1–4} we believe that the indications for radical endoscopic therapy must be limited to well differentiated adenocarcinoma within the mucosa that is less than 2 cm in diameter and without ulcerous change, which is expected to have no lymph node metastasis. We have usually selected clinical treatment on the basis of whether the lesion is within the indications for endoscopic therapy on endoscopy and forceps biopsy. Further, when we need detailed information about the invasive depth of the tumor in the mucosa or submucosa, there is a probability that endoscopic ultrasonography (EUS) will provide it.^{5–13}

On EUS, the normal gastric wall is visualized as having a five-layer architecture.^{14,15} The mucosa corresponds to a combination of the first hyperechoic and second hypoechoic layers, and the submucosa corresponds to the third hyperechoic layer. The muscularis propria is visualized as the fourth hypoechoic layer, and the serosa, including the subserosa, corresponds to the fifth hyperechoic layer. According to our previous reports, the fine hypoechoic layer (about 0.2 mm in thickness) between the second and third hyperechoic layers is considered to be the muscularis mucosae and to give us much information on the depth of invasion of tumors.¹⁶

Our previous conclusion on EUS was that lesions with no changes in the hyperechoic third layer, which corresponds to the submucosa, should be diagnosed as mucosal cancer (EUS-M), and that lesions with changes, whether large or small, should be diagnosed as cancer with submucosal invasion (EUS-SM) or deeper. However, these criteria tended to result in over-staging.^{17,18}

To determine reliable standards for suggesting submucosal invasion, we reviewed findings on the EUS third layer in detail, and assessed the value of EUS, in combination with endoscopy, as a pre-treatment examination in early gastric cancer.

Patients and methods

Patients

This study included 78 endoscopically staged mucosal cancers without ulcerous changes, in addition to histologically differentiated adenocarcinoma on biopsy, both of which criteria are regarded as indications for endoscopic therapy, in 75 patients (3 patients had two lesions each). Thus, we excluded endoscopically staged submucosal cancers, lesions with ulcerous changes, and poorly differentiated or undifferentiated adenocarcinoma on biopsy, these being cancers which are unlikely to be indicated for endoscopic therapy.

We performed EUS in the above patients between January 1990 and August 1996 at the First Department of Internal Medicine of Yamaguchi University School of Medicine, and we histologically examined specimens that were resected endoscopically or surgically.

The lesions were macroscopically classified as mainly elevated ($n = 45$), and mainly depressed ($n = 33$) (Table 1). The patients were 56 men and 19 women (mean age, 69.6 years; range, 39 to 87 years).

EUS procedure

In this study we used 20-MHz thin endoscopic ultrasound probes with the Sonoprobe System, a linear SP-101 and radial/linear switchable SP-501 (Fujinon, Omiya, Japan).

Table 1. Lesions endoscopically diagnosed as mucosal gastric cancers without ulcerous changes

Macroscopic classification	Lesions (histologically, submucosal cancer)
Type 0 I (protruded)	13 (2)
II (superficial)	
IIa (elevated)	30 (1)
IIa + I	1
IIb + IIa	1
IIa + IIc	9 (3)
IIc (depressed)	23 (10)
IIc + IIa	1

Seventy-eight lesions in 75 patients were examined (includes 3 patients with 2 lesions each). There were 62 mucosal cancers and 16 submucosal cancers in the patients (56 men and 19 women; mean age, 69.6 years; range, 39 to 87 years)

Classification of EUS images of the submucosal layer

We chose the borderline between the second and third layers in the normal gastric wall around the tumor as the baseline.

In this study, a well experienced endosonographer retrospectively classified the features of the third layer (submucosa) on EUS images of tumor lesions into five groups. In the first group, the third layer was irregularly narrowed when the tumor echo reached into the third layer irregularly below the baseline (irregular narrowing). In the second group, an irregularly bordered low echo broke into the third layer within a width of 2 mm below the tumor, indicating budding (budding sign). In the third group, there were multiple echo-free spots below the tumor (multiple echo-free spots). In the fourth group, the architecture of the layer below the tumor was unclear (unclear). The fifth group was that in which no change was found in the third layer below the tumor lesion (no changes) (Fig. 1).

We vertically measured the depth of the changes from the baseline between the second layer and the third layer. When the low echo reflecting the muscularis mucosae was detectable, we regarded its deeper interface as the baseline.

Histology

Specimens were stained with hematoxylin and eosin (H&E), and the depth of invasion was classified as mucosal (m), submucosal (sm), or advanced (the tumor invaded the muscularis propria or deeper).

Statistics

Data were analyzed with the χ^2 test, t -test (two-sided), and Mann-Whitney U -test. A P value of less than 0.05 was considered significant.

Results

The relationship between changes in the EUS third layer and histological submucosal invasion of tumors is shown in Fig. 2.

The rate of submucosal invasion was 60.0% in the lesions with irregular narrowing, and 85.7% in those with the budding sign. The lesions with multiple echo-free spots or that were unclear had no submucosal invasion. The cause of wrong diagnosis in the lesions with multiple echo-free spots was histologically benign glands with cystic dilatation. Highly elevated lesions were often unclear due to high-frequency ultrasound beam attenuation. On the other hand, 7.3% of the lesions with no changes in the third layer (4/55 lesions)

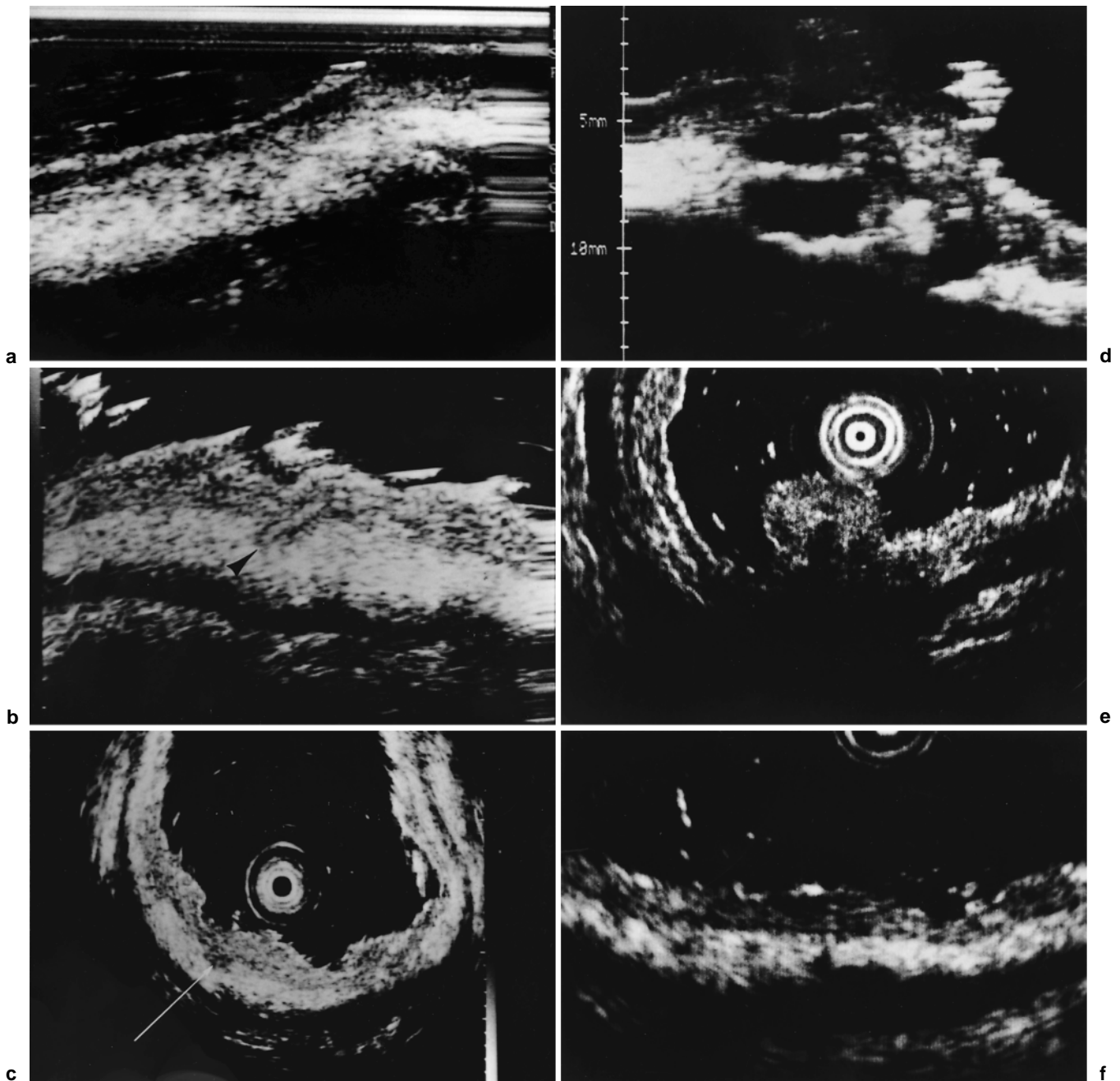


Fig. 1a–f. Classification of endoscopic ultrasonography (EUS) images of the submucosal layer. **a** Irregular narrowing; **b** budding sign (linear scan) (*arrowhead*); **c** budding sign (radial scan) (*arrow*); **d** multiple echo-free spots; **e** unclear; **f** no changes

had submucosal tumor invasion, but 3 of these 4 lesions had only minute invasion within a depth of 200 μm .

The histological results showed a significant relationship between the findings of irregular narrowing or a budding sign in the third layer on EUS and submucosal invasion of the tumor ($P < 0.01$) (Table 2).

The lesions that exhibited irregular narrowing or the budding sign in the third layer on EUS were shown to have a high frequency of submucosal tumor invasion.

Therefore we examined the relationship between the depths of these two changes in the third layer on EUS and histological submucosal tumor invasion (Fig. 3). The depth of the changes in the EUS third layer of mucosal cancers was $0.82 \pm 0.22\text{mm}$, and that of cancers invading into the submucosa was $1.41 \pm 0.59\text{mm}$ (means \pm SD). There was a significant difference ($P < 0.05$) between these depths. The maximum cutoff point for specificity and sensitivity was 0.9 mm. However, for

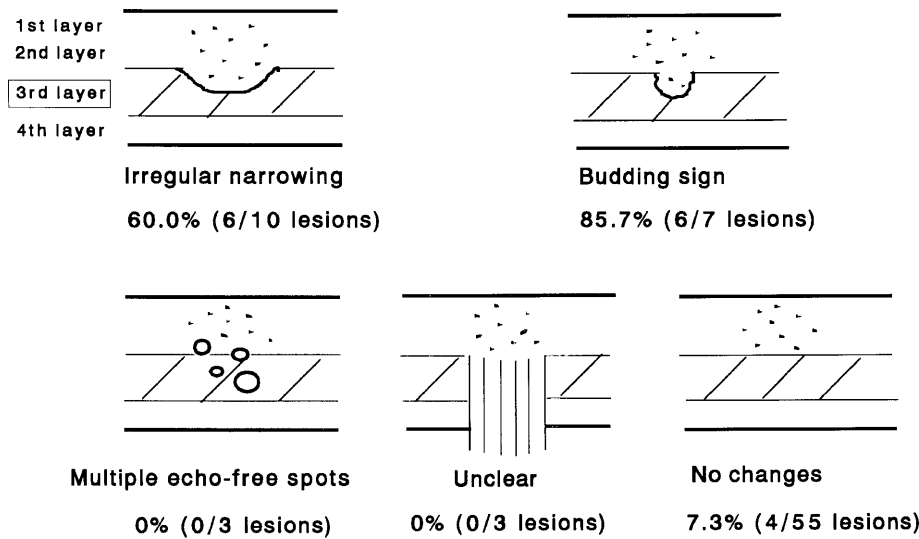


Fig. 2. Relationship between the changes in the endoscopic ultrasonography (EUS) third layer (corresponds to submucosa) and submucosal cancer invasion of early gastric cancer ($n = 78$); (lesions invading submucosa/number of lesions)

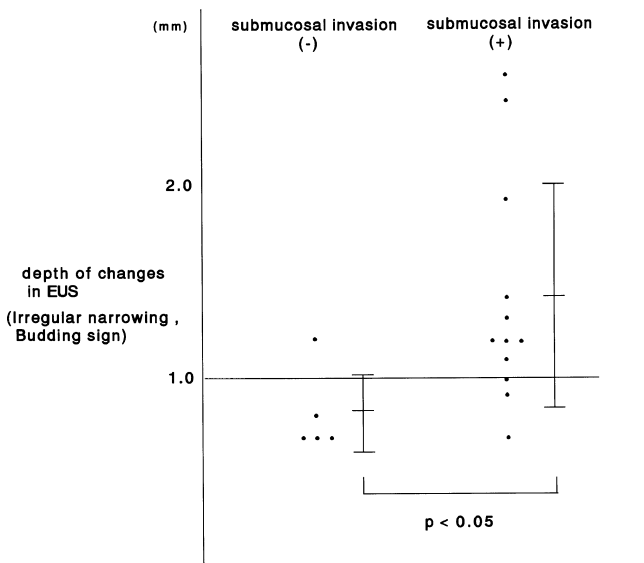


Fig. 3. Relationship between the depth of changes in the EUS third layer (irregular narrowing, budding sign) and submucosal invasion ($n = 17$)

the 20-MHz EUS procedure, the minimum cutoff point was 1 mm, so we chose 1 mm as a practical and reasonable cutoff value. Ten of the 11 lesions (90.9%) with irregular narrowing or a budding sign more than 1 mm in depth had histological submucosal tumor invasion. One should bear in mind, however, that fibrosis due to the biopsy itself, together with a finding of 1.2-mm irregular narrowing may result in a mistaken diagnosis. On the other hand, only 33.3% of lesions (2/6) had submucosal invasion when the changes on these two findings were less than 1 mm in depth.

Discussion

A thin 20-MHz probe has the ability to visualize superficial or small early gastric cancer lesions.¹⁹ It has been reported that there are no significant differences between endoscopy and EUS in terms of accuracy of measurement of the depth of invasion, but EUS tends to result in over-staging, while endoscopy tends to result in under-staging.¹⁷

In this study, the accuracy of endoscopy alone in staging mucosal cancer was 79.5%, and that of our previous diagnosis on EUS was 80.8%. Thus, there was no significant difference. For endoscopy, all the wrong diagnoses were due to under-staging, because the patients had endoscopically diagnosed mucosal cancers. For EUS, over-staging was the predominant staging error.

Currently, when some changes in the layer structure, regardless of degree, are found below tumor lesions on EUS, tumor invasion is diagnosed as submucosal. An unclear or wavy borderline between the second and third layers on EUS may be the cause of misdiagnosis of submucosal invasion. Thus, it is important to analyze the EUS findings of lesions that are diagnosed as submucosal cancers on EUS, and to determine reliable guidelines for submucosal tumor invasion.

The objective of this study was to determine potential indications for endoscopic treatment. The most important EUS findings for the diagnosis of submucosal tumor invasion were irregular narrowing of the third layer on EUS and the budding sign. Benign glands with cystic dilatation were found histologically in lesions with multiple echo-free spots that showed smoothly bordered echo-free areas of all sizes. In these lesions, it was possible to discriminate such areas from the budding sign, which showed a single low echo. As cystic

Table 2. Relationship between change in the third layer on endoscopic ultrasonography (irregular narrowing, budding sign) and submucosal invasion of early gastric cancer

EUS third layer (corresponds to submucosa)	Histology		Total
	Submucosal invasion-positive	Submucosal invasion-negative	
Irregular narrowing and budding sign-positive	12 (70.6%)	5 (29.4%)	17 (100%)
Irregular narrowing and budding sign-negative	4 (6.6%)	57 (93.4%)	61 (100%)
Total	16	62	78

($P < 0.01$)

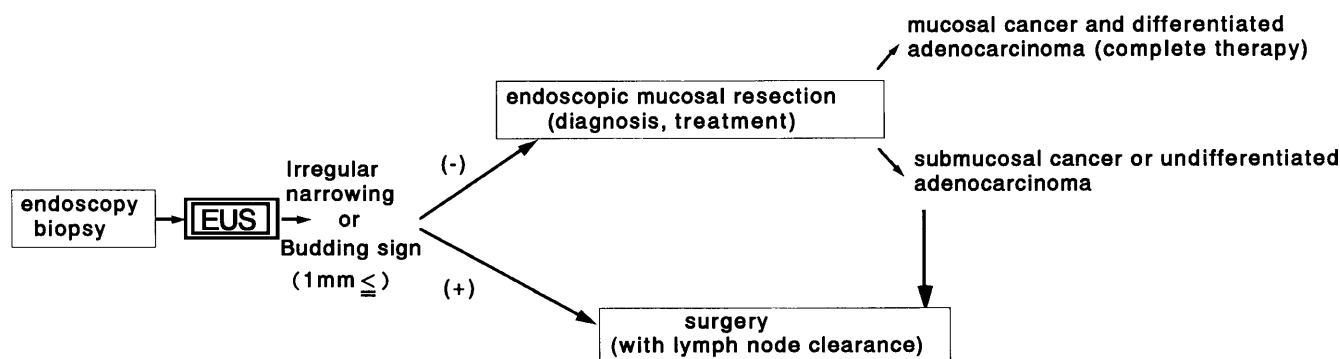


Fig. 4. Possible role of EUS as a pre-treatment examination in early gastric cancer

dilatation of the glands with cancerous cells often presented an irregularly bordered low echo, we classified it as irregular narrowing or the budding sign. Among the lesions with no changes in the third layer on EUS, three had minute invasion of the tumor within a depth of 200 μ m. Such minute invasion is thought to be difficult to diagnose, as EUS resolution is around 0.2mm on 20-MHz EUS instruments at present.

In this study, 10 of the 11 lesions with irregular narrowing and the budding sign, in which changes were more than 1mm in depth, strongly suggested submucosal tumor invasion (90.9%). Ten of the 16 (62.5%) submucosal cancers diagnosed wrongly as mucosal cancer by endoscopy were diagnosed as submucosal cancer on EUS. In addition, this EUS method is objective, because it measures depth. Thus, this objective standard will lead to an increase in the accuracy of diagnosis by decreasing dependence on the subjective opinion of the operator.

There may be some diagnostic discrepancies between Japanese pathologists and Western pathologists in the differentiation of definite carcinoma from high-grade dysplasia. From a practical viewpoint, complete endoscopic resection would be recommended for borderline

mucosal tumors that are difficult to differentiate from high-grade dysplasia. The diagnosis of invasive depth by EUS may be useful in decisions on the treatment for such borderline lesions.^{20,21}

Our conclusions concerning the role of EUS as a pre-treatment examination in early gastric cancer are shown in Fig. 4. Even if the lesions are thought to correspond to the indications for curative endoscopic therapy by endoscopy and biopsy, if there are findings of irregular narrowing or a budding sign of more than 1mm in depth, surgery involving lymph node clearance may be considered.

A further prospective study of these findings of the third layer on EUS in early gastric cancers is thus warranted.

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