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TOPIC HIGHLIGHT

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Endoscopic ultrasound using ultrasound probes for the diagnosis of early esophageal and gastric cancers

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Abstract

Endoscopic ultrasound (EUS) devices were first designed and manufactured more than 30 years ago, and since then investigators have reported EUS is effective for determining both the staging and the depth of invasion of esophageal and gastric cancers. We review the present status, the methods, and the findings of EUS when used to diagnose and stage early esophageal and gastric cancer. EUS using high-frequency ultrasound probes is more accurate than conventional EUS for the evaluation of the depth of invasion of superficial esophageal carcinoma. The rates of accurate evaluation of the depth of invasion by EUS using high-frequency ultrasound probes were 70%-88% for intramucosal cancer, and 83%-94% for submucosal invasive cancer. But the sensitivity of EUS using high-frequency ultrasound probes for the diagnosis of submucosal invasive cancer was relatively low, making it difficult to confirm minute submucosal invasion. The accuracy of EUS using high-frequency ultrasound probes for early gastric tumor classification can be up to 80% compared with 63% for conventional EUS, although the accuracy of EUS using high-frequency ultrasound probes relatively decreases for those patients with depressed-type lesions, undifferentiated cancer, concomitant ulceration, expanded indications, type 0- Ⅰ lesions, and lesions located in the upper-third of the stomach. A 92% overall accuracy rate was achieved when both the endoscopic appearance and the findings from EUS using high-frequency ultrasound probes were considered together for tumor classification. Although EUS using high-frequency ultrasound probes has limitations, it has a high depth of invasion accuracy and is a useful procedure to distinguish lesions in the esophagus and stomach that are indicated for endoscopic resection.

Key words: Endoscopic ultrasound; High-frequency ultrasound probe; Esophageal cancer; Gastric cancer; Depth diagnosis

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INTRODUCTION

Endoscopic ultrasound (EUS) devices were first designed and manufactured in the early 1980s. Since then, EUS has been adapted not only for pancreatic lesions but also for gastrointestinal and perigastrointestinal lesions, such as gastrointestinal cancers, gastrointestinal stromal tumors,

and abdominal and mediastinal lymphadenopathy. Some investigators have reported EUS is effective for the staging of esophageal and gastric cancers[1,2], and EUS is also useful for determining the depth of invasion of early esophageal and gastric cancers. Ever since Gotoda *et al*[3] described the incidence of lymph node metastasis from early gastric cancer, and with the development of endoscopic submucosal dissection (ESD), many early gastric cancer lesions have been resected endoscopically. In addition, ESD has recently been adapted for excision of esophageal lesions. It is important to accurately estimate the depth of the lesion before endoscopic resection of early esophageal and gastric cancers; a vague estimation of lesion depth may allow residual cancer to remain, leading to recurrences and additional resections.

We review the present status of, the methods used for, and the findings of EUS using high-frequency ultrasound probes for diagnosing and staging early esophageal and gastric cancer.

EUS FOR EARLY ESOPHAGEAL CANCERS

Present status

The depth of early esophageal squamous cell cancer invasion is classified according to six categories that range from only penetrating the epithelium to reaching the proper muscle layer: cancer limited to the epithelium is described as m1; cancer limited to the lamina propria is m2; invasion reaching the muscularis mucosa or invading the muscularis mucosa is m3; invasion of the submucosa less than 200 μm in the endoscopically resected specimen or invasion of the first third of submucosa is sm1; invasion of the submucosa by more than 200 μm in the endoscopically resected specimen or invasion of the second third of submucosa is sm2; and that reaching the proper muscle layer is classed as sm3[4] (Figure 1). The rates of lymph node metastasis in m1 and m2 cancers are estimated at less than 5%, while those of m3 and sm1 cancers are 12%-27%, and those of sm2 and sm3 cancers are 36%-46%[5]. This evidence suggests that invasion depth confined to m1 or m2 regions is a good indication for excision using a procedure such as endoscopic mucosal resection (EMR) or ESD. Therefore, an accurate determination of invasion depth will help distinguish indicated lesions from contra-indicated lesions.

Because EUS using high-frequency ultrasound probes is more accurate than conventional EUS in the evaluation of the depth of invasion of early esophageal carcinoma[6], usually EUS using high-frequency ultrasound probes is performed to evaluate tissue penetration. In previous reports, the accuracies of the depth of invasion measurements by ultrasound probes were 70%-88% for intramucosal cancer, and 83%-94% for submucosal invasive cancer[6-8]. Murata *et al*[4] reported the extent of cancer invasion had been correctly determined in 81% of m1 and m2 lesions, in 60% of m3 and sm1 lesions, and in 87% of sm2 and sm3 lesions. But in another report, the sensitivity for submucosal invasive cancer was only 48%[9], and overall accuracy, sensitivity, and specificity to

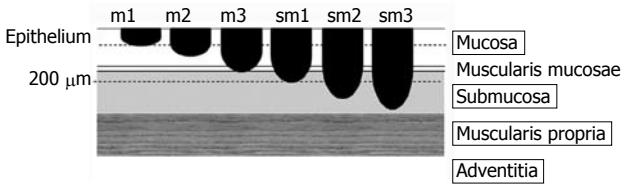

Figure 1 Scheme of the depth of esophageal cancer invasion.

differentiate submucosal invasive cancers from intramucosal cancers were 74%, 62%, and 77%, respectively[10]. Especially, May *et al*[9] reported the diagnostic accuracy was not yet satisfactory with submucosal invasive cancers located at the esophagogastric junction (EGJ) or with infiltration of the first third of the submucosa. In addition, it is difficult to distinguish between cancer invasion and inflammatory cell infiltration[4]. Thus, although EUS can distinguish between definite intramucosal cancers and definite submucosal invasive cancers, it is relatively difficult to confirm minute submucosal invasion even when using high-frequency probes.

Although water introduced normally into the esophagus can provide acoustic coupling for EUS, it is difficult to submerge the target lesion because the water flows off easily. To solve this problem, some investigators developed EUS devices utilizing either a water-filled balloon method[11], a device for continuous irrigation of water[12], or a jelly-filled method[13]. However, the balloon interferes with the diagnosis of m1 and m2 cancer, so the water or the jelly-filled methods may be preferred[4,13,14]. In our institute, we use an endoscope with a water-jet system to provide irrigation.

EUS methods in our institute

Our EUS procedure is performed using a 20 MHz ultrasound probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) with an endoscopic ultrasound system (EU-M2000; Olympus) through a forward-viewing endoscope with a water-jet system (GIF-Q260J; Olympus). Deaerated water is boiled at least one day before the procedure and then allowed to rest to remove any bubbles. This preparation is necessary to achieve accurate data from the EUS procedure (Figure 2A and B).

For premedication, scopolamine butylbromide as an antispasmodic and midazolam as a sedative, and, occasionally, pethidine hydrochloride as an analgesic, are administered to the patients. After the patients have received the premedication, their blood pressure, heart rate, and arterial oxygen saturations are monitored until an hour after the procedure is finished.

With patients lying in a left lateral decubitus position, we insert an endoscope into the esophagus and attempt to visualize a lesion; if one is discovered, mucus and saliva on the lesion are washed away gently (Figure 3A). An ultrasound probe is inserted through an instrument channel and we begin irrigating with deaerated water through a water jet channel operated by an assistant, while we watch the lesion directly. After sufficient deaerated water is present to act as an acoustic coupling medium, ultra-

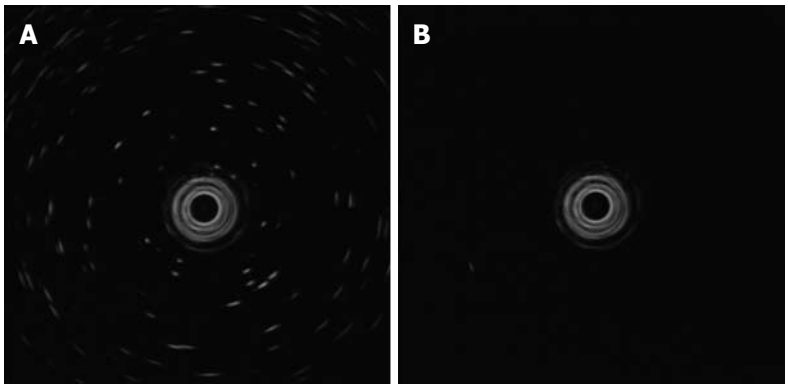

Figure 2 Differences in endoscopic ultrasound features with quality of water used for irrigation. A: Water from a faucet ; B: Deaerated water.

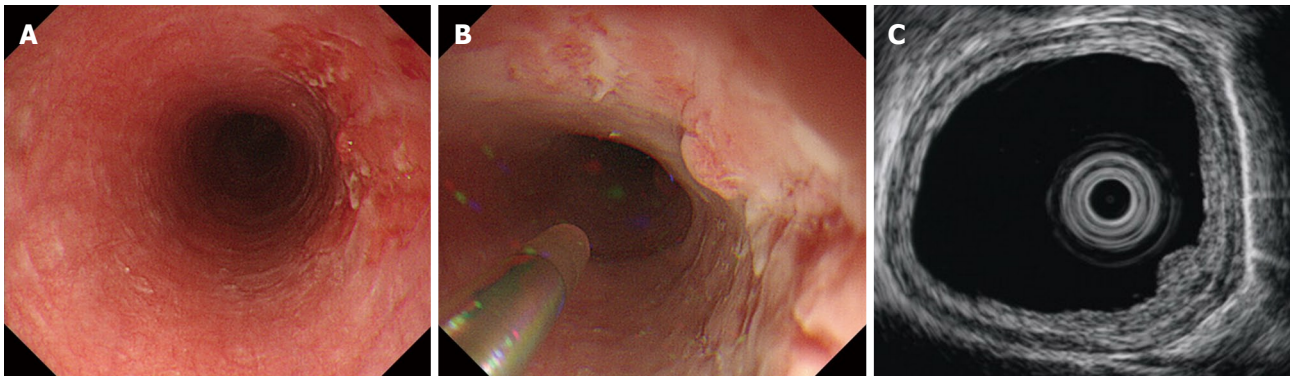

Figure 3 Endoscopic ultrasound procedure for early esophageal cancer as performed at the National Cancer Center Hospital. A: Endoscopic features after washing mucus and saliva from the lesion; B: Endoscopic features after region is filled with deaerated water. Endoscopic ultrasound (EUS) can be performed under direct vision of the lesion; C: EUS features.

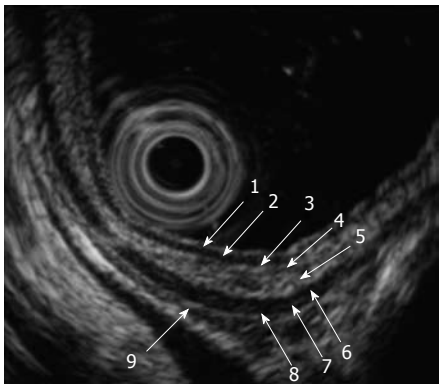

Figure 4 Endoscopic ultrasound features of normal esophageal wall. Each numbered circle, 1-9, with a white arrow, indicates the corresponding numbered tissue layer, first through ninth.

sound scanning is begun (Figure 3B and C). Technically, it is difficult to scan lesions which are located near EGJ precisely because the lower esophagus is sometimes spastic or not distended.

EUS findings for early esophageal cancers

When we use high-frequency ultrasound probes, the esophageal wall is delineated as nine alternating high- and low-echo layers[4]. The first to the fourth layers represent the mucosa, with the first and second layers corresponding to the epithelium, the third layer to the lamina propria, and the fourth layer to the muscularis mucosa. The fifth layer is the submucosa. The sixth to eighth layers are the proper muscle layers, with the sixth layer corresponding to the circular muscle, the seventh to the connective tissue and interface, and the eighth layer to the longitudinal muscle. The ninth layer is the adventitia (Figure 4).

Cancers are visualized as hypoechoic lesions, and it should be recognized which layers are destroyed and which layers are normal. An m1 cancer is located in the first and second layers[4], and sometimes it is difficult to recognize the lesion (Figure 5A-D). An m2 cancer invades the third layer, but the fourth layer under the lesion is preserved (Figure 6A-D). Cancers with m3 to sm1 invasion penetrate the fourth layer, but the fifth layer is intact[4] (Figure 7A-D). In some cases of sm1 cancer, the fifth layer under the lesions appears slightly irregular (Figure 8A-D). An sm2 cancer invades the fifth layer, but there is a hyperechoic layer between the cancer and the sixth layer[4] (Figure 9A-D).

EUS FOR EARLY GASTRIC CANCERS

Present status

According to the report by Gotoda *et al*[3], the expanded indications of endoscopic resection for gastric cancer are defined as follows: (1) differentiated type, no lymphatic or venous invasion, intramucosal cancer without ulceration, regardless of tumor size; (2) intramucosal cancer with ulceration, less than 3 cm diameter; (3) minute submucosal cancer that invades less than 500 μm in the submucosa,

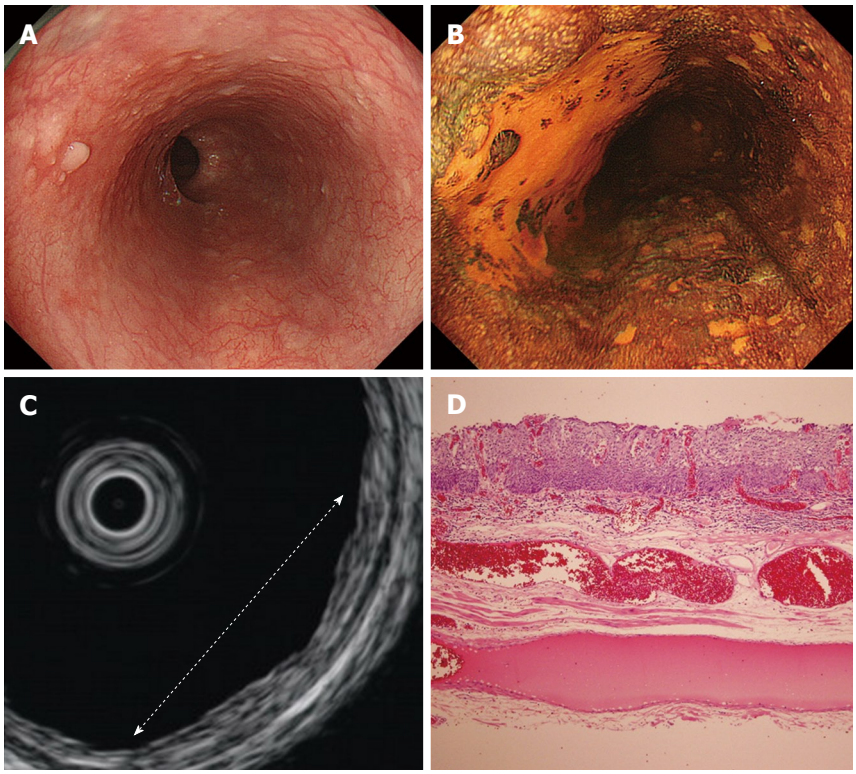

Figure 5 Findings for an m1 cancer of the esophagus. A: Endoscopic features. A reddish depressed lesion was located on the anterior and left wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed an irregularity of the first layer and a slight thickness of the second layer; D: Pathological findings. The tumor was confined to the epithelium. (Hematoxylin and eosin stain, × 40).

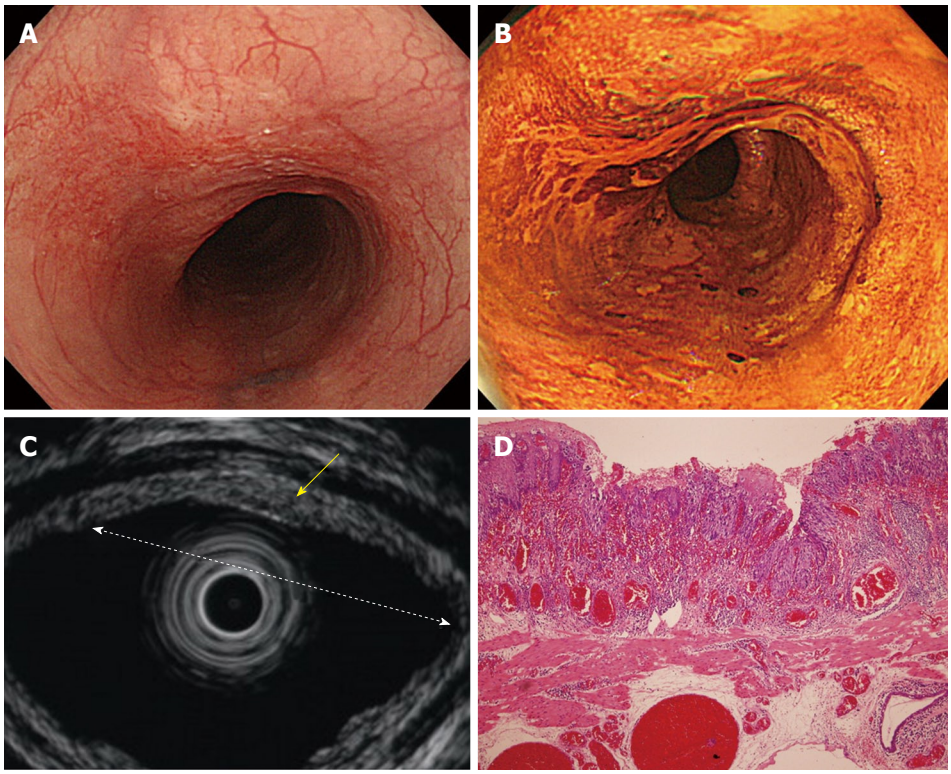

Figure 6 Findings for an m2 cancer of the esophagus. A: Endoscopic features. A reddish flat lesion was located on the anterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness in the second layer and a disappearance of the third layer. The yellow line with an arrow indicates the intact fourth layer; D: Pathological findings. The tumor was confined to the lamina propria. (Hematoxylin and eosin stain, × 100).

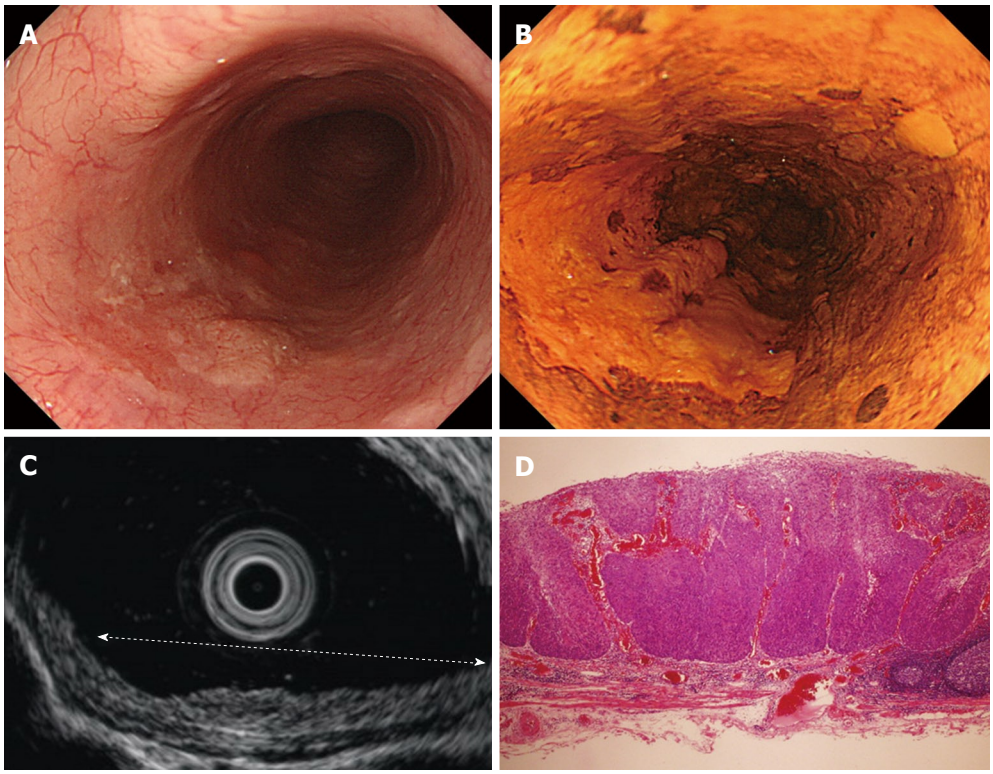

Figure 7 Findings for an m3 cancer of the esophagus. A: Endoscopic features. A reddish flat and partially elevated lesion was located on the posterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer seemed to be intact; D: Pathological findings. The tumor was reaching and partially invading the muscularis mucosae. (Hematoxylin and eosin stain, × 40).

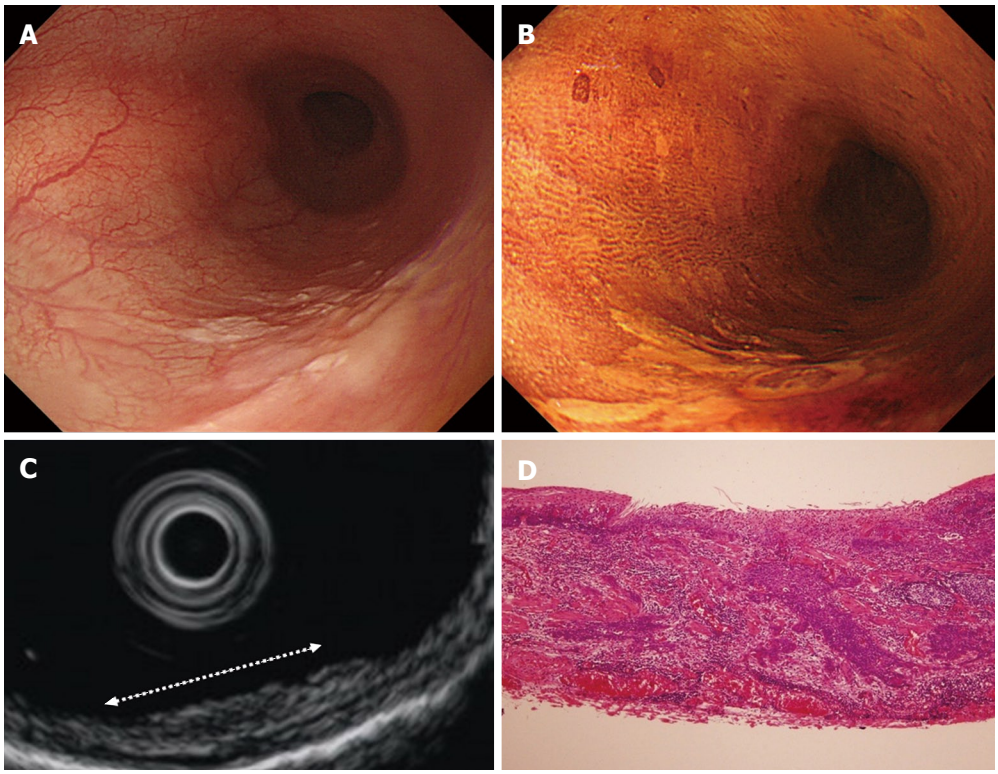

Figure 8 Findings for an sm1 cancer of the esophagus. A: Endoscopic features. A depressed, white, flat lesion was located on the posterior wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer seemed to be slightly irregular; D: The tumor was invading the submucosal layer to about 170 μm in depth. (Hematoxylin and eosin stain, × 40).

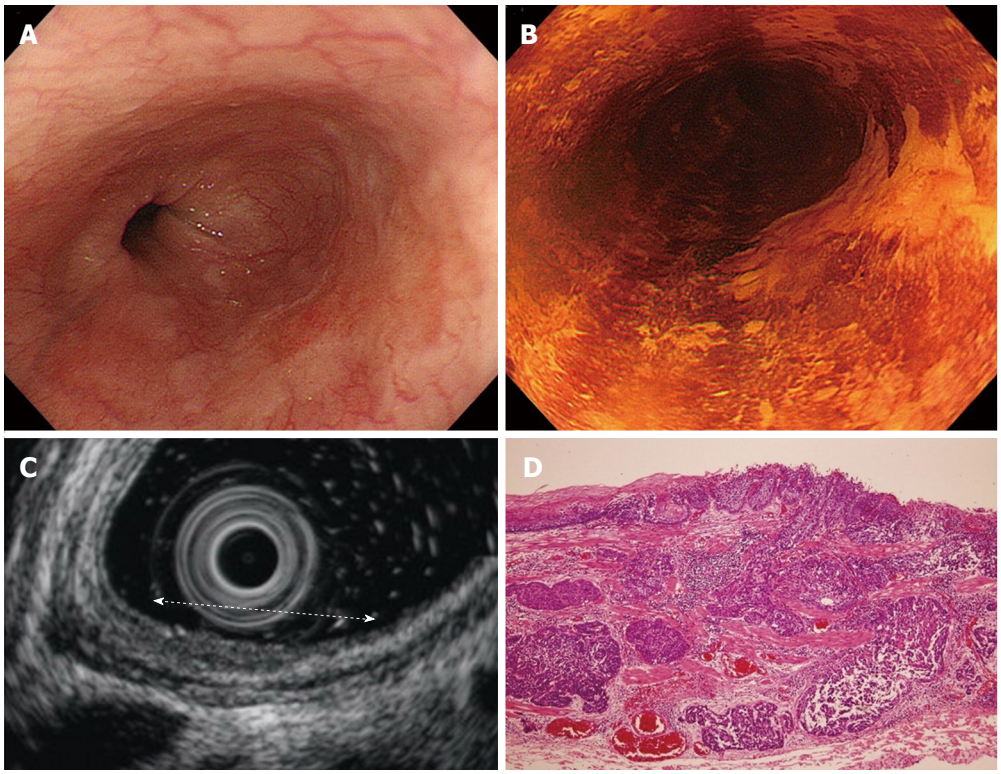

Figure 9 Findings for an sm2 cancer of the esophagus. A: Endoscopic features. A depressed lesion was located on the posterior and right wall of the middle esophagus; B: Endoscopic features after iodine dye. Biopsy specimens showed squamous cell carcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a disappearance of the third and fourth layer. The fifth layer had become thin, but the sixth layer was intact; D: Pathological findings. The tumor was invading the submucosal layer to a 320 μm depth. (Hematoxylin and eosin stain, × 40).

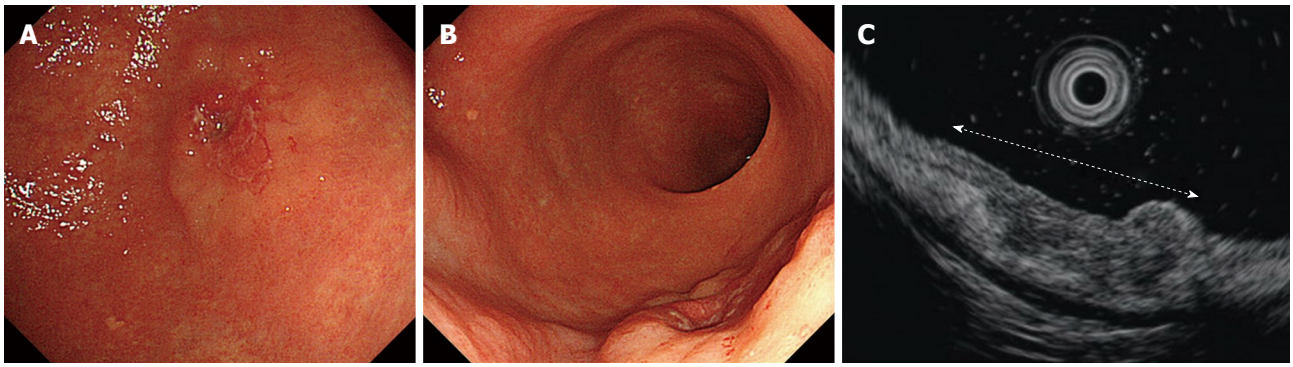

Figure 10 Endoscopic ultrasound procedure as performed at the National Cancer Center Hospital when it is difficult to approach lesions horizontally. A: Elevated lesion with central depression was located on the greater curvature of the angle; B: The lesion could be approached horizontally when using a multi-bending endoscope; C: Endoscopic ultrasound features after region is filled with deaerated water.

less than 3 cm diameter; and (4) undifferentiated type, no lymphatic or venous invasion, intramucosal cancer without ulceration, less than 2 cm diameter. Therefore, we should distinguish intramucosal (m) cancer, minute submucosal invasive (sm1) cancer, and massive submucosal invasive (sm2) cancer.

The accuracies of EUS using high-frequency ultrasound probes for the staging of early gastric cancer have been described as up to 80% compared with 63% for conventional EUS[15]. Rodriguez *et al*[16] mentioned that many endosonographers now feel that catheter-based miniprobes scanning at 20 MHz may be better suited to staging early gastric cancers. In previous reports, the overall accuracies of the depth of invasion by the ultrasound probes were 65%-86%[17-20]. In those reports, the accuracy of EUS relatively decreased for those patients with lesions of depressed type, undifferentiated cancer[18,19], concomitant ulceration, the expanded indications that we described[19], type 0-I lesions, and lesions located in the upper-third of the stomach[20]. Also, Akahoshi *et al*[18] mentioned that the accuracy decreased as tumor size increased. In addition, over staging of early gastric cancers with the 20 MHz probe occurs in 19%-24% of patients due to peritumoral fibrosis mimicking deeper invasion[16,17,21]. But when both the endoscopic appearance and EUS findings were applied together for tumor classifica-

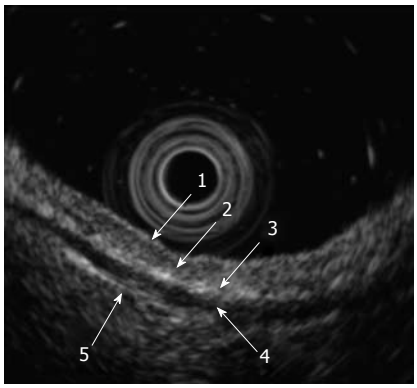

Figure 11 Endoscopic ultrasound features of normal gastric wall. Each numbered circle, 1-5, with a white arrow, indicates the corresponding numbered tissue layer, first through fifth.

tion, a 92% overall accuracy rate was achieved[17]. Though Mouri *et al*[22] reported both high-frequency ultrasound probes and conventional EUS are useful for accurately determining the depth of invasion of gastric cancer without ulcerous change, they did not distinguish between intramucosal cancers and minute submucosal invasive cancers in terms of the expanded indication of endoscopic resection, and they also excluded the lesions that EUS could not sufficiently evaluate. In other words, it is still difficult to distinguish those cancers, especially with ulcerous change, and EUS cannot evaluate all gastric lesions.

EUS methods in our institute

Our preparations and patient premedications are the same for both gastric and esophageal EUS procedures. Usually, we use a conventional endoscope that can be bent more than 180 degrees, both because we don't need to use a water jet system for gastric EUS and because sometimes we need to scan at the retroflex position.

After washing the lesion and removing water collected in the stomach, we start irrigating with deaerated water introduced through an instrument channel. After the area to be imaged is filled with deaerated water, an ultrasound probe is inserted through an instrument channel and ultrasound scanning is begun. When it is difficult to approach lesions horizontally (Figure 10A) it is sometimes impossible to scan. In such cases we use a multi-bending endoscope (GIF-2TQ260M; Olympus) to approach lesions horizontally (Figure 10B and C). Technically, it is sometimes difficult to scan lesions which are located in the angle and the antrum because lesions are located on the curve or not submerged under water.

EUS findings for early gastric cancer

When we use high-frequency ultrasound probes, the normal gastric wall is visualized as the mucosa (combination of the first hyperechoic and second hypoechoic layers) and the submucosa (the third hyperechoic layer). The muscularis propria is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa including the subserosa (Figure 11)[17]. According to the report by Yanai *et al*[23] the fine hypoechoic layer between the second and third layers is considered to correspond to the muscularis mucosae.

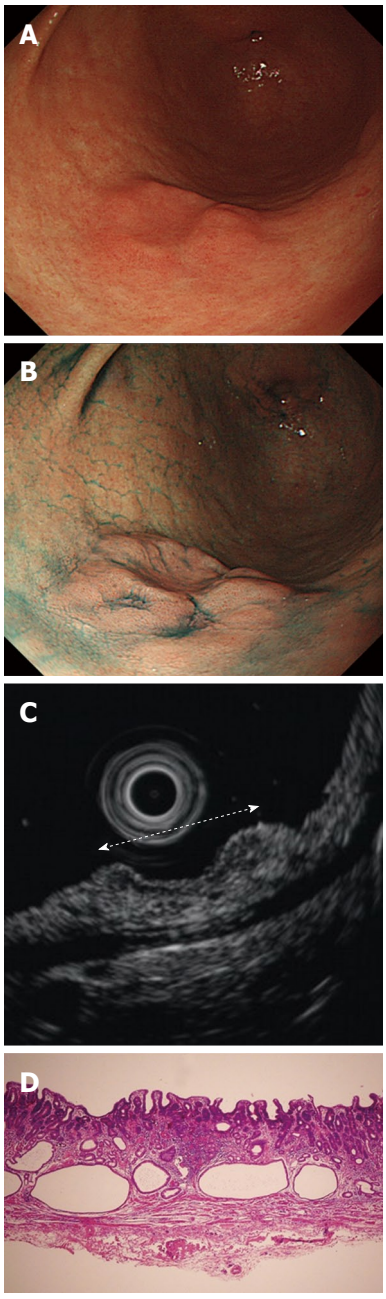

Figure 12 Findings for an m cancer of the stomach. A: Endoscopic features. A depressed lesion with surrounding elevation was located on the greater curvature of the antrum; B: Endoscopic figure after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed an irregularity of the first layer and a slight thickness of the second layer; D: Pathological findings. The tumor was confined to the lamina propria. (Hematoxylin and eosin stain, × 40).

The EUS images were interpreted with regard to tumor invasion according to the five layer architecture of the gastric wall, and lesions were classified as m cancers (Figure 12A-D) and submucosal invasive (sm) cancers[17] (Figure 13A-D). Although the fifth layer under the lesions seems to be slightly irregular in some cases of sm1 cancer (Figure 14A-D), it is difficult to distinguish m and sm1 definitively.

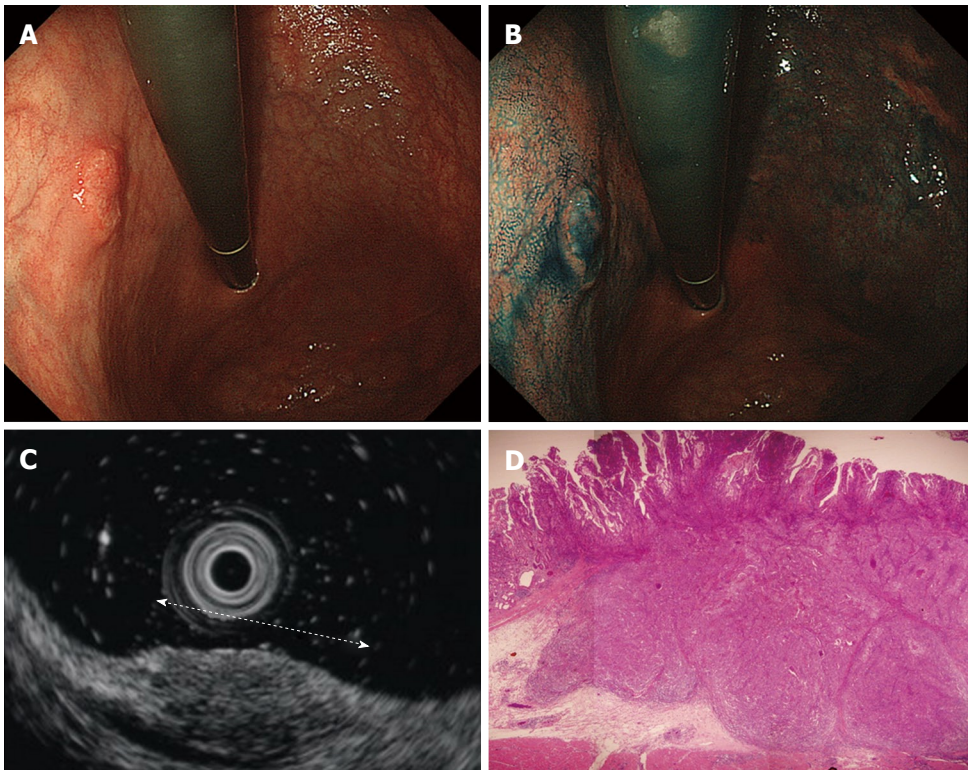

Figure 13 Findings for an sm2 cancer of the stomach. A: Endoscopic features. An elevated lesion was located on the posterior wall of the upper gastric body; B: Endoscopic features after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a thin third layer, but the fourth layer was intact; D: Pathological findings. The tumor was invading the submucosa massively. (Hematoxylin and eosin stain, × 12.5).

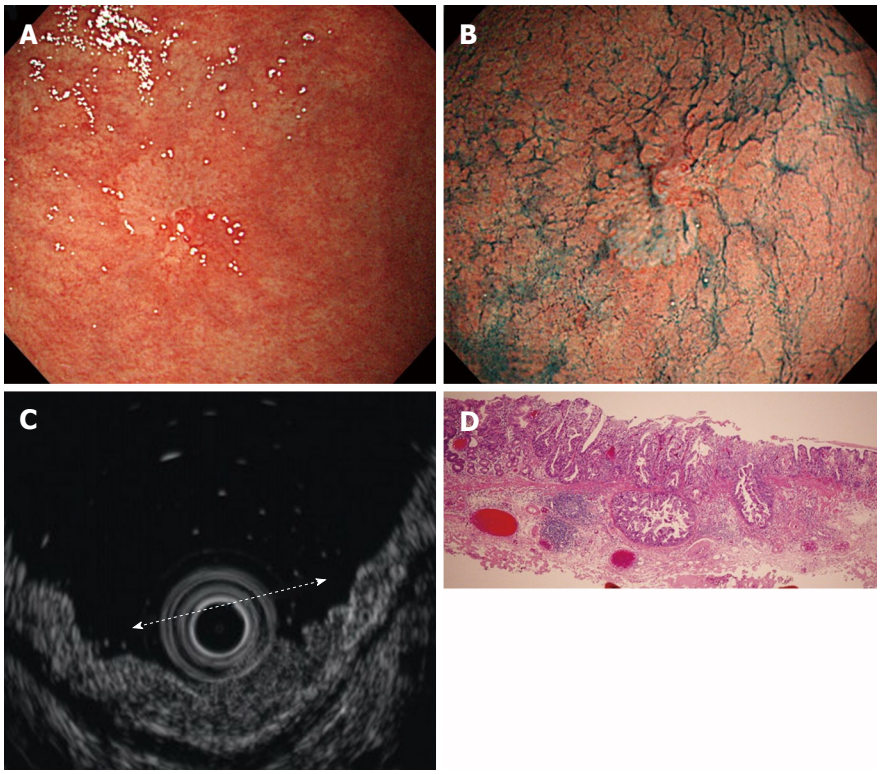

Figure 14 Findings for an sm1 cancer of the stomach. A: Endoscopic features. A white, flat lesion with central elevation was located on the greater curvature of the angle; B: Endoscopic features after indigo carmine dye. Biopsy specimens showed adenocarcinoma; C: Endoscopic ultrasound (EUS) features. The white dotted line indicates the extent of the lesion. EUS revealed a thickness of the second layer and a slightly irregular third layer; D: Pathological findings. The tumor was invading the submucosal layer to a 400 μm depth. (Hematoxylin and eosin stain, × 40).

COMPLICATIONS OF EUS

Fortunately, no severe complications of EUS have been reported so far, but aspiration of water occurs occasionally. There is a larger risk for this when patients have a hiatal hernia, as water collected in the stomach runs back easily. Therefore, conscious sedation, rather than deep sedation, is more suitable for EUS. If possible, a balloon should be fixed oral to the tips of an endoscope to prevent water reflex[4] for esophageal lesion procedures.

CONCLUSION

We reviewed the present status of, the methods used for, and the findings of, EUS using high-frequency ultrasound probes to diagnose and stage early esophageal and gastric cancer. Although EUS using high-frequency ultrasound probes still has some limitations, such as low accuracy for minute submucosal invasion cancers and lesions with ulcerous change, it still has good accuracy for determining the depth of invasion of early esophageal and gastric cancers. Because determining the depth of malignant invasion is essential to distinguish lesions indicated for endoscopic resection, EUS is a useful clinical procedure. When both the endoscopic and EUS diagnoses are considered, clinicians can achieve a high accuracy of staging of early esophageal and gastric cancers.

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