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DISEASES OF THE ESOPHAGUS

Original article

Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma

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SUMMARY. **The invasion depth of superficial esophageal squamous cell carcinoma is important in determining therapeutic strategy. The aim of this study was to prospectively investigate the clinical utility of magnifying endoscopy with narrow band imaging compared with that of non-magnifying high-resolution endoscopy or high-frequency endoscopic ultrasonography in predicting the depth of superficial esophageal squamous cell carcinoma. The techniques were carried out in 72 patients with 101 superficial esophageal squamous cell carcinomas, which were then resected by either endoscopic mucosal resection or esophagectomy. The histological invasion depth was divided into two: mucosal or submucosal carcinoma. We investigated the relationship between endoscopic staging and histology of tumor depth. Non-magnifying high-resolution endoscopy, magnifying endoscopy with narrow band imaging, and high-frequency endoscopic ultrasonography had overestimation/underestimation rates of 7/5, 4/4 and 8/3%, respectively. The sensitivity rates for the three techniques were 72, 78, and 83%, respectively, and the specificity rates were 92, 95, and 89%, respectively. There were no statistically significant differences among the three endoscopic techniques. Clinical utility of magnifying endoscopy with narrow band imaging does not seem to be significantly different from that of non-magnifying high-resolution endoscopy or high-frequency endoscopic ultrasonography in predicting the depth of superficial esophageal squamous cell carcinoma. Magnifying endoscopy with narrow band imaging may have potential to reduce overestimation risks of non-magnifying high-resolution endoscopy or high-frequency endoscopic ultrasonography.**

KEY WORDS: **endoscopic ultrasonography, esophageal squamous cell carcinoma, magnifying endoscopy, narrow band imaging, superficial esophageal cancer.**

INTRODUCTION

Superficial esophageal squamous cell carcinoma (ESCC) is defined as that in which infiltration is confined to the mucosa or submucosa.[1] The tumor depth has been precisely subdivided into six layers: three distinct mucosal layers correspond to the epithelium (m1), the lamina propria (m2), and the muscularis mucosae itself (m3), and the submucosa is arbitrarily divided into three successive sectors of equivalent thickness in surgical specimens in which the full thickness of the wall is available.[2]

The invasion depth of superficial esophageal cancer is an especially important factor in determining therapeutic strategy because the frequency of lymph node metastasis increases in proportion to the tumor depth. Previous studies of patients with superficial esophageal cancer revealed that 0–8.7% of mucosal carcinoma had lymph node metastasis, whereas the rate of incidence in those with submucosal carcinoma was significantly higher at 33–38.9%.[3–5]

Endoscopic mucosal resection (EMR) is now regarded as standard therapy for m1- or m2-ESCC because of their very low risk of lymph node metastasis (0–1.4%).[5–7] In the case of m3-ESCC, because of its higher risk of lymph node metastasis (0–12.2%), surgical resection with lymph node dissection has been commonly indicated.[5–7] However, EMR alone has

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been used recently for m3-ESCC, with no evidence of lymph node or organ metastasis.[8] In addition, another recent report indicated that EMR combined with chemoradiotherapy is equally as effective as esophagectomy for m3-ESCC, even if it has spread to the local lymph nodes.[9] Thus, nonsurgical therapy based on EMR can be chosen as a curative treatment for the large majority of patients with mucosal ESCC. On the other hand, esophagectomy with lymph node dissection, which has high mortality and morbidity rates, should be the first-line therapy for patients with submucosal carcinoma, which has a high rate of lymph node metastasis.[3–5] Moreover, the prognosis of submucosal carcinoma is significantly worse than that of mucosal carcinoma.[5] Therefore, it has been necessary to distinguish between mucosal and submucosal carcinoma for pre-therapeutic endoscopic staging.

Endoscopic ultrasonography (EUS) has played a central role in endoscopic work-up for staging of esophageal cancer.[10] Several reports have shown high-frequency EUS (HF-EUS, using a 15–30 MHz miniprobe) to give a high diagnostic accuracy of superficial ESCC invasion depth.[11,12] However, it is still unclear whether HF-EUS is more accurate than non-magnifying high-resolution endoscopy (N-HRE).[13] Moreover, HF-EUS remains more difficult in the esophagus than in the other digestive tract because filling the esophageal lumen with water is often inhibited by esophageal peristalsis, or cardiac/aortic motion prevents the taking of a fine EUS image.[14] In addition, filling the esophagus with water could itself increase the risk of aspiration.[15]

Narrow band imaging (NBI) is an optical image enhancement technology installed in endoscopy systems, which can display the mucosal surface layer in high contrast, especially for hemoglobin-rich areas such as blood vessels. Combined with magnifying endoscopy, it can capture the microvascular patterns on the lining of the digestive tract.[16]

In the late 1990s, Inoue and coworkers first observed a characteristic microvascular pattern using magnifying endoscopy; the pattern was named intrapapillary capillary loop (IPCL) in intact squamous cell epithelium of the esophagus.[17] They then reported characteristic IPCL changes in the intra-epithelial ESCC (carcinoma *in situ*).[18] Their recent studies have revealed the correlation between IPCL alterations visualized by magnifying endoscopy and the invasion depth of superficial ESCC.[19,20] In addition, they have suggested that the NBI system has advantages over ordinary white light systems in accurately staging the tumor depth.[20]

However, to the best of our knowledge, there has been no other report on the use of magnifying endoscopy with narrow band imaging (ME-NBI) in predicting invasion depth of superficial ESCC; its clinical utility compared with that of N-HRE or HF-EUS remains unknown. The aim of this prospective study was to verify the clinical utility of ME-NBI in predicting the depth of superficial ESCC and to compare it with N-HRE and HF-EUS.

MATERIALS AND METHODS

Patients

Between September 2003 and March 2006, 83 consecutive patients with 115 ESCC lesions, who were referred for EMR, underwent N-HRE, ME-NBI, and HF-EUS at the Jikei University Hospital. We excluded patients who had (i) a remnant or recurrent lesion after EMR; (ii) a lesion arising from the irradiated squamous epithelium; and who had (iii) a lesion in the remaining esophagus after subtotal esophagectomy. In addition, three patients with three advanced ESCC lesions were also excluded from this study. One hundred and one lesions were histologically diagnosed as superficial ESCC with resected specimens, either by EMR or esophagectomy at our hospital. Seventy-two patients with 101 superficial ESCC lesions were included in this study. Written informed consent was obtained from all patients before examination, EMR, and surgery.

Endoscopic procedure

All endoscopic inspections were carried out under conscious sedation (intravenous flunitrazepam 0.3–0.6 mg [Rohypnol, Chugai Pharmaceutical Co., Ltd.; Tokyo, Japan] and pethidine hydrochloride 35–70 mg [Opystan, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan]), with continuous monitoring of heart rate and oxygen saturation. The intestinal antispasmodic agents scopolamine butylbromide 20–40 mg (Buscopan, Boehringer Ingelheim GmbH, Ingelheim, Germany) or Glucagon 1–2 mg (Glucagon G Novo, Novo Nordisk, Bagsværd, Denmark) were also administered intravenously.

In N-HRE and ME-NBI, we used a high-resolution zoom endoscope (GIF-Q240Z; Olympus Medical Systems Co., Tokyo, Japan) equipped with the NBI system. We attached a cap (disposable distal attachment, D-201-11802, Olympus Medical Systems Co.) to the distal tip of the endoscope. The cap is transparent and maintains a distance of about 2 mm between the mucosa and the tip of the endoscope.

HF-EUS was performed using a 20 MHz miniprobe (UM-3R; Olympus Medical Systems Co.) through a dual-channel endoscope (GIF-2T240; Olympus Medical Systems Co.). The ultrasonic miniprobe was attached to an ultrasound image-processing unit equipped with a multi-freezing system (EU-IP2; Olympus Medical Systems Co.). Distilled water was poured into the esophageal lumen through another channel of the scope using a pump system.

Patients lay supine on their left side, with their shoulder raised in an anti-Trendelenburg position. No complications were recorded.

The three endoscopic procedures were all conducted by one endoscopist (K. G.) who had clinical experiences of ME-NBI and HF-EUS for more than 50 cases of superficial ESCC. The three kinds of endoscopic examination were undergone in a fixed turn: HR-WE, ME-NBI, and HF-EUS on the same day. The endoscopist immediately reported the endoscopic staging of the tumor depth after he finished one of the three endoscopic techniques.

ENDOSCOPIC STAGING OF TUMOR DEPTH

N-HRE

We evaluated the tumor for location (esophagogastric junction, lower, middle, or upper part of the esophagus), depth (mucosal or submucosal carcinoma), and macroscopic morphology. Superficial macroscopic morphology was classified as subtype 0, which was adopted in Japan to distinguish it from types 1 to 4 in Borrmann's classification of advanced cancer. The morphological classification was published as follows: 0-I, polypoid (0-Is, sessile type; 0-Ip, pedunculated type); 0-IIa, elevated; 0-IIb, flat; 0-IIc, depressed; and 0-III, excavated lesion.[1,2] Polypoid, sharply depressed, excavated configurations, and ulcerations were regarded as endoscopic signs of a higher rate of submucosal invasion.

ME-NBI

Endoscopic staging by ME-NBI was determined in reference to the classification described by Inoue and coworkers.[17,18] Under ME-NBI observation, normal IPCLs could be seen as single microvascular loops of the final branch of the arborescent vessels arising from the submucosal vein (Fig. 1). Modified IPCLs demonstrating four characteristic changes, which were dilatation, tortuosity, caliber change in one IPCL, and various shapes in multiple IPCLs, were frequently observed in carcinoma *in situ* (m1). When the modified IPCLs involved an elongated change, the tumor was more likely to be m2-ESCC. If the tumor invasion reached the muscularis mucosae (m3), vanishing IPCLs (destruction of papillae began) and/or marked elongated IPCL and interconnection of adjacent IPCLs often appeared in the tumor. When the tumor involved these IPCL alterations corresponding to the m1- to m3-ESCC, it was estimated as mucosal carcinoma. If the IPCLs vanished (the papillae were severely destroyed) or tumor vessels showing shaggy formation with significantly irregular shape appeared in the tumor, it was estimated as submucosal carcinoma.

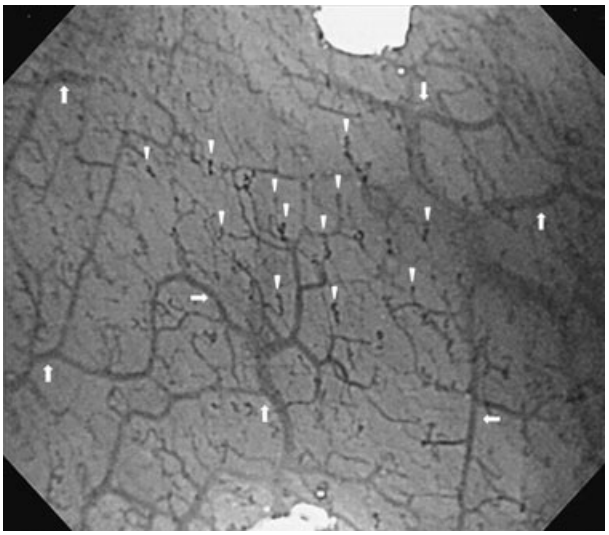

Fig. 1 Magnifying endoscopy with narrow band imaging demonstrates many of normal intrapapillary capillary loops (IPCLs) (arrow heads pointing to representative ones). IPCLs can be recognized rising from the so-called arborescent vascular network (arrows pointing to representative ones).

HF-EUS

According to previous reports, we interpreted ultrasound images as histological layers and estimated the tumor depth as follows.[11,21]

In a seven-layer image, the first, second, and third layers correspond to the epithelium plus the interface echo, lamina propria plus muscularis mucosae, and submucosa, respectively. Tumors without change in the seven-layered structure or change involving the first two layers, not including the third layer, were staged as mucosal carcinoma, and tumors involving the first three layers without involvement of the fourth layer were staged as submucosal carcinoma.

In a nine-layer image, the first, second, third, fourth, and fifth layers corresponded to the superficial epithelium plus the interface echo, deep epithelium, lamina propria plus the interface echo, muscularis mucosae minus the interface echo, and submucosa, respectively. Tumors without change in the nine-layered structure or involving the first four layers without the fifth layer were staged as mucosal carcinoma, and tumors involving the first five layers but not the sixth layer were staged as submucosal carcinoma.

Representative endoscopic pictures of mucosal and submucosal ESCC are shown in Figures 2 and 3, respectively.

Histopathology

Tissue specimens obtained by esophagectomy or EMR were serially cut after fixing in 10% buffered formalin. The sliced specimens were dehydrated in a gradual alcohol series and embedded in paraffin.

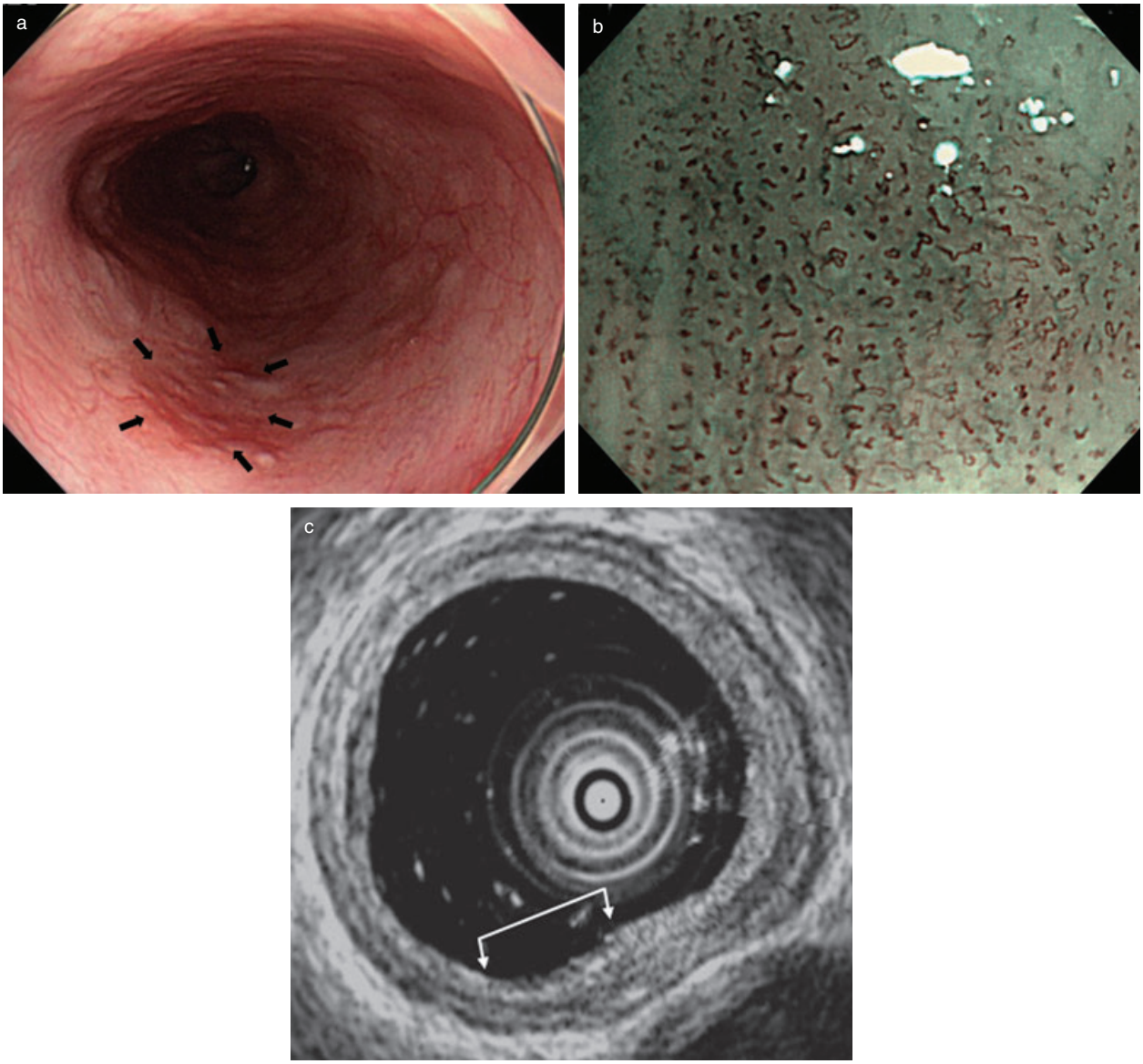

Fig. 2 Endoscopic images of a mucosal esophageal squamous cell carcinoma. (a) Non-magnifying high-resolution endoscopy shows a reddish depressed lesion in the middle esophagus (arrows), suggested to be a mucosal tumor. (b) Magnifying endoscopy with narrow band imaging demonstrates modified intrapapillary capillary loops corresponding to a mucosal tumor (m1). (c) High-frequency endoscopic ultrasonography corresponds to a mucosal tumor (between two arrows) which shows a hypoechoic lesion to be confined to the first two layers in the seven-layer image. Histology from endoscopic mucosal resection revealed a squamous cell carcinoma *in situ* (m1).

Sections (4-μm thick) were cut from each paraffin block and stained with hematoxylin and eosin. The depth of tumor invasion was evaluated in accordance with the Guideline for the Clinical and Pathological Studies in Carcinoma of the esophagus.[1] All 101 resected tumors were histologically diagnosed by one pathologist (M. I.) experienced in diagnosing ESCC, who was blinded to their endoscopic staging.

Statistical analysis

Quantitative data are summarized as mean ± standard deviation (SD). Associations between tumor-depth diagnosis by endoscopy and histology were evaluated for sensitivity and specificity with a 95% confidence interval (95% CI). Differences in sensitivity and specificity between endoscopy techniques were evaluated by the exact McNemar's test. Statistical significance was established at the $P < 0.05$ level. All tests were performed using STATA 8.0 software (STATA Co., College Station, TX, USA).

RESULTS

The patient and tumor characteristics of the 72 patients with 101 superficial ESCCs are presented in Table 1. The patients comprised 62 men (86%) and 10

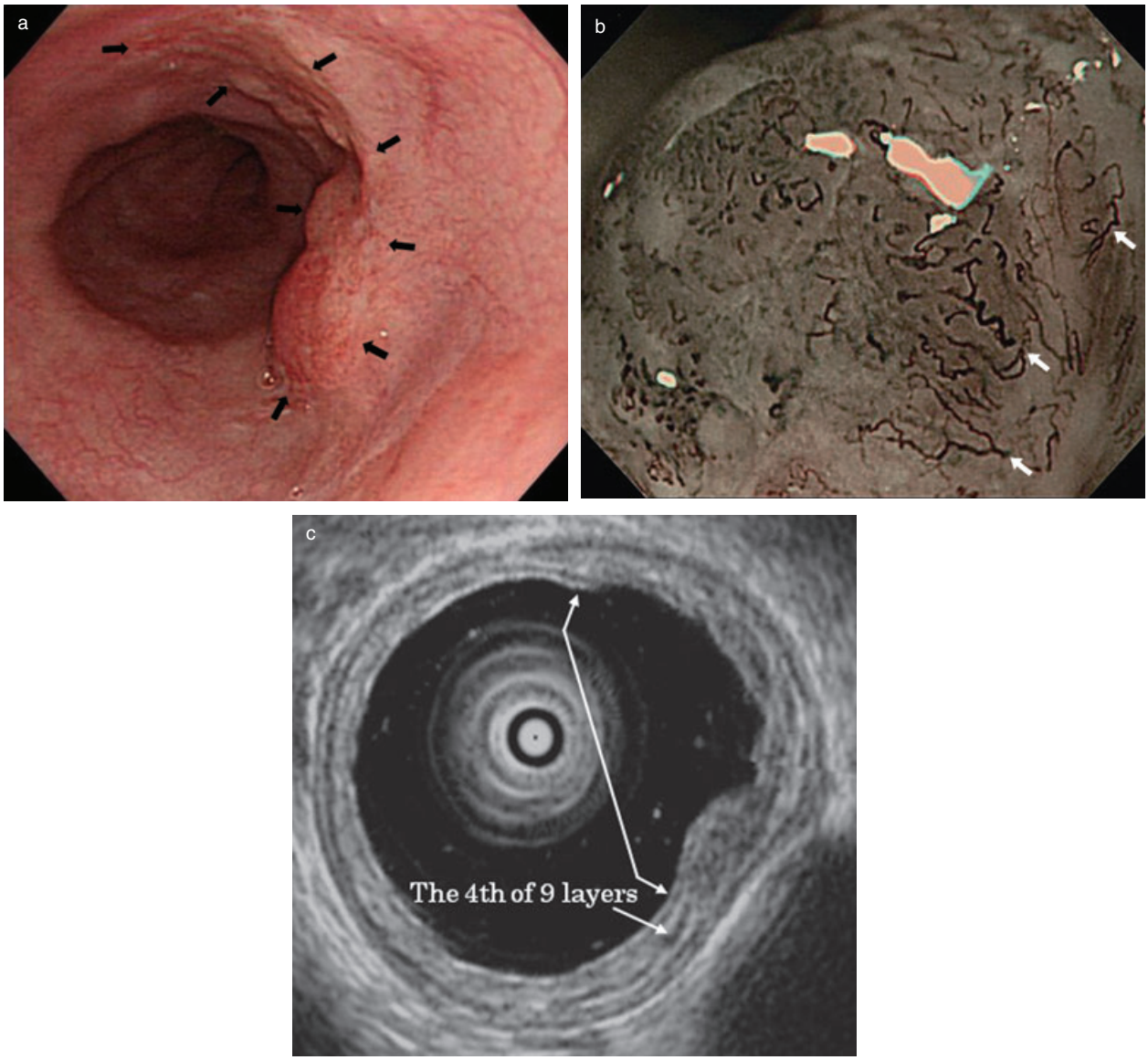

Fig. 3 Endoscopic images of a submucosal esophageal squamous cell carcinoma. (a) Non-magnifying high-resolution endoscopy shows a reddish polypoid lesion with a depressed area in the lower esophagus (arrows), which was suggested to be a submucosal tumor. (b) Magnifying endoscopy with narrow band imaging demonstrates that tumor vessels showing a shaggy formation with a significantly irregular shape (arrows) appear at the area where intrapapillary capillary loops vanished; this is evaluated as a submucosal tumor. (c) High-frequency endoscopic ultrasonography corresponds to a submucosal tumor (between two arrows) with elevated portion which shows a hypoechoic lesion involving the first five layers but not the sixth layer in the nine-layer image. Histology from surgical resection revealed a squamous cell carcinoma with deep tumor invasion of the submucosa.

women (14%) with a mean ± SD age of 65 ± 8 years. Fifty-six of the 101 lesions occurred in the middle esophagus, 29 in the lower esophagus, 12 in the upper esophagus, and 4 in the esophagogastric junction. The diameter of the tumors was 22 ± 23 mm: 58 of the 101 lesions were <20 mm in diameter and 43 were ≥20 mm. Macroscopically, 2 of the 101 lesions were classed as 0-Is, 4 as 0-Is + IIc or Is + IIb or Is + IIa + IIc, 1 as 0-IIa, 8 as 0-IIa + IIc or IIa + IIb, 20 as 0-IIb, 4 as 0-IIb + IIc, 51 as 0-IIc, and 11 as 0-IIc + IIb or IIc + IIa or IIc + Is + IIa. There was no 0-Ip and 0-III type ESCC. Histologically, there were 83 mucosal lesions (m1, 37; m2, 30; m3, 16) and 18 submucosal carcinomas. On HF-EUS images, the esophageal wall of the intact area surrounding the tumor was visualized as a seven- or nine-layered structure in 29 and 72 lesions, respectively.

Fifty-eight (81%) of 72 patients with 79 lesions underwent EMR; 14 patients (19%) with 22 lesions underwent subtotal esophagectomy with lymph node dissection. After EMR, two patients with m3- or submucosal ESCC received chemoradiotherapy, and one with submucosal ESCC underwent esophagectomy.

A comparison of endoscopic staging with histological tumor depth is shown as a 2 × 2 contingency table (Table 2). N-HRE overestimated the tumor

Table 1 Patient and tumor characteristics: $n = 72$ patients with 101 superficial esophageal squamous cell carcinomas

Age (years)	
Mean ± SD	65 ± 8
Range	45–85
Gender, *n* (%)	
Male	62 (86)
Female	10 (14)
Tumor location, *n*	
Upper	12
Middle	56
Lower	29
EGJ	4
Tumor diameter, mm	
Mean ± SD	22 ± 23
Range	4–210
Macroscopic tumor type, subtype 0, *n*	0-Is, 2; 0-Is + IIc or Is + IIb or Is + IIa + IIc, 4 0-IIa, 1; 0-IIa + IIc or IIa + IIb, 8 0-IIb, 20; 0-IIb + IIc, 4 0-IIc, 51; 0-IIc + IIb or IIc + IIa or IIc + Is + IIa, 11
Histological tumor depth, *n*	
m	83
m1	37
m2	30
m3	16
sm	18
Type of resection, *n* (%)	
EMR	58 (81)
Surgical resection	14 (19)

EGJ, esophagogastric junction; EMR, endoscopic mucosal resection; m, mucosa; SD, standard deviation; sm, submucosa.

depth in 7 of 101 lesions (7%), ME-NBI in 4 of 101 lesions (4%), and HF-EUS in 9 of 101 lesions (9%). N-HRE underestimated the tumor depth in 5 of 101 lesions (5%), ME-NBI in 4 of 101 lesions (4%), and HF-EUS in 3 of 101 lesions (3%). Images of tumor lesions overestimated by N-HRE and HF-EUS are shown in Figure 4.

The sensitivity and specificity rates of the three endoscopic techniques are given in Table 3. The sensitivity and specificity rates were highest in HF-EUS and ME-NBI, respectively. None of the differences between the techniques were statistically significant.

Table 2 Correlation between endoscopic staging and histology of invasion depth of superficial esophageal squamous cell carcinoma

	Histology ($n = 101$)	
Endoscopic staging	sm ($n = 18$)	m ($n = 83$)
N-HRE		
sm ($n = 20$)	13	7
m ($n = 81$)	5	76
ME-NBI		
sm ($n = 18$)	14	4
m ($n = 83$)	4	79
HF-EUS		
sm ($n = 24$)	15	9
m ($n = 77$)	3	74

HF-EUS, high-frequency endoscopic ultrasonography; m, mucosa; ME-NBI, magnifying endoscopy with narrow band imaging; N-HRE, non-magnifying high-resolution endoscopy; sm, submucosa.

DISCUSSION

HF-EUS has played a central role in predicting the invasion depth of superficial ESCC.[10,12] However, while recent reports have suggested magnifying endoscopy to be useful for estimating the superficial tumor depth,[19,20] and indicated the advantages of the NBI system over the ordinary white light system,[20] there has been no report on ME-NBI compared with non-magnifying endoscopy or EUS in predicting the invasion depth of superficial ESCC. We studied the clinical utility of ME-NBI relative to N-HRE or HF-EUS.

This study showed that N-HRE and HF-EUS tended to overestimate the tumor depth more often than ME-NBI. N-HRE overestimated such tumors as type 0-IIa lesion with central depression (0-IIa + IIc) and type 0-IIc lesion with a sharply depressed border or a small ulceration. Overestimation was more frequent using HF-EUS. In previous reports of HF-EUS limitations in staging superficial ESCC, the overestimation has sometimes been associated with the difficulty in distinguishing the cancer invasion from inflammatory cell infiltration or in creating an acoustic interface at the esophagogastric junction.[21,22] More than half of the lesions overestimated by HF-EUS (five of nine lesions, 56%) histologically demonstrated an inflammatory cell infiltration with lymphoid follicles, and two of the nine lesions (22%) were located at the esophagogastric junction. As with previous reports, inflammatory changes accompanying the tumor or the tumor location could lead to overestimation in this study. Moreover, two of four lesions (50%) overdiagnosed by ME-NBI were also accompanied by a dense inflammatory cell infiltration. However, three of four lesions (75%) overestimated by both N-HRE and HF-EUS were accurately diagnosed by ME-NBI. Therefore, ME-NBI may have the potential to reduce the overestimating risk, although a remaining one of those four lesions which had a small ulcer was overestimated by ME-NBI as well as N-HRE and HF-EUS.

All the underestimation rates were acceptably low, 5% or below. Most underestimated lesions histologically demonstrated submucosal ESCC with slight tumor invasion. However, more than 80% of the tumors in this study were mucosal carcinoma. Thus, if the study had included more submucosal carcinomas, the underestimation rate might have been higher.

There was no significant difference between the three kinds of endoscopic techniques in this study. All endoscopic procedures were carried out by one endoscopist who is an expert on superficial ESCC, and it might lead to the high accuracy rate of N-HRE. Although none of the differences between the three kinds of endoscopic techniques were statistically significant, the sensitivity and specificity rates were

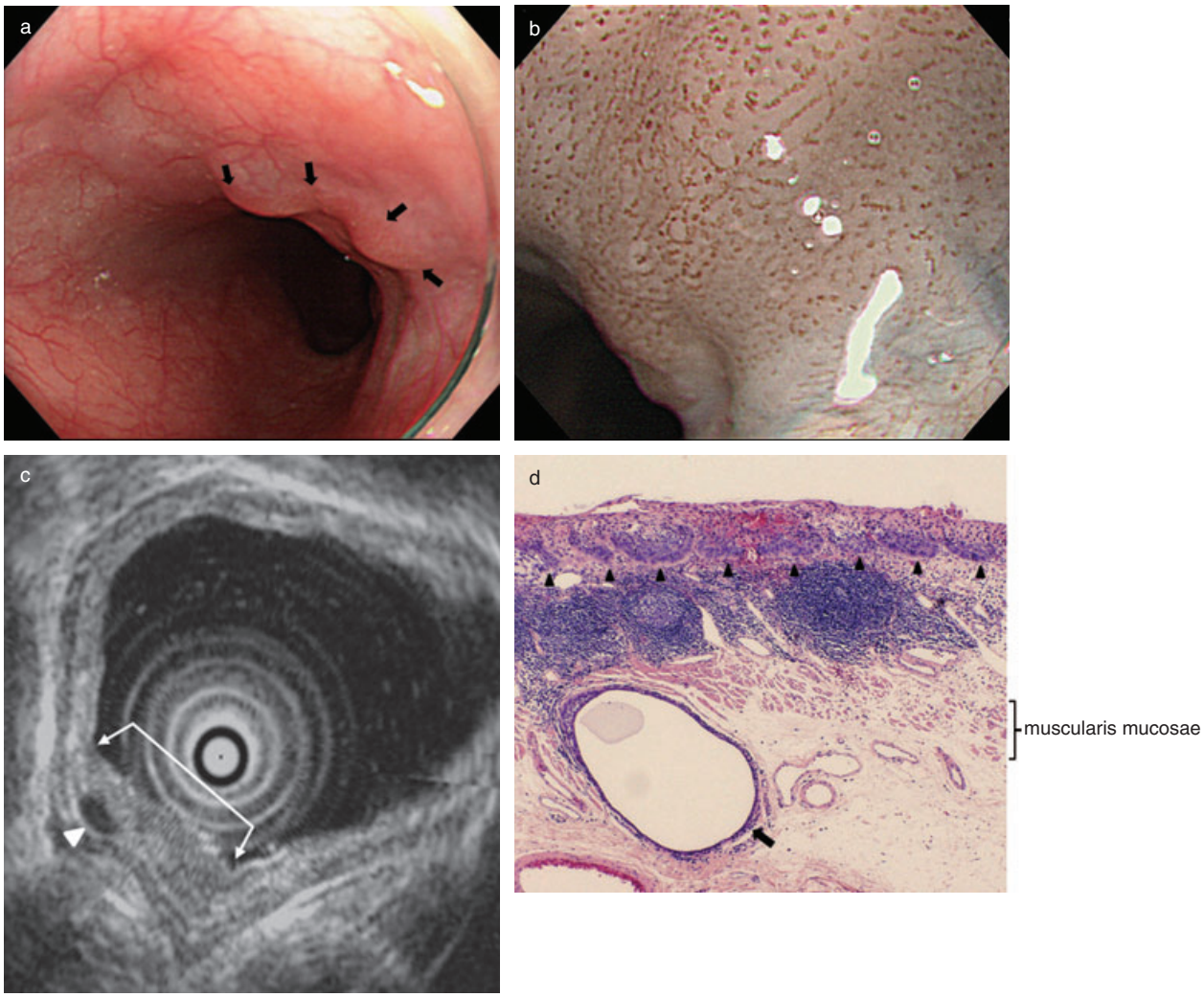

Fig 4 Images of the tumor lesion overestimated by non-magnifying high-resolution endoscopy (N-HRE) and high-frequency endoscopic ultrasonography (HF-EUS). (a) N-HRE shows a small nodular polypoid lesion with a depressed area in the middle esophagus (arrows). This lesion was estimated to be a submucosal tumor by N-HRE. (b) Magnifying endoscopy with narrow band imaging demonstrates modified intrapapillary capillary loops corresponding to a mucosal tumor (m1 or m2). (c) In the seven-layer image, HF-EUS shows localized hypoechoic thickening to be confined to the first three layers (between two arrows) and a small aechoic area (arrowheads) in the third layer. These findings were interpreted as submucosal tumor. (d) Histology from endoscopic mucosal resection (hematoxylin and eosin, original magnification ×100) revealed a mucosal squamous cell carcinoma (arrowheads) with proliferation of lymphoid follicle in the lamina propria and dilation of esophageal gland in the submucosa (arrow).

highest in HF-EUS and ME-NBI, respectively. Thus, HF-EUS might be suitable for picking up submucosal tumor invasion, and ME-NBI might be suited to extract mucosal carcinoma having an indication for EMR at high rates. HF-EUS has played a central role in estimating the invasion depth of superficial ESCC and high accuracy has been reported.[11,12] However, it is occasionally hard to obtain clear images of tumors in the cervical esophagus or the esophagogastric junction using HF-EUS, because it

Table 3 Sensitivity and specificity of the three endoscopic techniques in pre-therapeutic staging of invasion depth of superficial esophageal squamous cell carcinoma

Endoscopy techniques	Sensitivity (%) (95% CI)	*P*-value*		Specificity (%) (95% CI)	*P*-value*	
N-HRE	72 (47–90)	NS		92 (83–97)	NS	
ME-NBI	78 (52–94)		NS	95 (88–99)		NS
HF-EUS	83 (59–96)	NS		89 (80–95)	NS	

*Exact McNemar's test.
95% CI, 95% confidence interval; HF-EUS, high-frequency endoscopic ultrasonography; ME-NBI, magnifying endoscopy with narrow band imaging; N-HRE, non-magnifying high-resolution endoscopy.

is not easy to fill the whole esophagus with water or to emit ultrasound waves perpendicularly at the narrowing part. Therefore, we suggest that ME-NBI could be more feasible than HF-EUS in estimating the tumor depth of superficial ESCC.

Several limitations to this study must be described. First, the three endoscopy techniques were performed in a fixed turn by the same endoscopist, which we knew could lead to severe information bias that affected the interpretation of findings of the follow-on endoscopy technique. We ought to have conducted the two work-up endoscopy, ME-NBI and HF-EUS, in a random order. However, on the issue about the endoscopist, we did not have another endoscopist experienced in HF-EUS or ME-NBI for superficial ESCC. Second, we used the magnifying endoscopic classification of superficial ESCC invasion depth, which is based on IPCL morphological alteration.[19,20] This classification has never been validated by independent observer agreement study; however, it was the only available classification and revealed an adequate result in this study. We should have carried out a pilot study in advance to elucidate the interobserver variation. Third, we investigated the diagnostic utility of magnifying endoscopy only with NBI and not with ordinary white light imaging. Although Yoshida and colleagues[20] described how NBI improved the accuracy of ordinary magnifying endoscopy with white light imaging, there is still not enough clinical evidence on the impact of NBI on diagnosis by ordinary magnifying endoscopy. A randomized, blinded cross-over trial will be necessary to prove that NBI improves the diagnostic accuracy of white light imaging.

Clinical utility of ME-NBI does not seem to be significantly different from that of N-HRE or HF-EUS in predicting the depth of superficial ESCC. However, although a randomized cross-over study is absolutely imperative, ME-NBI may have potential to reduce overestimation risks of N-HRE or HF-EUS.

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