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ORIGINAL RESEARCH

Retrospective Assessment of the Diagnostic Accuracy of the Depth of Invasion by Narrow Band Imaging Magnifying Endoscopy in Patients with Superficial Esophageal Squamous Cell Carcinoma

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Abstract

Purpose Treatment strategies for superficial esophageal squamous cell carcinoma (S-ESCC) are determined mainly on the basis of the depth of invasion. We retrospectively studied the accuracy of the depth of tumor invasion, comprehensively assessed using the Japan Esophageal Society (JES) classification.

Methods The study group comprised 256 patients who underwent narrow band imaging (NBI) magnifying endoscopy, and endoscopic submucosal dissection for S-ESCC. The depth of invasion of S-ESCC was classified into three groups: EP/LPM, MM/SM1, and SM2. The following variables were studied retrospectively: (1) the diagnostic accuracy of non-magnifying white-light endoscopy, (2) the diagnostic accuracy of type B vessels, (3) the diagnostic accuracy of avascular area (AVA), (4) the diagnostic accuracy of the JES classification, and (5) the diagnostic accuracy of comprehensive diagnosis. The depth of invasion was assessed by white-light non-magnifying endoscopy, followed by NBI magnifying endoscopy.

Results The positive predictive value (PPV) of white-light non-magnifying endoscopy was 86% for EP/LPM, 53% MM/SM1, and 74% for SM2. The PPV of the diagnosis of type B vessels was 93% for EP/LPM, 62% for MM/SM1, and 74% for SM2. The PPV of the AVA diagnosis was 73% for EP/LPM, 89% for MM/SM1, and 100% for SM2. The PPV of diagnosis according to the JES classification was 93% for EP/LPM, 65% for MM/SM1, and 77% for SM2. The PPV of the comprehensive diagnosis was 94% for EP/LPM, 63%, for MM/SM1, and 75% for SM2.

Conclusions The additional use of NBI magnifying endoscopy can enhance the diagnostic accuracy of the depth of invasion in patients with S-ESCC.

Keywords Esophageal squamous cell carcinoma · Narrow band imaging · Magnifying endoscopy · Type B vessels · Avascular area · Japan Esophageal Society classification

Introduction

Treatment strategies for superficial esophageal squamous cell carcinoma (S-ESCC) are based mainly on the depth of tumor invasion. Guidelines for the Diagnosis and Treatment of Carcinoma of the Esophagus 2017 in Japan recommend endoscopic submucosal dissection (ESD) for the treatment of intramucosal S-ESCC [1]. Preoperative diagnosis of the depth of invasion is thus extremely important [2–10]. To estimate the depth of invasion, lesions are usually initially examined by white-light non-magnifying endoscopy to evaluate findings such as the flatness, consistency (hardness), and thickness of the lesion surface. Next, narrow band imaging (NBI) magnifying endoscopy is performed to further evaluate such findings. The depth of invasion is then comprehensively evaluated.

NBI magnifying endoscopy is a diagnostic modality used to estimate the depth of invasion of S-ESCC on the basis of changes in vascular patterns on the surface of the esophagus [11]. Initially, the Arima classification and Inoue classification, based

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Table 1 Clinical and histopathological characteristics of the patients

Number	256
Sex (male/female)	224/32
Age (median, range) (years)	71(46–91)
Tumor location (Ce/Ut/Mt./Lt)	6/16/169/65
Tumor size (mean ± SD, range) (mm)	20 ± 12(2–75)
Extent of the circumference (≤ 1/4, > 1/4 to ≤ 1/2, > 1/2 to ≤ 3/4, > 3/4)	133/103/16/4
Macroscopic appearance (I/IIa/IIb/IIc/III)	7/11/32/205/1
Histopathological depth of invasion (EP/LPM/MM/SM1/SM2)	82/90/49/5/30

Ce denotes the cervical esophagus, *Ut* the upper third of the esophagus, *Mt* the middle third of the esophagus, *Lt* the lower third of the esophagus, *EP* the epithelium, *LPM* the lamina propria mucosae, *MM* the muscularis mucosae, *SM1* the first layer of the submucosa, *SM2* the second layer of the submucosa

on microvascular changes, were proposed to classify the depth of invasion of S-ESCC [12–14]. Although these two classifications were widely used in routine clinical practice, the presence of two classifications led to considerable confusion. Therefore, the Japan Esophageal Society (JES) classification was proposed to integrate these two classifications into a single system for diagnosis of the depth of invasion of S-ESCC [15].

The JES classification was specifically designed to facilitate the differential diagnosis of cancerous lesions and non-cancerous lesions and the diagnosis of the depth of invasion and is more straightforward than the two previous classifications mentioned above. This new classification allowed the depth of tumor invasion to be easily diagnosed on the basis of standard criteria. However, the comprehensive diagnostic accuracy of the depth of invasion evaluated according to the JES classification is not supported by adequate evidence. We therefore retrospectively studied the accuracy of a comprehensive diagnosis of the depth of invasion derived with the use of the JES classification.

Methods

The study group comprised patients who underwent endoscopic submucosal dissection (ESD) for S-ESCC in Kitasato University Hospital from July 2005 through November 2015 and met the following criteria: (1) a histopathologically confirmed diagnosis of squamous cell carcinoma (SCC) and (2) assessable NBI magnifying endoscopic images.

The depth of invasion of S-ESCC was classified into three groups: tumor invades the epithelium or the lamina propria mucosae (EP/LPM), tumor invades the muscularis mucosae or the submucosa to a depth of 200 μm or less from the muscularis mucosae (MM/SM1), and tumor invades the submucosa to a depth of more than 200 μm (SM2). The following variables were studied retrospectively: (1) the accuracy of the diagnosis based on white-light non-magnifying endoscopy, (2) the accuracy of the diagnosis based on type B vessels, (3) the accuracy of the diagnosis based on avascular areas (AVAs), (4) the accuracy of the diagnosis based on the JES classification, and (5) the accuracy of comprehensive diagnosis.

The depth of invasion was assessed by performing white-light non-magnifying endoscopy, followed by NBI magnifying endoscopy. Magnifying endoscopy was performed with a GIF-Q240Z endoscope (Olympus Co., Ltd., Tokyo, Japan) or a GIF-H260Z endoscope (Olympus Co., Ltd.). At the time of NBI magnifying endoscopy, a black hood (MB162 or MB46, Olympus Co., Ltd.) was attached to the tip of the endoscope.

The depth of invasion on NBI magnifying endoscopy was classified according to the JES classification. Intralesional blood vessels that showed severe morphological changes were defined as type B vessels according to the JES classification, corresponding to SCC. Type B vessels were subclassified into three groups: B1, loop-like abnormal vessels showing dilation, tortuosity, caliber variation, and shape non-uniformity; B2, abnormal vessels without a loop-like formation; and B3, highly dilated, irregular vessels (irregular vessels more than about 60 μm in diameter, about three times thicker than B2

Table 2 Diagnostic accuracy of white-light non-magnifying endoscopy

		Pathological diagnosis			
		EP/LPM	MM/SM1	SM2	Total
Endoscopic diagnosis	EP/LPM	155 (86%)	20 (11%)	5 (3%)	180
	MM/SM1	17 (32%)	28 (53%)	8 (15%)	53
	SM2	0 (0%)	6 (26%)	17 (74%)	23
		172	54	30	256

Table 3 Diagnostic accuracy of type B vessels

		Pathological diagnosis			
		EP/LPM	MM/SM1	SM2	Total
Endoscopic diagnosis	Type B1	156 (93%)	8 (5%)	3 (2%)	167
	Type B2	15 (23%)	41 (62%)	10 (15%)	66
	Type B3	1 (4%)	5 (22%)	17 (74%)	23
		172	54	30	256

vessels). B1 vessels were defined as indicating EP/LPM invasion; B2 vessels, MM/SM1 invasion; and B3 vessels, SM2 invasion.

An area with no or low vascularity that was surrounded by type B vessels was defined as an AVA. AVAs were classified into three groups according to size: AVA-small (< 0.5 mm), AVA-middle (≥ 0.5 mm to < 3.0 mm), and AVA-large (≥ 3.0 mm). These groups were defined as corresponding to EP/LPM invasion, MM/SM1 invasion, and SM2 invasion, respectively. However, an AVA surrounded by B1 vessels was defined as corresponding to EP/LPM invasion regardless of size.

The JES classification was used to make a comprehensive diagnosis on the basis of the evaluation of type B vessels and AVA. The comprehensive diagnosis was based on all available findings.

The depth of invasion was determined by a single endoscopist (CK) who was blinded to the clinical information, using endoscopic images stored in an endoscopic image filing system. Our study was approved by the Institutional Ethics Committee of Kitasato University School of Medicine.

Results

Among 318 patients who underwent endoscopic submucosal dissection for S-ESCC, 27 patients with a histopathological diagnosis other than SCC and 35 patients with no assessable NBI magnifying endoscopic images were excluded from the study. The remaining 256 patients were included in analysis.

There were 224 men and 32 women, with a median age of 71 years (range, 46 to 91). The tumor was located in the cervical esophagus in 6 patients, the upper thoracic esophagus in 16 patients, the middle thoracic esophagus in 169 patients, and the lower thoracic esophagus in 65 patients. The mean tumor diameter was 20 ± 12 mm (range, 2 to 75). Overall, 133 tumors occupied one fourth or less of the esophageal circumference, 103 occupied more than one fourth to one half or less of the esophageal circumference, 16 occupied more than one half to three fourths or less of the esophageal circumference, and 4 occupied more than three fourths of the esophageal circumference. The macroscopic type was type I for 7 tumors, type IIa for 11 tumors, type IIb for 32 tumors, type IIc for 205 tumors, and type III for 1 tumor. The histopathological depth of invasion was EP in 82 tumors, LPM in 90 tumors, MM in 49 tumors, SM1 in 5 tumors, and SM2 in 30 tumors (Table 1).

The positive predictive value (PPV) of white-light non-magnifying endoscopy was 86% for EP/LPM invasion, 53% for MM/SM1 invasion, and 74% for SM2 invasion (Table 2). The PPV of the diagnosis of type B vessels was 93% for EP or LPM invasion, 62% for MM or SM1 invasion, and 74% for SM2 invasion (Table 3). The diagnostic accuracy of type B1 vessels had a sensitivity of 91%, a specificity of 87%, a PPV of 93%, a negative predictive value of 82%, and an accuracy of 89%.

An AVA was found in 74 (29%) of the 256 tumors. The PPV of the AVA diagnosis was 73% for EP/LPM invasion, 89% for MM/SM1 invasion, and 100% for SM2 invasion (Table 4). Among the six patients with large AVA, three patients had B3 vessels, and the other three had B2 vessels. The proportion of cases with no AVA according to the depth of invasion was 78% (135/172) for EP/LPM invasion, 54% (29/54) for MM/SM1 invasion, and 60% (18/30) for SM2 invasion.

The PPV of the diagnosis by the JES classification was 93% for EP/LPM invasion, 65% for MM/SM1 invasion, and 77% for SM2 invasion (Table 5). The PPV of the comprehensive diagnosis was 94% for EP/LPM invasion, 63% for MM/SM1 invasion, and 75% for SM2 invasion (Table 6).

Table 4 Diagnostic accuracy of avascular area

		Pathological diagnosis			
		EP/LPM	MM/SM1	SM2	Total
Endoscopic diagnosis	AVA-small	36 (73%)	8 (16%)	5 (10%)	49
	AVA-middle	1 (5%)	17 (89%)	1 (5%)	19
	AVA-large	0 (0%)	0 (0%)	6 (100%)	6
		37	25	12	74

Table 5 Diagnostic accuracy of the Japan Esophageal Society classification

		Pathological diagnosis			
		EP/LPM	MM/SM1	SM2	Total
Endoscopic diagnosis	EP/LPM	156 (93%)	8 (5%)	3 (2%)	167
	MM/SM1	15 (24%)	41 (65%)	7 (11%)	63
	SM2	1 (4%)	5 (19%)	20 (77%)	26
		172	54	30	256

Discussion

The depth of tumor invasion correlates with the rate of lymph-node metastasis in patients with S-ESCC. Guidelines for the diagnosis and treatment of esophageal cancer recommend the following treatment strategies: (1) endoscopic treatment is absolutely indicated for EP/LPM tumors because of the extremely low risk of lymph-node metastasis, (2) endoscopic treatment is relatively indicated for MM/SM1 tumors because the rate of lymph-node metastasis is 10 to 15, and (3) SM2 tumors should be treated by surgery or definitive chemoradiotherapy because the rate of lymph-node metastasis is 30 to 50% [16–19]. Therefore, an accurate assessment of the depth of invasion plays an important role in determining the treatment strategy of choice. Assessment of vascularity on NBI magnifying endoscopy is one useful modality for diagnosis [15]. In the present study, we retrospectively examined the accuracy of the depth of invasion, comprehensively evaluated with the use of the JES classification.

In patients with a histopathological diagnosis of EP/LPM invasion, the PPV was 86% for the diagnosis on white-light non-magnifying endoscopy, 93% for the type B vessel diagnosis, 73% for the AVA diagnosis, 93% for the diagnosis on the JES classification, and 94% for the comprehensive diagnosis, indicating very good results. Because the PPV of the type B vessel diagnosis (93%) was higher than that of the diagnosis on white-light non-magnifying endoscopy (86%), the additional use of NBI magnifying imaging can be expected to enhance the diagnostic accuracy for the depth of invasion.

In patients in whom the histopathological depth of invasion was MM/SM1, the PPV was 53% for the diagnosis on white-light non-magnifying endoscopy, 62% for the type B vessel diagnosis, 89% for the AVA diagnosis, 65% for the JES classification diagnosis, and 63% for the comprehensive diagnosis, indicating relatively poor results. The PPV of the type B vessel diagnosis (62%) was higher than that of the diagnosis on white-light non-magnifying endoscopy (53%). In patients with AVA-middle on NBI magnifying imaging, the PPV was 89%, indicating good results. Therefore, the additional use of NBI magnifying endoscopy may improve the diagnostic accuracy of the depth of invasion even in patients with a histopathological diagnosis of MM/SM1 invasion.

In patients with a histopathological diagnosis of SM2 invasion, the PPV was 74% for the diagnosis on white-light non-magnifying endoscopy, 74% for the type B vessel diagnosis, 100% for the AVA diagnosis, 77% for the JES classification diagnosis, and 75% for the comprehensive diagnosis, indicating relatively good results. The diagnosis on white-light non-magnifying endoscopy and the type B vessel diagnosis both had a PPV of 74%. In patients with AVA-large on NBI magnifying imaging, however, the PPV was extremely high (100%). Therefore, the additional use of NBI magnifying imaging is expected to improve the diagnostic accuracy for the depth of invasion.

In our study, the number of patients with a histopathological diagnosis of EP/LPM invasion was 172. Because the number was relatively large, our results are considered reliable. However, the numbers of patients with a histopathological diagnosis of MM/SM1 invasion (54 patients) or SM2 invasion (30 patients) were relatively small. Therefore, further studies in adequate numbers of such patients are needed.

AVA is a finding considered to reflect the tumor mass formed at sites of invasion. The AVA size is related to the size of a tumor mass and the degree of invasion. Previous studies have reported that the incidence of AVA is 8.4 and 23% [20, 21]. Therefore, AVA can be diagnosed in only relatively few patients. In our study, the PPV of the AVA diagnosis was 73% for EP/LPM, 89% for MM/SM1, and 100% for SM2. AVA-

Table 6 Diagnostic accuracy of the comprehensive diagnosis

		Pathological diagnosis			
		EP/LPM	MM/SM1	SM2	Total
Endoscopic diagnosis	EP/LPM	156 (94%)	8 (5%)	2 (1%)	166
	MM/SM1	16 (26%)	39 (63%)	7 (11%)	62
	SM2	0 (0%)	7 (25%)	21 (75%)	28
		172	54	30	256

middle was found in 19 patients and AVA-large in only 6 patients. The diagnostic accuracy of AVA-middle and AVA-large is therefore not supported by adequate data.

In our study, only 2 (1%) of the 166 patients who were given a comprehensive diagnosis of EP/LPM invasion had a histopathological depth of invasion of SM2. Therefore, ESD is most likely an appropriate treatment in patients who have a comprehensive diagnosis of EP/LPM invasion.

In our study, 16 (26%) of the 62 patients who were given a comprehensive diagnosis of MM/SM1 invasion had a histopathological depth of invasion of EP/LPM. Therefore, patients with a comprehensive diagnosis of MM/SM1 invasion should initially undergo ESD because surgery can be avoided in a considerable proportion of such patients.

In the Japan Clinical Oncology Group Study JCOG0508, patients who had a diagnosis of S-ESCC with SM invasion initially underwent ESD. Patients who were found to have a histopathological diagnosis of MM invasion with lymphovascular invasion and patients with a histopathological diagnosis of SM invasion additionally received chemoradiotherapy. The 3-year overall survival rate was 90.7% in patients who had a histopathological diagnosis of MM invasion with lymphovascular invasion and patients with a histopathological diagnosis of SM invasion who additionally received chemoradiotherapy. Because the outcomes were good, ESD followed by chemoradiotherapy was reported to be a treatment option for such patients [22, 23].

In our study, 7 (25%) of the 28 patients with a comprehensive diagnosis of SM2 invasion had a histopathological depth of invasion of MM or SM1. Therefore, patients who have a comprehensive diagnosis of SM2 invasion most likely include patients in whom surgery can be avoided. Because patients who have a histopathological diagnosis of MM invasion with lymphovascular invasion or a histopathological diagnosis of SM invasion would additionally receive chemoradiotherapy, initially performing ESD may be considered an appropriate treatment strategy even in patients who have a comprehensive diagnosis of SM2 invasion.

In this study, patients who underwent ESD were included, but the patients with SM2 invasion who underwent surgery were not included. The accuracy of invasion depth for SM2 may vary if the patients who underwent surgery had been included. Our study was retrospective and performed in a single center by a single endoscopist. In the future, further multicenter prospective studies of large numbers of patients who have S-ESCC with histopathological MM or SM invasion are needed to validate the diagnostic accuracy for the depth of invasion. To further improve the diagnostic accuracy for the depth of invasion, the effectiveness of combining NBI magnifying endoscopy with other useful modalities should be evaluated. At present, we are planning a multicenter prospective study to assess the diagnostic accuracy of NBI magnifying endoscopy combined with EUS for the depth of invasion.

In conclusion, a comprehensive diagnosis of the depth of invasion derived with the use of the JES classification provided an accurate assessment of the depth of invasion in patients who had S-ESCC with a histopathological diagnosis of EP/LPM invasion. The additional use of NBI magnifying endoscopy can be expected to enhance the diagnostic accuracy of the depth of invasion in patients with S-ESCC.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. The Japan Esophageal Society. Guidelines for diagnosis and treatment of carcinoma of the esophagus 2017. Tokyo: Kanehara Co Ltd; 2017. (in Japanese)
2. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of the responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery. 1998;123:432–9.
3. Endo M, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus. 2000;13:125–9.
4. Araki K, Ohno S, Egashira A, Saeki H, Kawaguchi H, Sugimachi K. Pathologic features of superficial esophageal squamous cell carcinoma with lymph node and distal metastasis. Cancer. 2002;94:570–5.
5. Shimizu Y, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Long-term outcome aft er endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. Gastrointest Endosc. 2002;56:387–90.
6. Ishihara R, Tanaka H, Iishi H, Takeuchi Y, Higashino K, Uedo N, et al. Long-term outcome of esophageal mucosal squamous cell carcinoma without lymphovascular involvement after endoscopic resection. Cancer. 2008;112:2166–72.
7. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol Hepatol. 2006;4:688–94.
8. Takahashi H, Arimura Y, Masao H, Okahara S, Tanuma T, Kodaira J, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus. Gastrointest Endosc. 2010;72:255–64.
9. Katada C, Muto M, Momma K, Arima M, Tajiri H, Kanamaru C, et al. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae—a multicenter retrospective cohort study. Endoscopy. 2007;39:779–83.
10. Yamashina T, Ishihara R, Nagai K, Matsuura N, Matsui F, Ito T, et al. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. Am J Gastroenterol. 2013;108:544–51.
11. Goda K, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, et al. Magnifying endoscopy with narrow band imaging for

predicting the invasion depth of superficial esophageal squamous cell carcinoma. Dis Esophagus. 2009;22:453–60.
12. Inoue H, Honda T, Yoshida T, et al. Ultra-high magnification endoscopy of the normal esophageal mucosa. Dig Endosc. 1996;8:134–8.
13. Inoue H, Honda T, Nagai K, et al. Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus. Dig Endosc. 1997;9:16–8.
14. Arima M, Tada M, Arima H. Evaluation of microvascular patterns of superficial esophageal cancers by magnifying endoscopy. Esophagus. 2005;2:191–7.
15. Oyama T, Inoue H, Arima M, Momma K, Omori T, Ishihara R, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. Esophagus. 2017;14:105–12.
16. Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, et al. Guidelines for diagnosis and treatment of carcinoma of esophagus April 2012 edited by the Japan Esophageal Society. Esophagus. 2015;12:1–30.
17. Eguchi T, Nakanishi Y, Shimoda T, Iwasaki M, Igaki H, Tachimori Y, et al. Histopathological criteria for additional treatment aft er endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. Mod Pathol. 2006;19:475–80.
18. Tajima Y, Yoshimura K, Kusano M, et al. Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. Cancer. 2000;88:1285–93.
19. Kim DU, Lee JH, Min BH, Shim SG, Chang DK, Kim YH, et al. Risk factors of lymph node metastasis in T1 esophageal squamous cell carcinoma. J Gastroenterol Hepatol. 2008;23:619–25.
20. Ishihara R, Aoi K, Matsuura N, et al. Significance of AVA for prediction of infiltration depth of esophageal cancer. Stomach Intest. 2014;49:204–11. (in Japanese with English abstract)
21. Hirasawa D, Fujita N, Maeda Y, et al. Clinical significance of AVA in diagnosing of invasion depth of superficial esophageal cancer. Stomach Intest. 2014;49:196–203. (in Japanese with English abstract)
22. Kurokawa Y, Muto M, Minashi K, Boku N, Fukuda H. A phase II trial of combined treatment of endoscopic mucosal resection and chemoradiotherapy for clinical stage I esophageal carcinoma: Japan Clinical Oncology Group Study JCOG0508. Jpn J Clin Oncol. 2009;39:686–9.
23. Muto M, Minashi K, Nihei K et al (2016) Efficacy of combined endoscopic resection and chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma (ESCC): a single-arm confirmatory study (JCOG0508). J Clin Oncol 34 (suppl):abstr 4013.