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World J Gastroenterol 2017 June 28; 23(24): 4317-4472



EDITORIAL

- 4317 Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C
Aggeletopoulou I, Konstantakis C, Manolakopoulos S, Triantos C
- 4324 Role of new endoscopic techniques in inflammatory bowel disease management: Has the change come?
Goran L, Negreanu L, Negreanu AM

REVIEW

- 4330 Implication of the Hedgehog pathway in hepatocellular carcinoma
Della Corte CM, Viscardi G, Papaccio F, Esposito G, Martini G, Ciardiello D, Martinelli E, Ciardiello F, Morgillo F

ORIGINAL ARTICLE

Basic Study

- 4341 Indole phytoalexin derivatives induce mitochondrialmediated apoptosis in human colorectal carcinoma cells
Tischlerova V, Kello M, Budovska M, Mojzis J
- 4354 Naringenin prevents experimental liver fibrosis by blocking TGF β -Smad3 and JNK-Smad3 pathways
Hernández-Aquino E, Zarco N, Casas-Grajales S, Ramos-Tovar E, Flores-Beltrán RE, Arauz J, Shibayama M, Favari L, Tsutsumi Y, Segovia J, Muriel P
- 4369 Intestinal anti-inflammatory activity of Ground Cherry (*Physalis angulata* L.) standardized CO₂ phytopharmaceutical preparation
Almeida Junior LD, Quaglio AEV, de Almeida Costa CAR, Di Stasi LC
- 4381 *Maytenus erythroxylon* Reissek (Celastraceae) ethanol extract presents antidiarrheal activity *via* antimotility and antisecretory mechanisms
Formiga RO, Quirino ZGM, Diniz MFFM, Marinho AF, Tavares JF, Batista LM
- 4390 Gastric cancer-derived heat shock protein-gp96 peptide complex enhances dendritic cell activation
Lu WW, Zhang H, Li YM, Ji F
- #### Retrospective Cohort Study
- 4399 Para-aortic node involvement is not an independent predictor of survival after resection for pancreatic cancer
Sperti C, Gruppo M, Blandamura S, Valmasoni M, Pozza G, Passuello N, Beltrame V, Moletta L

Retrospective Study

- 4407** Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: Retrospective, single-center study

Moon HS, Yun GY, Kim JS, Eun HS, Kang SH, Sung JK, Jeong HY, Song KS

- 4416** New magnifying endoscopic classification for superficial esophageal squamous cell carcinoma

Kim SJ, Kim GH, Lee MW, Jeon HK, Baek DH, Lee BE, Song GA

- 4422** Procalcitonin as a diagnostic marker to distinguish upper and lower gastrointestinal perforation

Gao Y, Yu KJ, Kang K, Liu HT, Zhang X, Huang R, Qu JD, Wang SC, Liu RJ, Liu YS, Wang HL

Observational Study

- 4428** Healthcare utilization and costs associated with gastroparesis

Wadhwa V, Mehta D, Jobanputra Y, Lopez R, Thota PN, Sanaka MR

- 4437** Variability of anti-human transglutaminase testing in celiac disease across Mediterranean countries

Smarrazzo A, Magazzù G, Ben-Hariz M, Legarda Tamara M, Velmishi V, Roma E, Kansu A, Mičetić-Turk D, Bravi E, Stellato P, Arcidiaco C, Greco L

- 4444** Appropriateness of the study of iron deficiency anemia prior to referral for small bowel evaluation at a tertiary center

Rodrigues JP, Pinho R, Silva J, Ponte A, Sousa M, Silva JC, Carvalho J

Randomized Clinical Trial

- 4454** Comparing reduced-dose sodium phosphate tablets to 2 L of polyethylene glycol: A randomized study

Ako S, Takemoto K, Yasutomi E, Sakaguchi C, Murakami M, Sunami T, Oka S, Kenta H, Okazaki N, Baba Y, Yamasaki Y, Asato T, Kawai D, Takenaka R, Tsugeno H, Hiraoka S, Kato J, Fujiki S

CASE REPORT

- 4462** Case of pediatric traditional serrated adenoma resected *via* endoscopic submucosal dissection

Kondo S, Mori H, Nishiyama N, Kondo T, Shimono R, Okada H, Kusaka T

- 4467** Pancreatic T/histiocyte-rich large B-cell lymphoma: A case report and review of literature

Zheng SM, Zhou DJ, Chen YH, Jiang R, Wang YX, Zhang Y, Xue HL, Wang HQ, Mou D, Zeng WZ

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Retrospective Study

New magnifying endoscopic classification for superficial esophageal squamous cell carcinoma

Su Jin Kim, Gwang Ha Kim, Moon Won Lee, Hye Kyung Jeon, Dong Hoon Baek, Bong Eun Lee, Geun Am Song

Su Jin Kim, Department of Internal Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan 50612, South Korea

Gwang Ha Kim, Moon Won Lee, Hye Kyung Jeon, Dong Hoon Baek, Bong Eun Lee, Geun Am Song, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan 49241, South Korea

Author contributions: Kim GH designed the research/study; Kim SJ, Lee MW and Jeon HK analyzed the data; Kim SJ and Kim GH performed the study; Baek DH and Lee BE collected the data; Song GA reviewed the study population data; Kim SJ and Kim GH wrote the paper; all authors read and approved the final manuscript.

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Correspondence to: Gwang Ha Kim, MD, PhD, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, 179, Gudeok-ro, Seo-Gu, Busan 49241, South Korea. doc0224@pusan.ac.kr
Telephone: +82-51-2407869
Fax: +82-51-2448180

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Abstract**AIM**

To assess the accuracy of a new magnifying endoscopy (ME) classification for predicting depth of invasion of superficial esophageal squamous cell carcinoma (SESCC).

METHODS

This study included a total of 70 lesions in 69 patients with SESCO who underwent ME with narrow-band imaging (ME-NBI) before resection from August 2010 to July 2016. Accuracy of ME-NBI for predicting depth of invasion of SESCO was analyzed by using a new ME classification proposed by the Japan Esophageal Society (JES), and interobserver agreement was assessed.

RESULTS

Overall accuracy of ME-NBI for estimating depth of invasion of SESCC was 78.6%. Sensitivity and specificity of type B1 for tumors limited to the epithelial layer (m1) or invading into the lamina propria (m2) were 71.4% and 100%, respectively. Sensitivity and specificity of type B2 for tumors invading into the muscularis mucosa (m3) or superficial submucosa ($\leq 200 \mu\text{m}$, sm1) were 94.4% and 73.1%, respectively, while those of type B3 for tumors invading into the deep submucosa ($> 200 \mu\text{m}$, sm2) were 75.0% and 97.8%, respectively. Interobserver agreement was excellent ($\kappa = 0.86$, 95%CI: 0.76-0.95).

CONCLUSION

The recently developed JES ME classification is useful for predicting depth of invasion of SESCC, with reliable interobserver agreement.

Key words: Narrow-band imaging; Esophageal cancer; Squamous cell carcinoma; Magnifying endoscopy

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Core tip: Recently, the Japan Esophageal Society proposed a new magnifying endoscopic classification for superficial esophageal squamous cell carcinoma (SESCC) based on two previous classifications. This classification is simple and useful for predicting depth of invasion of SESCC, with reliable interobserver agreement.

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INTRODUCTION

Depth of invasion of superficial esophageal squamous cell carcinoma (SESCC) is the most important factor in selecting therapeutic options. Risk of lymph node (LN) metastasis is mainly determined by depth of tumor invasion^[1-3]. Because tumors limited to the epithelial layer (m1) or invading into the lamina propria (m2) have very low risk of LN metastasis, endoscopic resection of such tumors is appropriate. However, incidence of LN metastasis increases to 26.5% for tumors invading into but not through the muscularis mucosa (m3) or invading into the superficial submucosa ($\leq 200 \mu\text{m}$, sm1), and to 30.4% to 41.9% for tumors invading into the deep submucosa ($> 200 \mu\text{m}$, sm2). Therefore, for these tumors, surgical resection with LN dissection or chemoradiation therapy is recommended^[4-6]. Because endoscopic resection has many advantages over esophagectomy, such as preservation of the

esophagus, maintenance of quality of life, and low post-treatment morbidity and mortality, Japanese guidelines for treatment of esophageal cancer suggest that m3 to sm1 cancers are a relative indication of endoscopic resection^[7,8].

Accuracy of endoscopic diagnosis with white-light imaging (WLI) is limited because of lack of standardized diagnostic criteria for depth of invasion of SESCC. Recent advancements in magnifying endoscopy (ME) have enabled visualization of mucosal details that cannot be seen with standard endoscopy^[9,10]. The combination of ME with narrow-band imaging (ME-NBI) can further enhance detailed observation of microcapillary patterns of the mucosa^[11]. ME-NBI enables examination of intrapapillary capillary loops (IPCLs) of the esophageal mucosa, which works as an indicator of tissue atypia in the squamous epithelium^[12,13]. To date, two different ME classifications, established by Inoue and Arima, have been reported to be useful for predicting depth of invasion of SESCC^[14,15]. However, in the clinical setting, both classifications are difficult to apply because of their complicated criteria. Recently, the Japan Esophageal Society (JES) proposed a new ME classification based on these two classifications, and performed a prospective multicenter study^[16]. It was demonstrated that the new ME classification is simple and useful for estimating depth of invasion of SESCC^[16]. However, interobserver agreement of this new classification was not evaluated in this previous study. Therefore, we aimed to investigate the accuracy of the new ME classification for predicting depth of invasion of SESCC, and to assess the interobserver agreement of this classification.

MATERIALS AND METHODS

Patient characteristics

We retrospectively analyzed a database of all patients with endoscopically suspected SESCC who underwent ME-NBI for pretreatment staging at Pusan National University Hospital (Busan, South Korea) or Pusan National University Yangsan Hospital (Yangsan, South Korea) from August 2010 to July 2016. Patients who previously received chemotherapy or radiotherapy or did not undergo endoscopic or surgical resection were excluded. A total of 70 lesions in 69 patients with pathologically confirmed SESCC were included in this study. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by the Institutional Review Board of Pusan National University Hospital.

ME-NBI

ME assessment was performed using a magnifying video endoscope (GIF-H260Z; Olympus, Tokyo, Japan) combined with NBI. A soft black hood (2-mm depth, MB-46; Olympus) was attached to the distal tip of the scope to maintain the distance from the lesion. ME-NBI was performed by two endoscopists (Kim GH and Kim SJ) who had experience with ME-NBI of the esophagus.

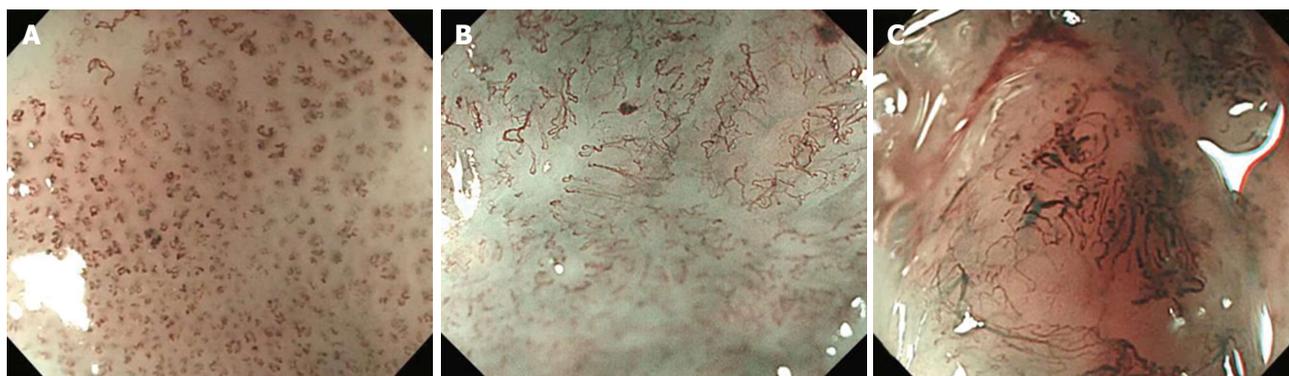


Figure 1 Magnifying endoscopy classification for esophageal squamous cell carcinoma. A: Type B1, abnormal microvessels with four characteristic findings (meandering, dilation, caliber change, and various shapes) and a conserved loop-like formation; B: Type B2, stretched and markedly elongated transformations without a loop-like formation; C: Type B3, highly dilated irregular vessels with a caliber that appears to be more than three times that of type B2 vessels.

Examinations were performed under intravenous conscious sedation (2-5 mg midazolam). After routine examination using WLI, ME-NBI assessment of the target area was performed to evaluate the microvessels.

Diagnostic criteria of the new JES classification are based on changes in IPCLs observed by ME-NBI^[16]. Type A tumors consist of normal or abnormal microvessels without severe irregularity that have three or fewer IPCL changes: meandering, dilation, caliber change, and various shapes; type A suggests normality, inflammation, and low-grade dysplasia. Type B tumors consist of abnormal microvessels with severe irregularity that have all four IPCL changes; type B suggests SCC and is classified into three subtypes^[16]. Type B1 tumors consist of abnormal microvessels with four characteristic findings and a conserved loop-like formation; type B1 is considered to correspond to m1 or m2 SESCO (Figure 1A). Type B2 tumors consist of stretched and markedly elongated transformations without a loop-like formation; type B2 is considered to correspond to m3 or sm1 SESCO (Figure 1B). Type B3 tumors consist of highly dilated irregular vessels with a caliber that appears to be more than three times that of type B2 vessels; type B3 is considered to correspond to sm2 or deeper SESCO (Figure 1C).

Two endoscopists reviewed the recorded series of ME-NBI images independently without any pathologic information. In discordant cases, microvessel types were adjudicated according to the agreement of the two endoscopists.

Clinicopathologic review

We performed endoscopic resection or esophagectomy within 2 to 4 wk following ME-NBI. Resected specimens were cut serially into 2-mm slices in parallel and embedded in paraffin, and then sectioned and stained with hematoxylin and eosin. Tumor location, macroscopic shape, tumor size, tumor differentiation, and depth of invasion were reviewed according to recommendations of the World Health Organization^[17]. Depth of invasion was classified as m1 to m2, m3 to sm1, or sm2 according to Japanese criteria^[7].

Statistical analyses

The χ^2 test or Fisher's exact test was used to assess the accuracy of ME-NBI in relation to clinicopathologic characteristics. The Student's *t* test was used for non-categorical variables. Interobserver agreement was assessed by kappa statistics using a weighted method. Kappa values were interpreted as follows: fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and excellent, > 0.81. Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS, Inc., Chicago, IL, United States), with *P* values of < 0.05 considered statistically significant.

RESULTS

Clinicopathologic characteristics of patients with SESCO

Clinicopathologic characteristics of patients with SESCO are summarized in Table 1. Patients comprised 62 men and 7 women with a mean age of 66 years (range, 47-81 years). Of the 70 tumors, 52 occurred in the mid-esophagus, 15 in the lower esophagus, and 3 in the upper esophagus. Macroscopically, 24 tumors were classified as elevated, 27 as flat, and 19 as depressed. Mean tumor size was 25 mm (range, 4-70 mm). Histopathologically, there were 43 mucosal cancers (m1 in 8, m2 in 20, m3 in 15) and 27 submucosal cancers (sm1 in 3, sm2 in 24). Thirty-two lesions were treated with endoscopic resection, while 38 were treated surgically. Characteristics of the lesions are summarized in Table 1.

Accuracy of ME-NBI to estimate the invasion depth

Overall accuracy of ME-NBI for estimating depth of invasion of SESCO was 78.6% (55 of 70 tumors), as listed in Table 2. Type B1 tumors, corresponding to m1 to m2 cancer, showed an accuracy of 88.6% (95%CI: 78.2%-94.6%) with a sensitivity and specificity of 71.4% (95%CI: 51.1%-86.0%) and 100% (95%CI: 89.6%-100%), respectively (Table 3). Type B2 tumors, corresponding to m3 to sm1 cancer, showed an accuracy of 78.6% (95%CI: 66.8%-87.1%) with a sensitivity

Table 1 Baseline characteristics of patients with superficial esophageal squamous cell carcinoma *n* (%)

Characteristics	
Male/female	62/7
Mean age, yr (range)	66 (47-81)
Location	
Upper esophagus	3 (4.3)
Mid-esophagus	52 (74.3)
Lower esophagus	15 (21.4)
Macroscopic shape	
Elevated	24 (34.3)
Flat	27 (38.6)
Depressed	19 (27.1)
Mean tumor size, mm (range)	25 (4-70)
Differentiation	
Well differentiated	34 (48.6)
Moderately differentiated	31 (44.3)
Poorly differentiated	5 (7.1)
Depth of invasion	
Mucosa	43 (61.4)
m1	8
m2	20
m3	15
Submucosa	27 (38.6)
sm1	3
sm2	24
Resection method	
Endoscopic resection	32 (45.7)
Surgical resection	38 (54.3)

and specificity of 94.4% (95%CI: 70.6%-99.7%) and 54.8% (95%CI: 36.3%-72.2%), respectively. Type B3 tumors, corresponding to sm2 cancer, showed an accuracy of 90.0% (95%CI: 79.9%-95.5%) with a sensitivity and specificity of 75.0% (95%CI: 52.9%-89.4%) and 97.8% (95%CI: 87.0%-99.9%), respectively. Depth of invasion was overestimated in 8 type B2 tumors (11.4%), underestimated in 6 type B2 tumors (8.6%), and underestimated in 1 type B3 tumor (5.3%).

Of 48 lesions < 3 cm in size, 20 were classified as B1 tumors, 19 as B2 tumors, and 10 as B3 tumors. Of 21 lesions \geq 3 cm in size, 12 were classified as B2 tumors and 9 as B3 tumors. The accuracy of ME-NBI for estimating depth of invasion of SESCC was lower in lesions \geq 3 cm than in lesions < 3 cm, but the difference was not statistically significant (61.9% vs 85.7%, $P = 0.053$).

Interobserver agreement

Kappa value of the JES classification for estimating depth of invasion of SESCC was excellent at 0.87 (95%CI: 0.77-0.97). Kappa values of the JES classification were 0.75 (95%CI: 0.48-1.02) for m1 to m2 cancer, 0.64 (95%CI: 0.05-1.33) for m3 to sm1 cancer, and 0.80 (95%CI: 0.53-1.07) for sm2 cancer.

DISCUSSION

Pretreatment prediction of depth of invasion of SESCC is very important in deciding treatment modalities. In the

Table 2 Comparison of pretreatment diagnosis by magnifying endoscopy with narrow-band imaging and histopathology of superficial esophageal squamous cell carcinoma

ME-NBI	No. of cases	Histopathology, <i>n</i>		
		m1-m2	m3-sm1	sm2
B1	20	20	0	0
B2	31	8	17	6
B3	19	0	1	18

ME-NBI: Magnifying endoscopy with narrow-band imaging.

present study, we used the new ME-NBI classification recently developed by the JES for predicting depth of invasion of SESCC. As a result, overall accuracy was 78.6%, and interobserver agreement was excellent.

Because the JES classification is simplified compared with two previous classifications (developed by Inoue and Arima, respectively), there is a possibility that the accuracy for predicting depth of invasion will decrease. However, in the present study, accuracy of the JES classification was 78.6%, which is similar to the results of our previous study using Inoue's classification^[18]. Recently, a prospective multicenter study using the JES classification in Japan also demonstrated a high overall accuracy rate (90.5%) for type B vessels^[16]. Although the accuracy rate in that study was higher than in our present results, there were limitations including high proportion of m1 to m2 cancers (77.3%), and changes in IPCLs were analyzed by participating endoscopists without a central review. In the present study, proportions of m1 to m2, m3 to sm1, and sm2 cancers were evenly distributed (40.0%, 25.7% and 34.3%, respectively), and changes in IPCLs were adjudicated according to the agreement of two endoscopists in discordant cases.

Although the sensitivities of type B1 and type B3 tumors were suboptimal (71.4% and 75.0%, respectively), the specificities were 100% and 97.8%, respectively. Because the recommended treatment modalities for type B1 and type B3 tumors are endoscopic resection and surgical resection, respectively, type B1 or type B3 tumors can guide the physician to decide the optimal treatment. However, the specificity of type B2 tumor was 73.1%; 8 m1 to m2 cancers were overestimated to m3 to sm1 cancers, and 6 sm2 cancers were underestimated to m3 to sm1 cancers. Therefore, compared with type B1 and type B3 tumors, type B2 tumors showed an insufficiency for estimating depth of invasion. It has been reported that m3 to sm1 cancers without lymphovascular invasion have very low risk of LN metastasis^[3,19], and, as such, are potential candidates for curative treatment by endoscopic resection. Thus, because it is important to detect underestimated sm2 cancers in type B2 tumors, additional use of endoscopic ultrasonography or another diagnostic modality to estimate depth of invasion may be helpful^[18].

In the present study, interobserver agreement was excellent at 0.87, which is slightly high compared with

Table 3 Accuracy, sensitivity, specificity, and positive and negative predictive values of magnifying endoscopy with narrow-band imaging for predicting depth of invasion of superficial esophageal squamous cell carcinoma (%)

ME-NBI	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
B1	88.6 (78.2-94.6)	71.4 (51.1-86.0)	100 (89.6-100)	100 (80.0-100)	84.0 (70.3-92.4)
B2	78.6 (66.8-87.1)	94.4 (70.6-99.7)	73.1 (58.7-84.0)	54.8 (36.3-72.2)	97.4 (84.9-99.9)
B3	90.0 (79.9-95.5)	75.0 (52.9-89.4)	97.8 (87.0-99.9)	94.7 (71.9-99.7)	88.2 (75.4-95.1)

ME-NBI: Magnifying endoscopy with narrow-band imaging; PPV: Positive predictive value; NPV: Negative predictive value.

that in a previous study using Inoue's classification ($\kappa = 0.61, 0.64$ and 0.71)^[14]. This result suggests that this simplified classification is reliable among observers. However, the kappa value was lowest ($\kappa = 0.64$) for type B2 tumors. Therefore, efforts to improve interobserver agreement *via* modification of the definition of type B2 or use of computer-aided analysis should be considered.

This study had several limitations. First, this was a retrospective study that analyzed ME-NBI images using the JES classification. Thus, there might have been potential bias when reviewing the ME-NBI images. During ME-NBI, we tried to take at least 4 images to show the characteristic features associated with depth of invasion, with hopes that this would compensate, to some degree, the limitation of this retrospective study. Second, both endoscopists involved in this study are experts. A further study including non-experts is needed to apply our results to general practice.

In conclusion, the recently developed JES classification is useful for predicting depth of invasion of SESCC, with reliable results between observers. However, its accuracy decreases for type B2 tumors. Therefore, establishment of a revised classification including modification of the definition of type B2 will be considered, and prospective multi-center studies are needed to validate our results.

COMMENTS

Background

In order to choose the appropriate management strategy for superficial esophageal squamous cell carcinoma (SESCC), accurate assessment of depth of tumor invasion is important. Recently, the Japan Esophageal Society (JES) proposed a new magnifying endoscopy (ME) classification for estimating depth of tumor invasion based on two previous classifications developed by Inoue and Arima.

Research frontiers

Since the new ME classification was recently proposed by the JES, there have been few studies to evaluate its utility. Furthermore, interobserver agreement of this classification has not been evaluated.

Innovations and breakthroughs

In this study, the JES classification was useful for estimating depth of invasion of SESCC. Overall accuracy was 78.6%, and interobserver agreement was excellent at 0.87. Type B1 tumors showed an accuracy of 88.6% with a sensitivity and specificity of 71.4% and 100%, respectively. Type B2 tumors showed an accuracy of 78.6% with a sensitivity and specificity of 94.4% and 54.8%, respectively. Type B3 tumors showed an accuracy of 90.0% with a sensitivity and specificity of 75.0% and 97.8%, respectively.

Applications

The JES classification is useful for predicting depth of invasion of SESCC, with reliable results between observers. This classification was particularly useful for selecting optimal treatment for type B1 and type B3 tumors.

Terminology

Diagnostic criteria of the new JES classification are based on changes in intrapapillary capillary loops (IPCLs) of the esophageal mucosa observed by ME with narrow-band imaging. Type B tumors consist of abnormal microvessels with severe irregularity that have all four IPCL changes (meandering, dilation, caliber change, and various shapes).

Peer-review

The work has great interest, due to the importance of the theme.

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