Classification of nuclear morphology in endocytoscopy of colorectal neoplasms

Toyoki Kudo, MD, PhD,[1] Shin-ei Kudo, MD, PhD,[1] Yuichi Mori, MD, PhD,[1] Kunihiko Wakamura, MD, PhD,[1] Masashi Misawa, MD, PhD,[1] Takemasa Hayashi, MD, PhD,[1] Hideyuki Miyachi, MD, PhD,[1] Atsushi Katagiri, MD, PhD,[1] Fumio Ishida, MD, PhD,[1] Haruhiro Inoue, MD, PhD[2]

Yokohama, Japan

Background and Aims: We investigated endocytoscopy (EC) findings that were considered risk factors for colorectal neoplasms and determined whether they could be used as new indices to identify carcinomas with massive submucosal invasion (SM-m) or worse outcomes.

Methods: We performed a multivariate analysis of 8 factors on EC images to determine whether they were associated with SM-m or worse. Based on the results, we divided the EC3a category of the EC classification into low grade or high grade and investigated the diagnostic accuracy of this subclassification. In addition, we compared the diagnostic ability of EC for SM-m with that of other modalities (narrow-band imaging and pit pattern).

Results: The multivariate analysis indicated that unclear glandular lumens (ULs), high degree of nuclear enlargement (HNE), and multilayered nuclei (MNs) were the most useful factors for the diagnosis of SM-m or worse. The odds ratios for these factors were 12.47, 12.29, and 10.48, respectively ($P < .001$). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratio for the diagnostic accuracy of the EC3a subclassification were 88.9%, 91.3%, 75.0%, 96.6%, 90.8%, and 10.2, respectively ($P < .001$). The sensitivity, negative predictive value, and accuracy of EC were significantly higher than those of narrow-band imaging and pit pattern.

Conclusions: From the EC findings, the presence of ULs, HNE, and MNs are important risk factors for SM-m or worse outcomes. Furthermore, the EC3a subclassification taking these findings into consideration could be effective for the diagnosis of SM-m or worse. (Clinical trial registration number: UMIN 000014906.) (Gastrointest Endosc 2017;85:628-38.)

The development of endoscopy with ultra-high magnification, known as endocytoscopy (EC), allows in vivo histopathologic diagnoses such as identification of cell nuclei. The usefulness of EC in making these diagnoses has been reported in numerous studies.[1-3] The recently developed integrated-type EC allows histopathologic diagnoses to be performed under instant magnification of 380× to 450×.[4-6] It was also reported that the EC classification of qualitative and invasion depth diagnoses of colorectal lesions led to good results.[5-7]

The use of endoscopic diagnosis to differentiate between carcinomas with scanty submucosal invasion (SM-s) and

Abbreviations: EC, endocytoscopy; HNE, high degree of nuclear enlargement; MCE, magnifying chromoendoscopy; MNs, multilayered nuclei; NBI-ME, narrow-band imaging with magnifying endoscopy; NPV, negative predictive value; PPV, positive predictive value; SM-s, carcinoma with scanty submucosal invasion; SM-m, carcinoma with massive submucosal invasion; ULs, unclear glandular lumens.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

Use your mobile device to scan this QR code and watch the author interview. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2016.10.039

Received March 15, 2016. Accepted October 31, 2016.

Current affiliations: Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama, Japan (1), Digestive Disease Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan (2).

Reprint requests: Toyoki Kudo, MD, PhD, Digestive Disease Center, Showa University Yokohama Northern Hospital, 35-1 Chigasaki-chuo, Tsuzuki, Yokohama 224-8503, Japan.

If you would like to chat with an author of this article, you may contact Dr Kudo at s6027@nms.ac.jp.

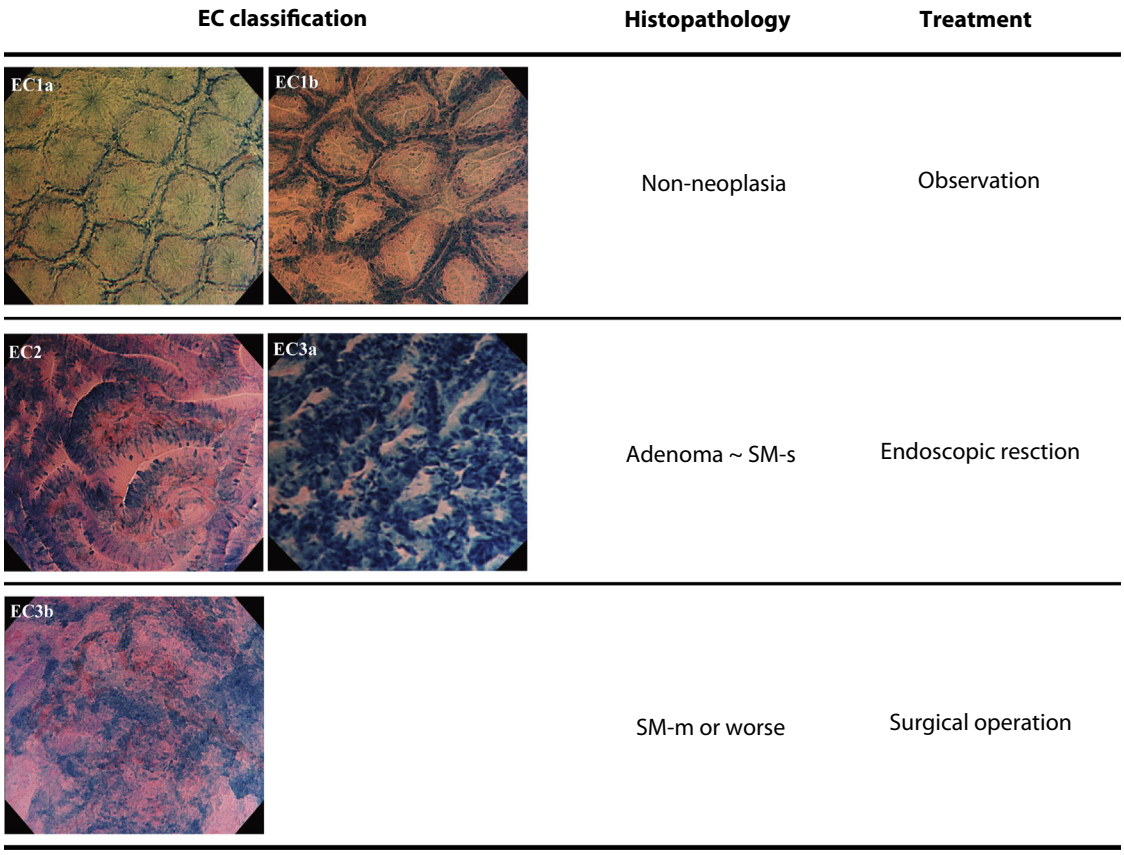

Figure 1. Description of the EC classification, predicted histopathology, and resultant treatment method. EC classification: EC1a, small round lumens with small fusiform nuclei of uniform size; EC1b, serrated lumens with agglomeration of small granular nuclei; EC2, slit-like lumens with slightly swollen fusiform nuclei or roundish nuclei; EC3a, irregular lumens with agglomeration of moderately swollen nuclei stained with methylene blue; and EC3b, unclear gland formation and agglomeration of highly swollen and irregular nuclei. The EC classification levels were considered to correspond to the following invasion depths: EC1a or EC1b, non-neoplastic; EC2, adenoma to M; EC3a, M to SM-s; and EC3b, SM-m or worse. However, the figure illustrates that SM-m lesions are sometimes present when EC3a findings are confirmed. *M*, carcinoma with intramucosal invasion; *SM-m*, carcinoma with massive submucosal invasion; *EC*, endocytoscopy.

massive submucosal invasion (SM-m) is important for subsequent treatment strategies.[8,9] This is because lesions up to SM-s have almost no risk of lymph node metastasis, whereas SM-m lesions have a 10% to 15% risk of lymph node metastasis.[10-12] It was also reported that favorable long-term outcomes were obtained in patients with low-risk SM invasive carcinomas, such as SM-s, and those who underwent endoscopic resection alone.[13-15] This is actually the basic rationale for applying EC, as well as other modalities such as magnifying chromoendoscopy (MCE) and magnifying endoscopy with narrow-band imaging (NBI-ME), to the diagnosis of colorectal neoplasms.

One of the problems with the currently used EC classification is its inability to differentiate between SM-s and SM-m (Fig. 1). We previously reported that the EC3b category was a very important and accurate finding suggestive of SM-m or deeper invasion and exhibited sensitivity and specificity of 83.1% and 99.1%, respectively.[7] The characteristics of the EC3b category, with findings of unclear gland lumens and agglomeration of distorted nuclei, may indirectly reflect high cell density or stromal reactions, which are often observed in fixed pathologic specimens of SM-m or deeper invasion. In addition, we reported that the EC3a category indicates lesions up to SM-s but has lower accuracy than EC3b because considerably more SM-m would be diagnosed with EC3a.[16] Furthermore, in protruding lesions the diagnostic accuracy of EC3b was 87.0% (80.6%-93.2%), whereas that of EC3a was only 51.2% (42.2%-60.1%). Consequently, if EC3a findings were to be considered a good index for lesions up to SM-s, this would make it difficult to differentiate between SM-s and SM-m. Therefore, we believe there is a need to reconsider EC3a findings that can differentiate between SM-s and SM-m.

In the present study we investigated whether factors related to EC findings could be used to create a new SM-m index to improve the diagnostic accuracy of EC3a. In addition, we retrospectively compared the diagnostic performance of EC with that of other modalities (NBI-ME and MCE) for evaluating the invasion depth of colorectal neoplasms.

METHODS

Patients and lesions

This was a retrospective study of 668 neoplastic lesions. The lesions were observable using EC and other modalities