学 位 論 文 の 要 旨

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学 位 論 文 名　　　　Simplified Classification of Capillary Pattern in Barrett Esophagus Using Magnifying Endoscopy With Narrow Band Imaging: Implications for Malignant Potential and Interobserver Agreement

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論 文 内 容 の 要 旨

INTRODUCTION

Endoscopic surveillance of Barrett's esophagus (BE) aims to reduce morbidity and mortality by early detection and endoscopic therapy of dysplasia or esophageal adenocarcinoma. Magnifying endoscopy with narrow band imaging (ME-NBI), which enables detailed inspection of mucosal morphology without the use of staining agents, is one of the most promising tools for accurate endoscopic diagnosis corresponding to histology findings. To date, several classification systems have been developed for evaluation of BE using ME-NBI based on the detailed characterization of both mucosal and capillary (CP) pattern, and the usefulness of these classifications has been reported. However, that has not been shown in subsequent validation studies mainly due to their complexity. Therefore, none are widely used in clinical settings and a standard protocol remains to be established. The aim of this study was to establish a simplified

classification of mucosal morphology focusing only on CP for detecting specialized intestinal metaplasia (SIM) and dysplasia, as well as markers related to malignant potential in BE patients.

MATERIALS AND METHODS

We enrolled 108 consecutive adult BE patients who underwent endoscopic examinations between July 2011 and December 2012. Patients who did not have an indication for biopsy were excluded. The protocol of this study was approved by the ethics committee of Shimane University School of Medicine. Written informed consent was obtained from all patients.

All endoscopic examinations were performed using an ME-NBI endoscope. After insertion of the endoscope, recognized BE was observed in fully zoomed images to evaluate CP. Then, the pit pattern of the same area was observed without magnification after spraying of crystal violet (CV). Finally, biopsy specimens were obtained from the observed lesions to confirm the histology.

CP was divided into the following categories; type I, uniform branched or vine-like pattern with a clear shape that is able to be traced smoothly, and type II, coiled or spiral pattern with a non-uniform shape that can not be traced sufficiently and with increased vascularity. In addition, pit patterns shown by CV chromoendoscopy were classified into closed and open type, according to the previously reported classification.

For each biopsy specimen, dysplasia and SIM were diagnosed with hematoxylin and eosin staining. Moreover, mucin phenotype, and the expression of CDX2, COX-2, CD34, PCNA were investigated immunohistochemically as representative markers related to malignant potential.

Percentage of microvascular density and interobserver agreement for observed endoscopic images were evaluated to confirm the objectivity of the CP classification. Microvascular density, defined as the percentage area occupied by a vascular bed within the whole area was calculated using image analysis software. Interobserver agreement for CP classification was determined using Kappa statistics. Sixty-five images taken by ME-NBI were evaluated and classified into type I and type II by 8 raters including 4 experts and 4 non-experts with ME-NBI.

RESULTS AND DISCUSSION

Of the 130 analyzed BE lesions from 91 patients, 84 were shown to be type I and 46 as type II by CP classification, while 90 were classified as closed type pit pattern and 40 as open

type by CV chromoendoscopy findings. Eight (9.5%) of the type I and 32 (69.6%) of the type II cases were open type pit pattern, indicating that type II CP was more closely associated with the open type pit pattern, which occurs more frequently with dysplastic Barrett's lesions.

As for histopathological findings, all areas with dysplasia (n=6) had type II CP (P=0.002), while 36 (42.9%) with type I and 28 (60.9%) with type II lesions had SIM (P=0.049). However, not all areas with dysplasia could be identified by mucosal pit pattern. In addition, the expression of COX-2, CDX2, CD34 and PCNA index were significantly higher in type II than in type I, while open type pit pattern had significant high grade expression of CD34 and PCNA index. These results suggested that CP classification is more sensitive to detect dysplastic areas in BE than mucosal pit pattern classification.

Microvascular density and grade of CD34 expression were greater in areas with type II CP than those with type I. This observation suggests that subjectively diagnosed areas with type II CP have high microvascular density that can be determined in an objective manner.

Elevated expression rates of COX-2, CD34, and PCNA suggest the presence of inflammation, angiogenesis, and high cellular proliferation. Multivariate analysis showed that type II CP was the best predictor for presence of dysplasia (OR 11.14), CD34 expression (OR 3.60), and PCNA (OR 3.29). Therefore, type II CP might indicate not only dysplasia, but also mucosa with a high malignant potential.

The κ-value of the CP classification was substantial for all raters (κ=0.66). There were no significant differences between experts and non-experts (κ=0.60 and 0.68, respectively), suggesting that this classification is readily available for clinical practice, irrespective of endoscopic expertise.

CONCLUSION

We present a simplified CP classification based on observation by ME-NBI. We found this system to be an adequate method for determining microvascular density and CD34 expression, which were useful as predictors for the presence of dysplasia, as well as expressions of COX-2 and PCNA. The strategy of using this system may overcome the shortcomings of previous ME-NBI classifications and lead to early diagnosis of dysplasia with high diagnostic concordance.