

# 学位論文の要旨

氏名 宇野 吾一

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

発表雑誌名 Medicine (in press)  
(巻, 初頁～終頁, 年)

著者名 Goichi Uno, Norihisa Ishimura, Yasumasa Tada, Yuji Tamagawa,  
Takafumi Yuki, Takashi Matsushita, Shunji Ishihara, Yuji Amano,  
Riruke Maruyama, Yoshikazu Kinoshita

## 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  $\kappa$ -value of the CP classification was substantial for all raters ( $\kappa=0.66$ ). There were no significant differences between experts and non-experts ( $\kappa=0.60$  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.

論文審査及び最終試験又は学力の確認の結果の要旨

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学位論文審査委員	主査	京 哲	   
	副査	並河 徹	
	副査	磯部 威	

論文審査の結果の要旨

Barrett腺癌は食道癌の中で最も増加率の高い癌として近年注目されている。申請者らはNarrow band imaging (NBI) という特殊光を用いた拡大内視鏡観察を行い、簡便で汎用性の高いBarrett食道粘膜の分類法の構築を目的に研究を行った。Barrett食道を有する患者を対象としてNBI拡大内視鏡観察を行い、粘膜血管の密度と形態に基づいたCapillary pattern (CP) 新分類を提唱し、粘膜をType IとType IIに分類した。この新分類法と従来からの色素内視鏡検査で判定される粘膜表層構造に基づいたPit pattern分類との相関性、さらに発癌に関連するとされる各種因子の発現との関係、血管密度、CP分類の検者間一致率を検討した。従来法との比較ではCP Type IIにおいてBarrett腺癌やBarrett異形上皮で認められるpatternが多くみられ、また生検組織の免疫染色において、腸上皮化生、炎症、血管新生、細胞増殖のマーカー（それぞれCDX2、COX-2、CD34、PCNA）の染色性が高値であった。さらに異型病変は全てCP Type IIに分類された。多変量解析ではCP Type IIが異型病変の検出、CD34高値、PCNA高値を予測しうる因子として同定された。CP分類の検者間一致率もこれまで報告されている粘膜表層構造に重点をおいた分類法よりもκ値が高く、優れているものと考えられた。これらの結果はBarrett食道において悪性度の高い粘膜を検出するのに新たに作成された内視鏡分類であるCP分類が有用であることを示しており、またその簡便性、汎用性を考慮すれば実地臨床への応用性が高く、十分に学位論文に値すると考えられた。

最終試験又は学力の確認の結果の要旨

申請者は、Narrow band imaging (NBI) という特殊光を用いた拡大内視鏡観察におけるBarrett食道粘膜の新分類法を提唱した。この分類法の特徴は従来の粘膜表層構造による分類とは異なり、血管密度とその形態に基づいた分類である。新分類法として血管構造に視点をあてた本論文はユニークであるが、本分類法の提唱により異型病変または悪性ポテンシャルを有する病変の選別能が向上し、また血管構造による分類は簡便で検者間一致率が高く、汎用性が高いこともアピールされた。したがって実地臨床への応用性に優れ、学位論文としての価値は高い。また申請者は審査員からの多岐にわたる質問にも全ての確に答え、十分に学位授与に値すると判断した。 (主査 京哲)

申請者は、narrow band imaging を用いた内視鏡観察技術を応用し、バレット癌につながる病変をより効率よく簡便に同定するための手法として血管パターンを観察が有用であることを示した。このことは今後のバレット癌診断技術の進展に資する臨床的に優れた成果である。背景の知識も豊富であり質疑応答も適確であったことから、学位授与に値すると判断した。 (副査 並河徹)

申請者は、日本でも増加傾向にあるバレット食道内に存在する癌化が予想される悪性度の高い粘膜を効率よく発見するために、narrow band imaging を用いた新しい内視鏡的血管パターン分類を構築した。この研究はバレット癌の早期診断に有用と考えられ、臨床的に優れた成果である。背景の知識も豊富であり質疑応答も適確であったことから、学位授与に値すると判断した。 (副査 磯部威)

(備考) 要旨は、それぞれ400字程度とする。