学 位 論 文 の 要 旨

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学　位　論　文　名　Magnification Endoscopy With Acetic Acid Enhancement and a Narrow-Band Imaging System for Pit Pattern Diagnosis of Colorectal Neoplasms

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論 文 内 容 の 要 旨

INTRODUCTION

Pit pattern (PP) analysis of colorectal neoplasms using magnification chromoendoscopy with crystal violet (CV-MCE) is useful for predicting histologic features, but it is time-consuming. Capillary pattern analysis via magnification endoscopy with narrow-band imaging (NBIME) is also believed to be useful, but its diagnostic accuracy may be inferior to that of CV-MCE. NBIME with acetic acid enhancement (A-NBIME) is effective for rapid detection of gastric mucosal microstructures. We performed a prospective study to compare the diagnostic reliability and feasibility of A-NBIME and CV-MCE in PP diagnosis of colorectal neoplasms.

MATERIALS AND METHODS

A total of 219 patients examined by colonoscopy at Tottori Municipal Hospital were enrolled in this study. The analysis consisted of three protocols (Studies 1, 2, and 3) approved by the medical ethics committee of the hospital, and informed consent was obtained from all participants.

Study 1: Diagnostic concordance of PP between A-NBIME and CV-MCE

A total of 51 patients with 56 colorectal lesions (7 hyperplasias, 28 adenomas, and 21 adenocarcinomas) were enrolled. PPs were photographed by A-NBIME and CV-MCE. A single expert endoscopist classified the PPs of CV-MCE images into eight types: type I, II, IIIs, IIIL, IV, VI-L, VI-H, and VN, according to the previously reported classifications. Lesions with a type I,

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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論文審査の結果の要旨

近年，早期大腸癌に対する内視鏡治療が積極的に行われているが，適応症例を的確に判断するためには組織型と壁深達度を含めた術前評価が重要となる。申請者は、特殊光内視鏡検査 Narrow-Band Imaging (NBI) と1.5%酢酸を併用した拡大内視鏡検査(A-NBIME)が，大腸ポリープの腺管開口部の形態(pit pattern)を迅速に視覚化し，従来の gold standard である crystal violet 染色を用いた色素拡大内視鏡検査(CV-MCE) より簡便かつ迅速に評価を行うことが可能で，pit pattern 診断能と病理組織像予測能も CV-MCE と同等であることを示した。研究は 3 つの prospective study で構成されている。Study1 では，大腸ポリープ 56 病変の同一部位を A-NBIME と CV-MCE で撮影し，両検査法で撮影された写真を 3 名の評価者が各々7 区分の pit pattern に分類した。その結果，各検査法の評価者間 pit pattern 診断一致率(κ 値)は A-NBIME 0.71、CV-MCE 0.80 で共に良好な再現性を示した。評価者 3 人それぞれの検査方法間の 7 区分 pit pattern 診断一致率は 0.79/0.80/0.74 といずれも良好で，A-NBIME と CV-MCE で視認される pit pattern の同一性が示された。Study2 では，大腸ポリープ 202 病変の A-NBIME による pit pattern と病理組織像の関連が検討された。A-NBIME で描出された pit pattern は病理組織像（過形成・腺腫・腺癌）および壁深達度との有意な関連性を示し，その病理組織像予測能は，既に有用性が示されている CV-MCE と同等であった。Study3 では，大腸ポリープを有する 100 人を A-NBIME 群と CV-MCE 群に 50 人ずつ無作為に割りつけ，1 病変の検査時間と pit pattern 視認率が比較された。1 病変の検査時間は A-NBIME 群が CV-MCE 群より有意に短く(中央値: 31 秒 vs. 81 秒)，pit pattern 視認率に差はないことが明らかとなった(98.9% vs. 98.3%)。本研究は，酢酸と特殊光を利用した拡大内視鏡検査が大腸ポリープの診断と治療に有用であることを明らかにするとともに，今後の大腸癌の内視鏡スクリーニング法にも重要な示唆を与える有益な研究であると考え，博士（医学）の学位授与に値すると判断した。

最終試験又は学力の確認の結果の要旨

申請者は，特殊光内視鏡検査と 1.5%酢酸を併用した拡大内視鏡検査が，大腸ポリープの腺管開口部の形態(pit pattern)を迅速に視覚化し，従来法より簡便かつ迅速に評価を行うことが可能で，診断能も同等であることを示した。学位審査における質疑応答も的確で，関連分野の知識も豊富であり，学位授与に値すると判断した。

（主査：田島 義証）

申請者は，大腸内視鏡検査における A-NBIME の pit pattern 視認性と手技の簡便性に着目し，これが現在主流の CV-MCE と同等の病理組織像予測能を持ち，迅速性においては優れていることを証明した。本研究成果は日常診療に役立つ有用な結果であり，学位審査における質疑応答も的確であり，学位授与に値すると判断した。

（副査：丸山 理留敬）

申請者は，大腸内視鏡検査において，画像強調内視鏡操作を行う際に，酢酸を併用する検査法が，従来の色素を用いた検査法と比較し，簡便かつ迅速で組織予測診断能が同等であることを明らかにした。公開審査における質疑応答も的確で背景，関連する分野の知識も充分であり，学位授与に値すると判断した。

（副査：礒部 威）

（備考） 要旨は、それぞれ４００字程度とする。

non-neoplastic standardized pattern were excluded from this study. Eight lesions each with type II, IIIs, IIIL, IV, VI-L, VI-H, and VN PPs diagnosed by CV-MCE (total of 56 cases) were enrolled. CV-MCE and A-NBIME images were independently reviewed by three expert endoscopists. The PPs of A-NBIME images were diagnosed principally according to that of CV-MCE images, but type V PPs were originally subclassified by our criteria via the slight difference of the appearance of PP. Kappa statistics with 95% confidence intervals were calculated as an interobserver agreement of PP diagnosis among reviewers for each modality, and intraobserver diagnostic agreement between modalities was also analyzed for each reviewer.

Study 2: Ability of PP recognized by A-NBIME to predict histological features

A total of 116 consecutive patients with colorectal lesions were enrolled and PPs were photographed by A-NBIME. Three expert endoscopists independently reviewed endoscopic images and diagnosed the PPs of the legions. In addition, the kappa statistics with 95% confidence intervals were calculated as a measure of interobserver agreement of PP diagnosis among reviewers. When two or all three reviewers agreed upon PP, it was diagnosed as the inherent PP of the lesion. However, when the lesion was diagnosed as different patterns by all reviewers, it was excluded as a nonconsensus lesion. The correlation between PPs visualized by A-NBIME and histologic features was analyzed.

Study 3: Feasibility of A-NBIME and CV-MCE

A total of 100 patients with colorectal polyps were enrolled and alternately allocated to the A-NBIME and CV-MCE groups. For the A-NBIME group, acetic acid solution was injected directly from the forceps channel. For the CV-MCE group, a dedicated tube was inserted from the forceps channel to allow dripping of the crystal violet solution onto the lesions, after which the lesions were washed out to eliminate excess stain solution. The procedure time to diagnosis of PPs and the visible ratio of PPs were compared between groups.

RESULTS AND DISCUSSION

Study 1:

The kappa values for interobserver agreement for A-NBIME and CV-MCE were 0.71 (0.66-0.75) and 0.80 (0.75-0.85), respectively. Those for intraobserver agreement between modalities for each reviewer were 0.79 (0.70-0.88), 0.80 (0.71-0.90), and 0.74 (0.67-0.82), respectively.

Study 2:

Overall, 202 lesions, including 27 hyperplasias, 144 adenomas, and 31 adenocarcinomas, were analyzed. PP diagnosis was agreed upon by two or all three reviewers for all lesions, and the kappa value for interobserver agreement was 0.69 (0.65-0.73). Hyperplasias, adenomas, and

adenocarcinomas were statistically related to type II, type IIIs/IIIL/IV, and type V, respectively ($P<0.01$). Mucosal or slightly invasive submucosal adenocarcinoma and massively invasive submucosal adenocarcinoma (submucosal invasion depth > 1 mm) were statistically related to type VI-L and type VI-H/VN, respectively ($P<0.01$).

Study 3:

In total, 97 lesions in the A-NBIME group and 117 lesions in the CV-MCE group were analyzed. No statistical differences in macroscopic type, size, location, or histopathology of lesions were observed between groups. The median (range) procedure time was 31 (10-218) seconds with A-NBIME and 81 (43-349) seconds with CV-MCE; this difference was statistically significant ($P<0.01$). The visible ratio of PPs was 98.9% (96/97) with A-NBIME and 98.3% (115/117) with CV-MCE ($P=0.926$).

A-NBIME showed good interobserver diagnostic agreement both in Studies 1 and 2, suggestive of good applicability of this modality for PP diagnosis. In addition, the kappa value of the intraobserver agreement for PP diagnosis between A-NBIME and CV-MCE was statistically good for each reviewer, suggesting that PPs are similarly observed between the two modalities. Moreover, a good relationship between PP and histologic type was found by A-NBIME as previously proven by CV-MCE, which is suggestive of actual applicability of A-NBIME in the treatment of colorectal neoplasms. Above all, the primary advantage of A-NBIME was that this procedure was technically simpler and consequently less time-consuming than CV-MCE.

The kappa value of interobserver agreement for PP diagnosis by A-NBIME was good but somewhat smaller than that by CV-MCE in Study 1, just below statistical significance. We consider that the slight difference of PP appearance between modalities might have confused the reviewers who were well versed in CV-MCE but inexperienced in A-NBIME for PP diagnosis. Acetic acid is a hydrophilic carboxylic organic acid with a small molecular weight, and crystal violet is a hydrophobic dye with a large molecular weight. Acetic acid easily infiltrates crypts filled with mucus and quickly discolors the intervening region between crypts and the marginal crypt epithelium, so that pits are visualized as hollows of crypts in themselves. In contrast, crystal violet gradually infiltrates the crypts via its large molecular weight and hydrophobicity, and stains the intervening region, so that pits are visualized as unstained areas including crypts and marginal crypt epithelium. Therefore, the pits visualized by A-NBIME may be slightly smaller and more three-dimensional than those visualized by CV-MCE.

CONCLUSION

A-NBIME shows good interobserver agreement for PP diagnosis and good predictability of the histological features of colorectal lesions despite its simplicity relative to CV-MCE, suggesting that A-NBIME is a useful and feasible tool for PP diagnosis of colorectal neoplasms.