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論文内容の要旨

1 研究目的

Some early gastric cancers surrounded by atrophy and intestinal metaplasia show subtle morphological or color features and cannot be detected by white light imaging (WLI) alone, resulting in possible invasive surgery. It is essential to detect early gastric cancers as small as possible without missing in screening, enabling endoscopic treatments such as endoscopic submucosal dissection (ESD), which allow patients to live cancer-free with minimally invasive treatment.

Recent development in Image Enhanced Endoscopy (IEE), the linked color imaging (LCI) has enabled screening a large lumen such as the stomach with enough illumination. It provides high color contrast between various lesions and surrounding mucosa. Several articles described that LCI had an advantage in improving visibility for gastrointestinal malignant lesions with a higher score than WLI, supported by high color differences between the lesion and surrounding mucosa. However, the small number of early gastric cancers recruited in previous studies were not enough to demonstrate the effect of LCI on lesions with various histology, depth, and size, which determine an indication of endoscopic therapy. Also, there is no report of what number of obscure cancers nearly invisible by WLI can be easily visualized by LCI.

Moreover, the significance of lower resolution ultrathin endoscopy with LCI in the detection of EGC is unknown. Ultrathin endoscopy is used via the nasal route in routine upper gastrointestinal endoscopy due to minimal pain and gag reflex during the examination compared with standard endoscopy. It is necessary to clarify which is more important during the short time of screening endoscopy, high-resolution images, or high color contrast using LCI.

The main aim of thesis was to clarify the clinical significance of LCI and its superiority over conventional WLI in the early detection of gastric cancer. For this purpose, we have conducted two separate studies with different designs

2 研究方法

Study I. A total of 665 malignant gastric lesions resected using endoscopic submucosal dissection between January 2015 and April 2018 were retrospectively reviewed. Obviously detectable lesions were not included in the main analysis when determining the target lesion. WLI/LCI images of 508 endoscopically obscure malignant lesions were included in the final analysis and evaluated by three non-expert and three expert endoscopists using visibility scores for detection and extent.

Study II. This is a retrospective analysis with prospectively collected video including consecutive 166 cases of EGC or gastric atrophy alone. Ninety seconds of screening video was collected using standard and ultrathin endoscopes with both WLI and LCI for each case. Three expert endoscopists assessed each video and the sensitivity of detecting EGC calculated. Color difference calculations were performed.

3 研究成果

Study I. The detection visibility scores using LCI were significantly higher than those using WLI regardless of lesion characteristics including location, size, histological type, depth of invasion, and H. pylori status. The detection score improved in 46.4% cases and deteriorated in 4.9% when the modality changed from WLI to LCI. A mixed-effects multivariate logistic regression analysis showed that use of LCI (odds ratio [OR] 2.57), elevated type (OR 1.92), invasion to submucosa (OR 2.18) were significantly associated with improved visibility of EGC.

Study II. Sensitivities using ultrathin WLI, ultrathin LCI, standard WLI, and standard LCI for the identification of cancer were 66.0%, 80.3%, 69.9%, and 84.0%, respectively. The color difference between malignant lesions and surrounding mucosa with ultrathin LCI and standard LCI were significantly higher than using ultrathin WLI or standard WLI, supported subjectively by the visibility score. Ultrathin LCI color difference and visibility score were significantly higher than standard WLI.

4 考察

The study I results demonstrate that LCI improves the visibility of obscure EGC at a distant view regardless of lesion characteristics including location, depth, pathology, size and H. pylori status. Even undifferentiated and small cancers are more visible using LCI compared with WLI. The multivariate analysis in the present study clarifies several factors which affect the visibility of EGC and LCI had the highest odds ratio among those factors such as elevated morphology and submucosal invasion. This result suggest that high color contrast might be one of the most important factors affecting the endoscopic visibility of EGCs. When the endoscopic modality changed from WLI to LCI, the visibility improvement rate was 46.4% and deterioration rate was 4.9%. Most of obscure EGCs missed by WLI can be detected using LCI, while the visibility of a small number EGCs might be decreased when using LCI. Most of lesions with deteriorated score were red using WLI but purple when using LCI. Malignant lesions exhibiting a redder color than the surrounding mucosa using WLI can become purple when using LCI.

However, most endoscopic courses and lectures about LCI focus on the major EGC type which has a similar color to the surrounding mucosa and are poorly visible using WLI but turn orange using LCI and are easier to detect. This implies that additional education about the significance of observing purple color using LCI is necessary. This is the first report that analyzes the factors which influence the detection of EGC in a large series and evaluates both the advantages and disadvantages of LCI.

Study II is the first report to demonstrate that the color contrast between a malignant lesion and its surrounding mucosa is more important than high resolution images when screening for EGCs. The results show both ultrathin LCI and standard LCI improve the ability to detect EGCs compared with ultrathin WLI and standard WLI, respectively. Ultrathin LCI had a higher diagnostic sensitivity, significantly higher visibility scores and color difference than standard WLI. This suggests that color contrast is more important than resolution for the identification of EGC. The introduction of ultrathin LCI seems to be suitable for EGC screening in clinical practice including routine health examinations. The specificity of LCI was lower than WLI both with ultrathin and standard endoscopes. Most non-malignant gastric lesions such as intestinal metaplasia, erosions and regenerative epithelium exhibit mucosal changes with lower color contrast to the surrounding mucosa on WLI, but with high color contrast on LCI, which may result in lower specificity of LCI compared with WLI. Using LCI, suspicious lesions may increase with blue light imaging (BLI) allows endoscopists to differentiate the malignant lesion due to better visualization of surface patterns without magnification. The final diagnosis is made by target biopsy. Thus, LCI is an optimal mode for detection of EGC, but not as the final endoscopic diagnosis tool.

5 結論

The results of the studies described in this thesis indicate that LCI is a clinically useful method to improve the detection of EGCs by increasing the color contrast between malignant lesion and its surrounding mucosa and improving lesion visibility regardless of their characteristics, even with a lower resolution endoscope. In conclusion, LCI is strongly expected to become an IEE useful in screening for gastric cancer in clinical practice and shall be recommended in the future guidelines.

論文審査の結果の要旨

論文表題：早期胃癌の存在診断における Linked Color Image の有用性の検証試験

現在、本邦では、画像強調イメージ内視鏡が広く普及され、臨床で使用されている。しかし、日本消化器内視鏡学会は、上部消化管、早期胃癌の内視鏡診断については、「通常画像内視鏡: White light imaging (WLI)と比べ強調画像内視鏡の絶対的優位性については明らかになっていない」という立場である。

本学位論文は二つの検証試験から構成されている。Study1 は自治医大での多くの症例数（508例を抽出）を後ろ向きに検討し、Linked Color Image (LCI) が WLI に比べて診断力が高いことを、スコアを用いることで客観的に示すことができた。これは新知見であり、Digestive Endoscopy に Accept された。Study2 では、(学位申請がなされた時点では、前向き試験が申請締め切りに間に合うか心配されたが) ビデオを用いての前向き比較試験で、LCI の優位性を示すことができた。こ

れも新知見であり、学術論文に **Accept** された。Study1 および 2 ともに学術的意義、新規性、独創性を認めることから、本論文は学位論文としてふさわしいと全員一致で認められた。問題点、改訂の必要性は特に認めなかった。

なお、本研究は自治医科大学の大学院医学研究科 第 6 回大学院生ワークショップで発表し、「Best presentation of 6th JMU Workshop」を受賞した。また、日本消化器内視鏡学会 2021 年でも発表され、「Young investigation award Japan Gastroenterological Endoscopy Society 2021」をも受賞した。

最終試験の結果の要旨

申請者は、学位論文の内容にそって英語での発表を行った。すでに、Study1 および Study2 の成果については論文化され、また自治医科大学の第 6 回大学院生ワークショップや日本消化器内視鏡学会 2021、その他にも学会からの発表依頼を受けた経験を重ねてきたこともあり、プレゼンテーションは洗練されていた。1 次審査、2 次審査とは格段に進歩した内容であった。研究の背景、目的、方法、結果、考察は明確で独自性、新規性、学問的意義を認めた。

審査員からは、Linked Color Image のデメリットについての質問があったが、適切に返答し、学位論文を訂正する必要はないと判断した。他の審査員からは Study2 において、科学的技術を用いてのコントラスト評価を行うことにより客観性を高めるアドバイスがあった。これに対しても適切に対応し、今後の展望を期待できるディスカッションになった。審査委員長は、申請者は本学附属病院で積極的に臨床での内視鏡検査、治療内視鏡に参加ししていることを知っている。よき指導者に恵まれ、本研究が臨床経験と客観性に基づいて、新たな知見を見出した研究成果であることを、申請者に告げた。研究に関連する周辺領域の知識も十分であった。

以上、申請者の発表および質疑応答から、審査審全員が最終試験に訂正事項なく合格と判断した。なお、モンゴルでは胃癌の罹患率、死亡率が高い。申請者がモンゴルに帰国してから、LCI を用いて早期胃癌の発見率向上に活躍することを期待したい。