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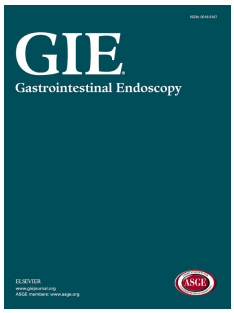

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Blue-light imaging has an additional value to white-light endoscopy in visualization of early Barrett's neoplasia. an international multicenter cohort study

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ABSTRACT

Background and Aims: Endoscopic features of early neoplasia in Barrett's esophagus (BE) are subtle. Blue-light imaging (BLI) may improve visualization of neoplastic lesions. The aim of this study was to evaluate BLI in visualization of Barrett's neoplasia.

Methods: Corresponding whit- light endoscopy (WLE) and BLI images of 40 BE lesions were obtained prospectively and assessed by 6 international experts in 3 assessments. Each assessment consisted of overview and magnification images. Assessments were as follows: Assessment 1: WLE only; Assessment 2: BLI only; and Assessment 3: corresponding WLE and BLI images. Outcome parameters were as follows: (1) appreciation of macroscopic appearance and surface relief (VAS-scores); (2) ability to delineate lesions (VAS-scores); (3) preferred technique for delineation (ordinal scores); and (4) quantitative agreement on delineations (AND/OR scores).

Results: Experts appreciated BLI significantly better than WLE for visualization of macroscopic appearance (median 8.0 vs 7.0, P<0.001) and surface relief (8.0 vs 6.0, P<0.001). For both overview and magnification images, experts appreciated BLI significantly better than WLE for ability to delineate lesions (8.0 vs 6.0, P<0.001 and 8.0 vs 5.0, P<0.001). There was no overall significant difference in AND/OR scores of WLE+BLI when compared with WLE, yet agreement increased significantly with WLE+BLI for cases with a low baseline AND/OR score on WLE, both in overview (mean difference 0.15, P=0.015) and magnification (mean difference 0.10, P=0.01).

Conclusions: BLI has additional value for visualization of BE neoplasia. Experts appreciated BLI better than WLE for visualization and delineation of BE neoplasia. Quantitative agreement increased significantly when BLI was offered next to WLE for lesions that were hard to delineate with WLE alone.

INTRODUCTION

Barrett's esophagus (BE) is a precursor lesion for esophageal adenocarcinoma (EAC). When detected at an early stage, patients with EAC can be treated endoscopically with an excellent prognosis [1]. BE patients therefore undergo regular endoscopic surveillance, consisting of inspection with white-light endoscopy (WLE) and quadrantic random biopsies every 2 cm [2, 3]. Endoscopic detection of early BE neoplasia with WLE is, however, difficult because its appearance can be subtle and random biopsies sample only a fraction of the surface area. Over the past decade, optical chromoscopy techniques have been developed and are now part of the standard set-up of endoscopy systems. These techniques use the excitation of blue light to enhance mucosal surface contrast and improve

visualization of mucosal morphology. Because of its short wavelength, blue light penetrates only superficially into the tissue, thereby causing less scattering. Furthermore, blue light is highly absorbed by hemoglobin and therefore improves visualization of mucosal vasculature [4, 5].
Most studies on optical chromoscopy have failed to show an additional value of optical chromoscopy over WLE for visualization of BE neoplasia, not surpassing performance thresholds set for imaging technologies to replace random biopsies by targeted biopsies during endoscopic surveillance of BE [6-11]. Most of these studies were performed using narrow-band imaging (ie, an optical chromoscopy technique integrated in Olympus endoscopy systems) and focussed on *irregularity of mucosal and vascular patterns in magnification* for detection as well as characterization of early neoplasia. The disappointing outcomes of these studies do not reflect the way most experts appreciate and use optical chromoscopy in daily practice. One of the features that may lead to the detection of early BE neoplasia in overview are subtle differences in surface relief (ie, subtle elevations and depressions relative to the normal-appearing flat surrounding mucosa). In our experience, surface relief is better appreciated with optical chromoscopy than with WLE. An example of the difference in appreciation of surface relief is shown in Figure 1. Better visualization of surface relief may improve detection of early neoplasia and/or description of the macroscopic appearance of the lesions according to the Paris classification because this classifies lesions according to their surface relief. Once a lesion has been detected and described according to its macroscopic appearance (ie, surface relief) the lesion needs to be delineated to allow for complete endoscopic resection. For this, most experts use optical chromoscopy in magnification because the demarcation line between neoplastic and non-neoplastic mucosa can be better appreciated with these techniques than with WLE. An example of the demarcation line in both WLE and BLI is shown in Figure 1.
The value of optical chromoscopy for appreciating subtle differences in surface relief in overview and visualization of the demarcation line in magnification, however, has not been formally evaluated.

The ELUXEO 7000 (FUJIFILM, Tokyo, Japan) is a new-generation endoscopy system that is equipped with high-intensity LED excitation and megapixel CMOS technology to enable full high-definition display. Blue-light imaging (BLI) is the high-quality optical chromoscopy technology of this system. The innovative 4-LED Multi Light technology is the first in its kind and enables state-of-the art enhanced endoscopy by superior visualization and differentiation of mucosal surfaces and vessel structures.

The aim of this study was to evaluate the additional value of BLI over WLE for delineation of early BE neoplasia, taking into account subtle differences in surface relief in overview and detection of the demarcation line of neoplastic versus non-neoplastic mucosa in magnified view.

METHODS

Setting and design

This multicenter prospective cohort study consisted of 2 phases. In the first phase, endoscopic images were prospectively collected in a standardized manner. In the second phase, 6 experts evaluated these images using a proprietary online scoring and delineation module. This study was conducted at the departments of Gastroenterology and Hepatology of 3 tertiary referral centers for detection and treatment of early Barrett's neoplasia in the Netherlands and Belgium.
The Medical Research Involving Human Subjects Act did not apply to this study. Official approval of this study was therefore waived by the Medical Ethics Review Committees of all participating centers. Informed consent was obtained from all patients. All authors had access to the study data and reviewed and approved the final manuscript.

ELUXEO 7000 endoscopy system

The ELUXEO 7000 endoscopy system (FUJIFILM, Tokyo, Japan) is a new-generation endoscopy system, that enables electronic chromoscopy by using a light source consisting of 4 LEDs with different wavelengths. By changing the intensity of these LEDs, a WLE-, BLI-, and linked-color imaging (LCI) mode is created. BLI is one of the key technologies of the system with a peak wavelength of 410 nm ± 10 nm, thereby improving visualization of mucosal vasculature. The CMOS image sensor chip in the tip of the endoscope reduces susceptibility to noise and provides high-resolution images.

Patients and endoscopic procedure

Patients with BE referred for endoscopic work-up of high-grade dysplasia (HGD) or EAC likely to require endoscopic resection were eligible for this study. Patients with reflux esophagitis were not eligible for this study.

All endoscopic procedures were performed according to standard practice, with the addition of obtaining multiple images using the different modes of the HDTV 7000 endoscopy system. All endoscopic procedures were performed by expert endoscopists (J.B., B.W., R.P., E.S., W.C., R.B.) with extensive experience in the use of advanced imaging techniques and endoscopic treatment of Barrett's neoplasia.
The esophagus was examined in overview and detail to assess for the presence of visible abnormalities after which the length of the Barrett segment was recorded according to the Prague Classification system [12]. After this, the WLE and BLI functions of the endoscope were used to inspect any present lesion again in overview. The location (distance from the incisors and endoscopic quadrant), diameter and lesion type according to the Paris Classification were recorded [13]. Then a

still image of the lesion in overview was obtained in WLE and BLI with the endoscope in the same position (figure 2). Subsequently the endoscope was removed and a transparent cap was attached to the end of the endoscope. The lateral margins of the lesion were inspected in detail, after which still images of 1 or 2 areas showing the lateral margin of the lesion were obtained in magnification (>40) in WLE and BLI with the endoscope in the same position. The selection of these areas was performed with either WLE or BLI to the discretion of the endoscopist. These images were obtained in such a way that the neoplastic lesion encompassed between 25% and 75% of the mucosal surface area, thereby showing the demarcation line in the center of the endoscopic screen (figure 2). All images were recorded in full-HD format (1280x1024 pixels). After this, the endoscopic procedure was completed according to standard practice.

Histological analysis

Histological analysis was performed according to standard protocol. All resection specimens were embedded in paraffin and stained with haematoxylin and eosin (H&E). Analysis was performed by expert gastroenterology pathologists with expertise in Barrett's neoplasia.

Online module assessment

A proprietary online scoring and delineation module (Meducati AB, Göteborg, Sweden) was used for this study. Software of this module allowed endoscopic images to be scored and delineated on a computer screen and subsequently enabled calculation of surface overlap of delineations (figure 2).

A group of 6 international Barrett's experts (J.B., R.B., O.P., E.S., A.M., H.N.) assessed the images using the online module, on a computer with a high-definition (HD) monitor. All experts were regular users of optical chromoscopy techniques including BLI. In total three assessments, each containing 2 parts, were performed. The order of images in each assessment was randomized between assessment rounds and assessors. Images were locked after being assessed: the assessors were not able to go back to earlier images. Each part of an assessment had to be completed in a single session. Assessment rounds were separated by a washout period of 2 weeks.

In the first assessment only the WLE images in overview (part 1) and magnification (part 2) were shown, to assess the appreciation of WLE images without bias due to comparison of corresponding BLI images. In the second assessment only the BLI images in overview (part 1) and magnification (part 2) were shown, to assess the appreciation of BLI images without being biased by a direct comparison with WLE images. In the third assessment, all WLE and corresponding BLI images were assessed side-to-side in overview (part 1) and magnification (part 2), to assess the appreciation of both techniques

when used together. A pilot assessment was performed to optimize procedural workflow and software.

Assessment 1

In the first assessment the experts scored and delineated images in WLE. For the overview images, the assessors had to complete the following items per image: (1) the Paris classification of the lesion; (2) appreciation of the Paris classification of the lesion (VAS score 1-10, where 1 reflects the lowest- and 10 the highest appreciation); (3) appreciation of the surface relief of the lesion (VAS score 1-10); (4) delineation of the lesion on the screen; 5) appreciation of the ability to delineate the lesion using WLE (VAS score 1-10).

For the magnification images, the experts had to complete the following items per image: (1) delineation of the lesion on the screen; (2) appreciation of the ability to delineate the lesion using WLE (VAS score 1-10).

Assessment 2

In the second assessment, the same items were scored as in assessment 1, yet now only BLI images were assessed.

Assessment 3

In the third assessment, the experts scored and delineated the WLE and BLI images in overview and magnification in a side-to-side display. For the overview images, the assessors had to complete the following items per image: (1) Paris classification; (2) choice of the best technique to appreciate the Paris classification (BLI or WLE) on an ordinal scale, ranging from -2 (BLI is much worse than WLE), -1 (BLI is a little worse than WLE), 0 (BLI is the same as WLE), +1 (BLI is a little better than WLE) to +2 (BLI is much better than WLE); (3) choice of the best technique to appreciate the surface relief (BLI or WLE) using the same ordinal scale; (4) delineation of the lesion on the preferred image (WLE or BLI); and (5) choice of the best technique to delineate the lesion (BLI or WLE) using the ordinal scale mentioned above.

For the magnification images, the experts had to complete the following items per image: (1) delineation of the lesion on the preferred image (WLE or BLI); (2) choice of the best technique to delineate the lesion (BLI or WLE) using the ordinal scale mentioned above.

Processing of online delineations

In order to develop a quantitative score for the level of agreement between assessors on their delineations, the AND/OR ratio was used in which the AND area was defined as the area delineated by ≥4 experts (ie, the majority of experts) and the OR area as the area delineated by ≥1 experts.

Figure 3 shows a graphical display of both areas. By using this quantitative method, a high level of agreement between assessors corresponds with a high AND/OR ratio. Perfect agreement between 6 experts (which is virtually impossible) would lead to an AND/OR score of one, absent agreement would lead to an AND/OR score of 0.

Outcome measurements

- Experts' appreciation of macroscopic appearance and surface relief, ie, the ability of experts to assess the macroscopic appearance and surface relief (VAS-scores);
- Experts' ability to delineate the lesion (VAS-scores);
- Experts' preferred technique for delineation (ordinal scores);
- Experts' quantitative agreement on lesion delineations (AND/OR scores).

Statistical analysis

Statistical analysis was performed with SPSS 24 Software for Windows. Because this was the first study in its kind, evaluating optical chromoscopy for appreciation of macroscopic appearance in overview and the demarcation line in magnification, no formal sample size calculation was conducted. For descriptive statistics mean (±SD) was used in case of a normal distribution of variables, and median (25%-75% percentile) for variables with a skewed distribution. For differences between scores the paired Student t-tests, Wilcoxon signed rank tests and McNemar tests were used. Spearman's rank tests were performed to measure association between VAS scores and AND/OR scores.

RESULTS

In total 68 patients with a single visible lesion were included in this study, out of which 40 pairs of overview images (WLE and BLI) and 80 pairs of magnification images (WLE and BLI) of 54 patients were selected. Twenty-eight pairs of overview images and 44 pairs of magnification images were excluded because of insufficient image quality or lack of similarity between the WLE and BLI image. This image exclusion process was performed by 2 experts (J.G. and W.C.) independently, followed by a consensus meeting. These experts did not participate in the assessment phase of this study. All lesions on the included images were removed with endoscopic resection. Histological evaluation of the endoscopic resection specimens showed HGD or EAC in all cases.

Overview images

Median expert VAS scores were significantly higher for BLI when compared with WLE for appreciation of Paris Classification (median 8.0 vs 7.0, P<0.001), appreciation of surface relief (median 8.0 vs 6.0, P<0.001), and ability to delineate the lesion (median 8.0 vs 6.0, P<0.001) (Table 1).

In assessment 3, experts preferred BLI over WLE for assessing the Paris Classification (27.5% vs 2.9% respectively, P<0.001) and surface relief (65.8% vs 3.3%, respectively, P<0.001) and as best technique for delineation (68.8% vs 12.1%, respectively, P<0.001) (Table 2). When given a choice between the 2 corresponding images, experts delineated the lesion more often on BLI than on WLE (201 vs 39 times, respectively).

There was a positive correlation between VAS scores for ability to delineate a lesion and AND/OR scores, in both assessment 1 and 2 (Spearman rank test, R=0.562 and R=0.691, respectively, P<0.001).

Overall, there was no significant difference in AND/OR scores between WLE versus BLI (median 0.51 vs 0.44, P=0.34), WLE versus WLE+BLI (median 0.51 vs 0.46, P=0.81) or BLI versus WLE+BLI (median 0.44 vs 0.46, P=0.67) (Table 3).

Subanalyses of the overview images showed that for the WLE images with a low baseline AND/OR score (ie, relatively difficult visualization and delineation of the lesion on WLE), AND/OR scores increased significantly with WLE+BLI (n=18, mean difference 0.15, P=0.015) (Table 3).
Subanalyses furthermore showed no significant difference in AND/OR scores between flat lesions (with a Paris Classification type IIb component, as scored by the endoscopist) and non-flat lesions in any of the assessments (P=0.398, P=0.445, and P=0.570 for assessment 1, 2, and 3 respectively).
The total OR area (ie, the total area delineated by ≥1 experts) did not increase significantly with BLI when compared with WLE (P=0.055).

Magnification images

Median expert VAS scores were significantly higher for BLI when compared with WLE for ability to delineate the lesion (median 8.0 vs 5.0, P<0.001). See table 1. In assessment 3, experts preferred BLI over WLE for delineation (81.0% vs 3.1%, respectively, P<0.001) (Table 2). When given a choice between the 2 corresponding images, experts delineated the lesion more often on BLI than on WLE (457 vs 23 times, respectively).

There was a positive correlation between VAS scores for ability to delineate a lesion and AND/OR scores in both assessment 1 and 2 (Spearman rank test, R=0.416 and R=0.540, respectively, P<0.001).

Overall, there was no significant difference in AND/OR scores between WLE versus BLI (median 0.59 vs 0.58, P=0.159), WLE versus WLE+BLI (median 0.59 vs 0.63, P=0.96) or BLI versus WLE+BLI (median 0.58 vs 0.63, P=0.074) (Table 3).

Sub-analyses of the magnification images again showed that for WLE images with a low baseline AND/OR score, scores increased significantly with WLE+BLI (n=40, mean difference 0.10, P=0.01) (Table 3).

DISCUSSION

This study is the first to evaluate blue light imaging (BLI), an optical chromoscopy technique integrated in a new-generation high-definition endoscopy system equipped with high-intensity LED excitation and megapixel CMOS technology.

In this study we took a different approach in studying the additional value of optical chromoscopy over WLE for BE neoplasia. Previous studies have mainly focussed on the role of optical chromoscopy for the *characterization* of BE neoplasia, without showing a clear additional value.
The disappointing outcomes of these studies, do not reflect the way optical chromoscopy is used in daily practice. One of the features that may lead to the detection of early BE neoplasia in overview is a subtle difference in surface relief. In our experience, surface relief is better appreciated with optical chromoscopy than with WLE. Better visualization of surface relief may improve detection of early neoplasia and/or description of the macroscopic appearance of the lesions according to the Paris classification because this classifies lesions according to their surface relief. Once a lesion has been detected and described according to its macroscopic appearance (ie, surface relief) the lesion needs to be delineated to allow for complete endoscopic resection. For this, optical chromoscopy in magnification is generally used because the demarcation line between neoplastic and non-neoplastic mucosa can be better appreciated with these techniques than with WLE. However, the value of optical chromoscopy for appreciating subtle differences in surface relief in overview and visualization of the demarcation line in magnification has not been formally evaluated.

In our study, international BE experts appreciated BLI significantly better than WLE both in overview and magnification for the visualization of BE neoplasia in terms of Paris Classification, surface relief and ability to delineate lesions. When given a choice between corresponding WLE and BLI images for delineation with the proprietary delineation tool, experts preferred the BLI images over WLE in the

vast majority of cases. These results indicate that experts have a strong preference to use BLI when compared with WLE for the visualization in overview and subsequent delineation of BE neoplasia in magnification.

There was a positive correlation between qualitative VAS scores for ability to delineate a lesion and quantitative AND/OR scores in both overview and magnification. This indicates that our AND/OR score is a credible method for quantification: when an expert is certain on his delineation, he is likely to also reach high quantitative agreement with his fellow experts.

In this study, overall quantitative agreement between experts on their delineations (AND/OR scores) did not differ significantly between WLE, BLI, or WLE+BLI. This lack in overall difference in quantitative agreement might partly be caused by the fact that overall agreement on both WLE and BLI was high, resulting in high AND/OR scores in all groups. This likely reflects the high quality of the WLE images with the current FUJIFILM system, which logically reduces the potential increase in AND/OR scores by any additional imaging technique. In addition, delineation of lesions by the 6 experts was associated by some disagreement, as is shown in the example of Figure 4. As a result, a small incremental value of BLI for the AND/OR scores may easily be lost against this background variability. Indeed, subanalyses showed that for lesions that were hard to delineate with WLE alone, quantitative agreement did increase significantly when BLI was offered next to WLE. This was found in both overview images and magnification images. These results therefore show that BLI has significant additive value as a supplement next to WLE for those lesions that are hard to delineate with WLE alone. There was no significant increase in quantitative agreement when BLI images were assessed without WLE. However, from a clinical perspective, optical chromoscopy is considered to be an adjunct to WLE, instead of an alternative. During endoscopy, endoscopists are likely to switch back and forth between WLE and BLI to obtain the best appreciation of the lesion.

This study has several limitations. Because a formal reference standard for correct delineation is lacking, we had to create an outcome measurement to quantify agreement between experts. Ideally, corresponding histology of the true demarcation line, separating the lesion from the nondysplastic surrounding mucosa, should be correlated to the endoscopic image. However, this is not feasible. We therefore choose to quantify agreement with the AND/OR score. We reasoned that high agreement between experts, resulting in a high AND/OR score, is the result of the ability to appreciate the “true” demarcation line, visualized by the technique used for the delineation. However, this approach proved to be associated with a wide heterogeneity in delineations, both in WLE and BLI. This is probably caused by different interpretations of the “true” demarcation line. Where some experts merely focused on the most abnormal parts of the lesion, as a target for endoscopic resection, others

also delineated the subtle extent of the lesion. This resulted in background variability, limiting the value of quantitative agreement as a measure in this study.

It is important to note that the set-up of this study may have been associated with different types of bias. Experts might have had a pre-existing preference for WLE or BLI, thereby possibly leading to researcher bias in the qualitative part of the study. Because 3 of the experts were also responsible for image acquisition, it can be argued that they had more profound knowledge of certain images than the other assessors. However, because our inclusion period extended over 20 months, assessments were separated by a wash-out period, and the order of images was randomized during the assessments, potential bias was minimalized. Furthermore, the exclusion of 28 overview images and 44 magnification images due to insufficient image quality or lack of similarity between the WLE and BLI image, could have led to selection bias because our dataset therefore only comprised of high-quality images. Finally, all assessors were experts in endoscopic delineation of BE neoplasia. This might have led to a higher extent of overall agreement than would be expected with less-experienced assessors. Further studies should investigate if BLI also has an additive value when used by less-experienced endoscopists.

It is important to emphasize that interpretation of real-time endoscopy can be more challenging. However, due to the high quality of the images and our unique delineation tool, we feel that our study mimics clinical practice to a high extent. Following this deduction, this study clearly showed the additive clinical value of optical chromoscopy in the endoscopic visualization and delineation of Barrett's neoplasia. BLI next to high-definition WLE can aid the endoscopist by providing a better visualization of subtle differences in surface relief in overview and the demarcation line in magnification, especially for those lesions that are hard to delineate with WLE alone.

In conclusion, this is the first study to demonstrate the additional value of BLI next to WLE for the visualization and delineation of BE neoplasia. International BE experts appreciated BLI better than WLE for the different aspects of visualization of BE neoplasia and preferred BLI for delineation with the proprietary delineation tool. Their quantitative agreement for delineation increased significantly when BLI was offered next to WLE for lesions that were hard to delineate with WLE alone.

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TABLES

Table 1. Expert VAS scores in assessment 1 and 2. Wilcoxon signed ranks tests.

Overview images	**WLE (assessment 1)**	**BLI (assessment 2)**	***P* value**
Appreciation Paris Classification (VAS scores)	7.0 (IQR 6-8)	8.0 (IQR 7-9)	<.001
Appreciation surface relief (VAS scores)	6.0 (IQR 4-8)	8.0 (IQR 7-9)	<.001
Ability to delineate the lesion (VAS scores)	6.0 (IQR 4-7)	8.0 (IQR 6-8)	<.001
Magnification images			
Ability to delineate the lesion (VAS scores)	5.0 (IQR 3-7)	8.0 (IQR 6-9)	<.001

Table 2. Expert ordinal scores in assessment 3. McNemar tests.

Overview images	**WLE+BLI (assessment 3) Preference WLE**	**WLE+BLI (assessment 3) Preference BLI**	***P* value**
Appreciation Paris Classification (ordinal scores)	7/240 (2.9%)	66/240 (27.5%)	P<0.001
Appreciation surface relief (ordinal scores)	8/240 (3.3%).	158/240 (65.8%)	P<0.001
Ability to delineate the lesion (ordinal scores)	29/240 (12.1%)	165/240 (68.8%)	P<0.001
Magnification images			
Ability to delineate the lesion (ordinal scores)	15/480 (3.1%)	389/480 (81.0%)	P<0.001

Table 3. Expert AND/OR scores in assessment 1, 2, and 3. Paired T tests and Wilcoxon signed ranks Tests.

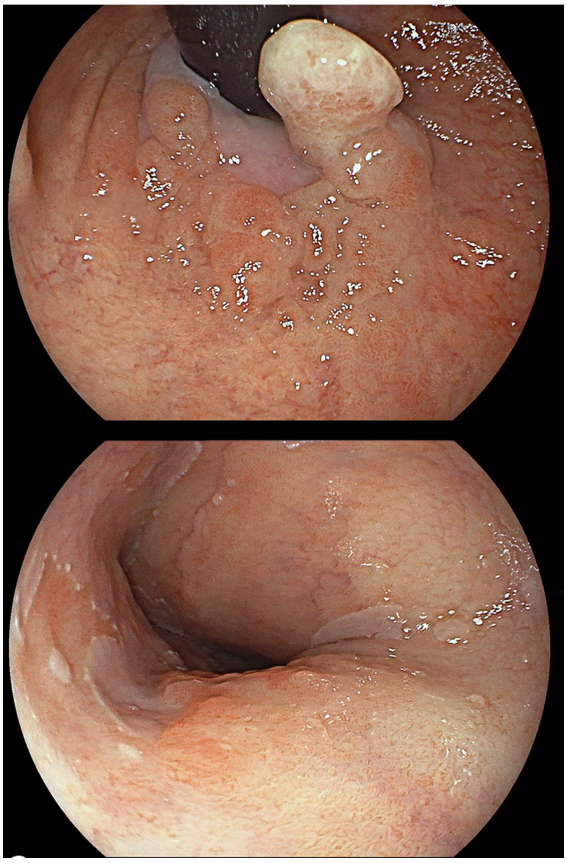
Overview images	**WLE (assessment 1)**	**BLI (assessment 2)**	**WLE+BLI (assessment 3)**	**WLE vs BLI**	**WLE vs WLE+BLI**
Median AND/OR score (n=40)	0.51	0.44	0.46	P=0.34	P=0.81
Subanalyses WLE image with low baseline AND/OR score, mean AND/OR score (n=18)	0.30	0.40	0.45	P=0.072	P=0.015
Magnification images					
Median AND/OR score (n=80)	0.59	0.58	0.63	P=0.159	P=0.96
Subanalyses WLE image with low baseline AND/OR score, mean AND/OR score (n=40)	0.46	0.49	0.57	P=0.40	P=0.01

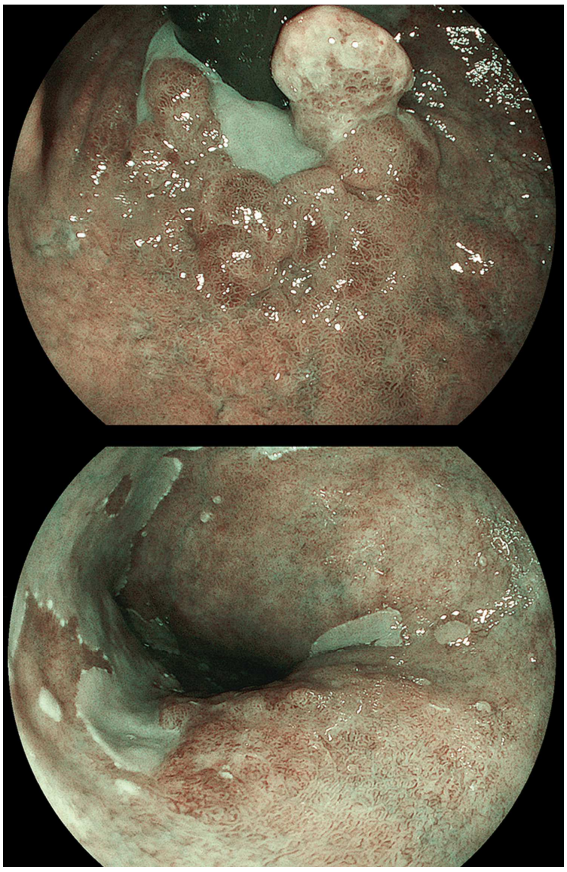
Figure 1: Examples of the difference between WLE and BLI in appreciation of surface relief (A and B) and demarcation line (C and D).

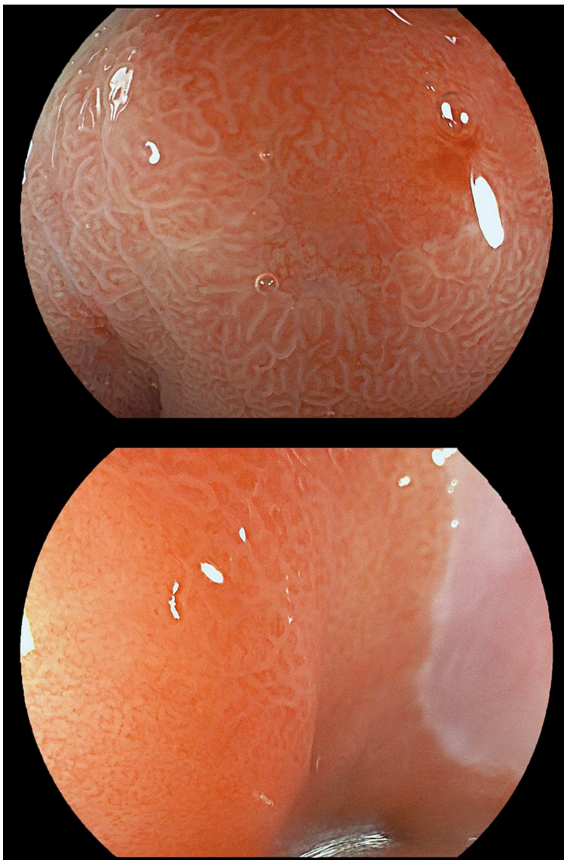
Figure 2: Examples of prospectively collected, corresponding images in WLE and BLI, before (A, B, E, F) and after online delineation by experts (C, D, G, H).

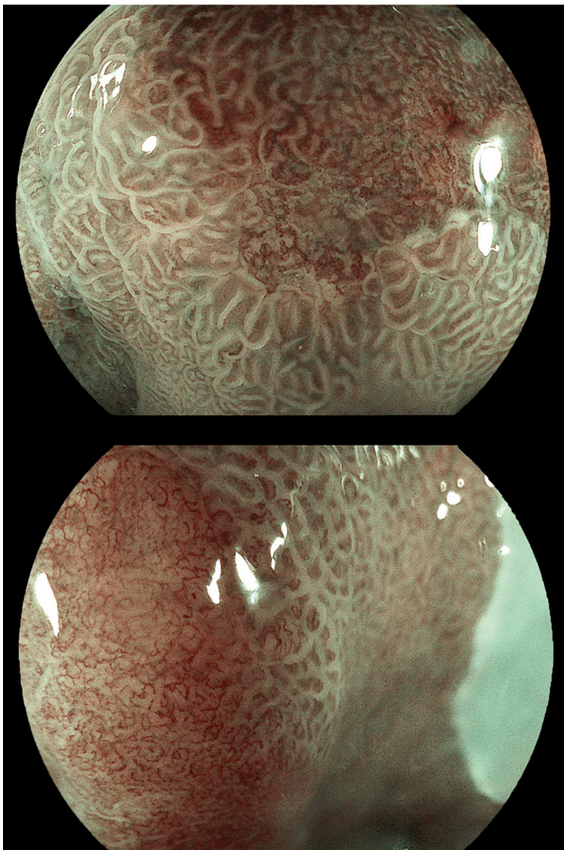
Figure 3: Graphical display of 6 expert delineations, the AND area (red) and the OR area (blue).

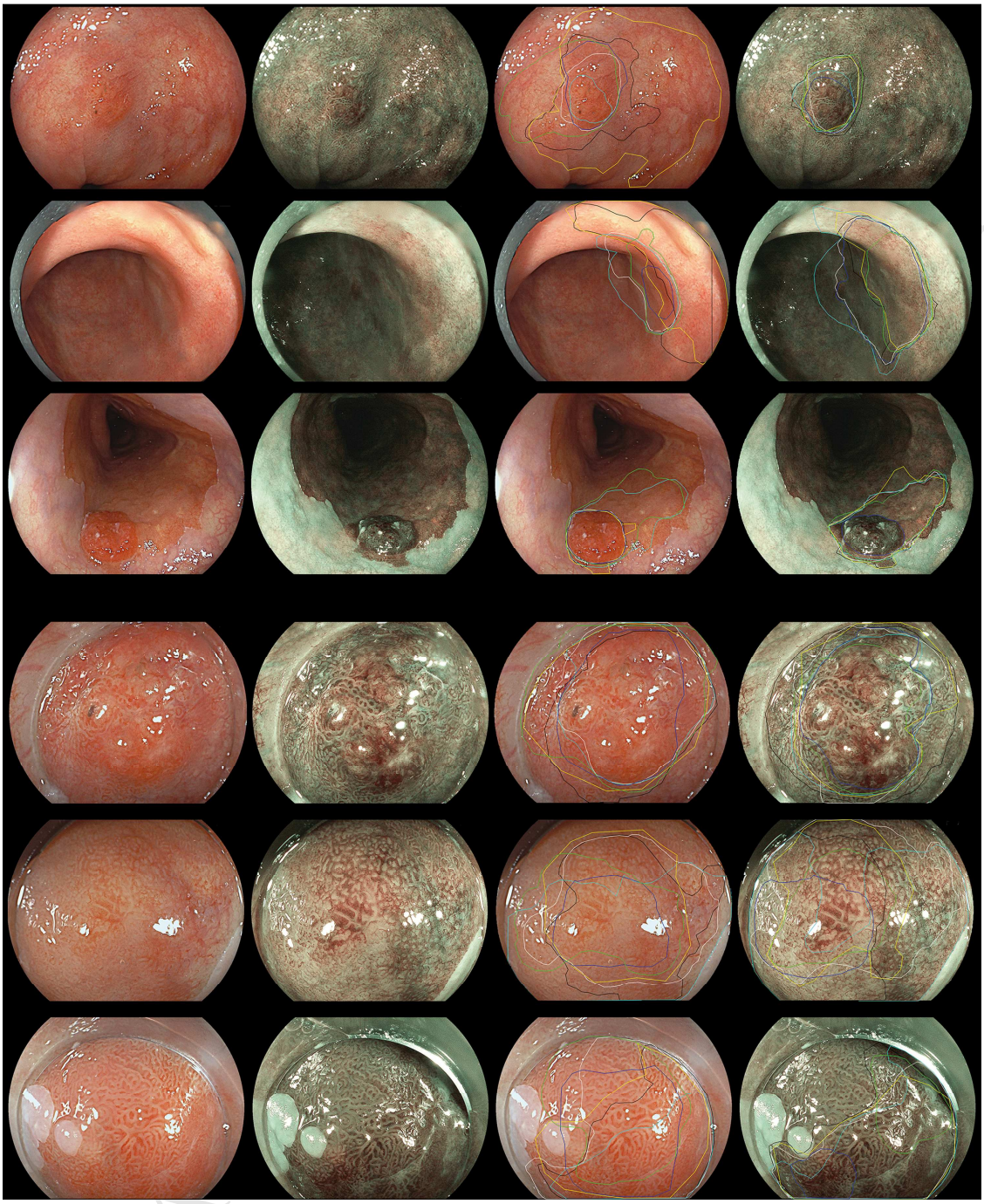
Figure 4: Examples of expert delineation disagreement in WLE (A) and BLI (B).

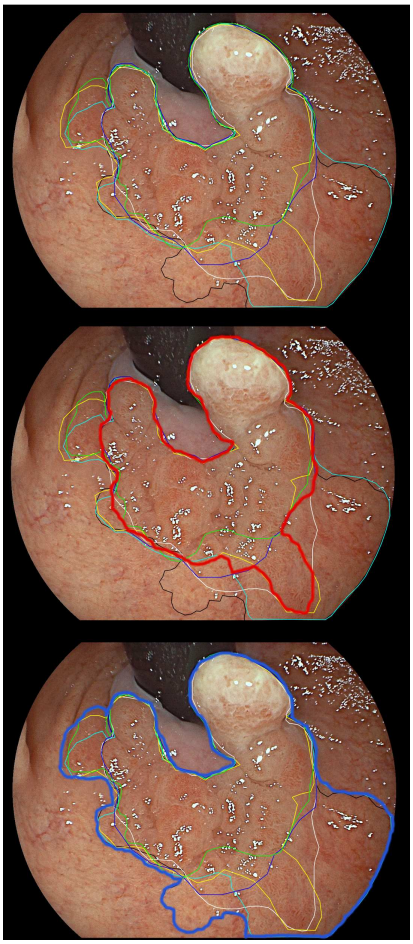


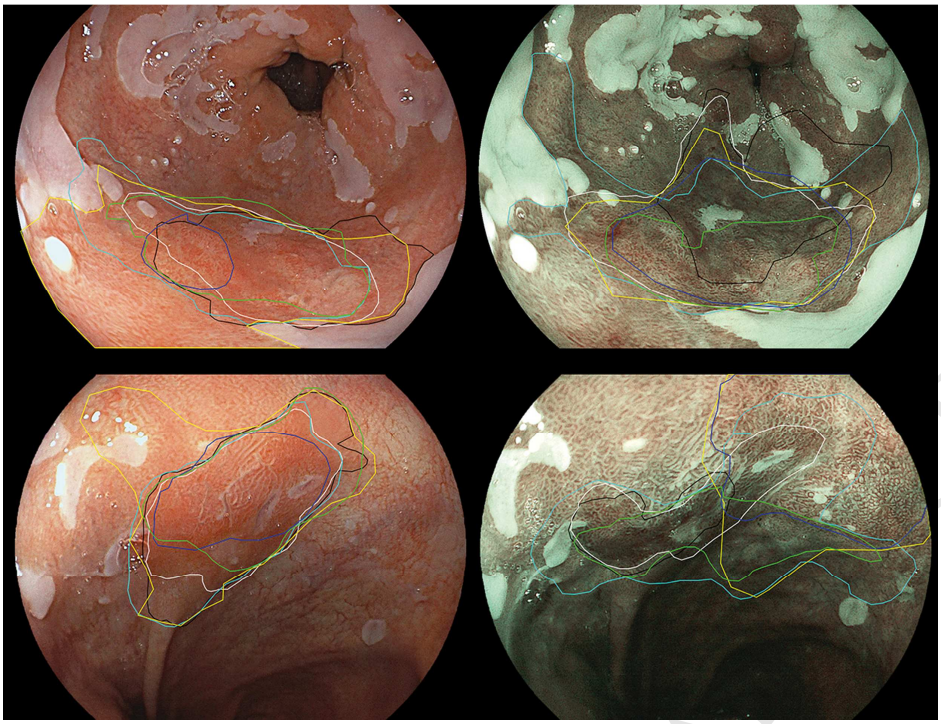












List of acronyms used in BLI study

BE: Barrett's esophagus
BLI: Blue light imaging
WLE: White light endoscopy
VAS: Visual analogue scale
EAC: Esophageal adenocarcinoma
LCI: Linked color imaging
HGD: High grade dysplasia
H&E: Haematoxylin and eosin