A Comparison of Blue Light Imaging (BLI) and White Light Endoscopy (WLE) in Patients with Barrett's neoplasia

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INTRODUCTION

Early neoplasia in Barrett's esophagus (BE) is difficult to distinguish with white light endoscopy (WLE). Over the past decades multiple advanced imaging techniques have been studied to improve detection of early lesions in the Barrett's segment. Chromoendoscopy is a technique where stains are used to enhance visualization of the mucosal and vascular patterns. However the use of dye is laborious and endoscopist dependent, furthermore it has not been proven to gain an incremental yield of detecting neoplastic lesions (1,2).

Optical chromoendoscopy techniques such as narrow band imaging (NBI; Olympus, Tokyo, Japan) and blue light imaging (BLI; Fujifilm, Tokyo, Japan) work through pre-processing technologies and can be applied by pushing a button which makes them much more user-friendly. Examples of digital chromoendoscopy – techniques based on post-processing – are Fuji intelligent chromo endoscopy (FICE; Fujifilm) and i-scan (Pentax, Tokyo, Japan). Most clinical studies have not shown an additional value of optical chromoendoscopy techniques on detection of BE neoplasia (3,4). Previous studies used irregularity of mucosal and vascular patterns as the main features of neoplasia (5–8). These features, however, require inspection in magnification and are not easy to detect in overview. In addition, magnification endoscopy is technically demanding and not generally used in the Western world. Furthermore, evaluation of magnified NBI images is associated with a significant interobserver variability (1,9). Which features are relevant for detection in an overview is yet unknown, but our impression is that minute differences in surface appearance ("surface relief") are better appreciated with these techniques than with WLE. This has, however, not been properly evaluated.

Another potential application of optical chromoendoscopy is the delineation of lesions prior to endoscopic resection. BLI may be superior to WLE for this purpose, however, formal studies are lacking here too. Detailed inspection with BLI allows for identification of the demarcation line, separating the area with an irregular mucosal and vascular pattern from its normal surroundings. Lesions with a clear demarcation line usually harbor invasive cancer. Visible lesions containing low-grade dysplasia or high-grade dysplasia often do not display an irregular mucosal or irregular vascular pattern and therefore lack a clear demarcation line. Their endoscopic detection is triggered by slight differences in surface relief. Such subtle differences in surface relief may be better appreciated by BLI in overview compared to WLE. For delineation, the demarcation line and surface relief should both be used.

Until recently, the use of NBI in overview for primary detection of neoplasia was limited by the relative darkness of the image in the overview and the loss of resolution of still images due to motion artefacts and interlaced video processing. The latest version of NBI systems and the recently introduced BLI system have overcome these technical limitations, which may allow their use as a

"red-flag technology." The HDTV 7000 system (Fujinon, Tokyo, Japan) is a new system that utilizes a combination of three modes: WLE, BLI and LCI to enhance mucosal pattern imaging and visualize vascular structures more optimal (10). These characteristics are reached because the blue light penetrates less deep into the tissue and encompasses the maximum absorption wavelength of hemoglobin. LCI enhances color differences in the mucosa.
The aim of this study is to evaluate BLI *in overview* and *in magnification* for the use of delineating early neoplastic Barrett's lesions compared to WLE, taking into account subtle differences in surface relief and differences in mucosal and vascular patterns.

METHODS

Setting

The study will be conducted in 6 tertiary referral centres in the Netherlands, Belgium, Germany and France which are all specialized in imaging, diagnosis and treatment of early Barrett's neoplasia.

Design

Multicenter prospective cohort study to collect endoscopic images which are subsequently evaluated using a proprietary online scoring and delineation module.

Objectives

1. To evaluate if BLI *in overview:*
    a. Provides a better image of the surface relief than WLE;
    b. Leads to a better characterization of the macroscopic appearance of the lesion (Paris classification) than WLE
    c. Allows for better delineation of the lesion than WLE
2. To evaluate if BLI *in magnification* provides a better image of the mucosal and vascular patterns than WLE and therefore allows for better delineation of the lesion.

Outcome measurements

1. VAS scores for assessment per lesion by different experts in terms of characterization (Paris classification and surface relief) and delineation: WLE vs. BLI assessment.
2. Inter-observer agreement for the characterization and delineation per lesion based on WLE vs. BLI assessment, both in overview and magnification.

Patients

In this study 40 patients with early Barrett's neoplasia will be included.

Inclusion criteria

- Age ≥ 18 years;
- Patients with BE referred for endoscopic work-up of HGD or EAC likely to require endoscopic resection (EMR or ESD);
- Lesions can be completely visualized in a single endoscopic image in overview;
- Lesions in which a type 0-II lesion is the dominant part (the more subtle lesions);
- Eligible for EMR or ESD;
- Signed informed consent.

Exclusion criteria:

- Prior history of surgical or endoscopic treatment for oesophageal neoplasia;
- Presence of erosive esophagitis (Los Angeles classification ≥A);
- Inability to undergo EMR/ESD and/or obtain biopsies (*e.g.* due to anticoagulation, coagulation disorders, varices);

HDTV 7000 endoscopy system

The HDTV 7000 endoscopy system (Fujifilm® Tokyo, Japan) is a new generation endoscopy system, which enables to provide a new electronic chromoendoscopy.

The light source consists of four LEDs with different wavelengths. By changing the intensity of each of the four LEDs a white light mode, a BLI mode and a LCI mode are realized as shown in Fig. 1.

Blue Light Imaging is one of the key technologies associated with the system and allows bright virtual chromoendoscopy.

With the use of the optical magnification scopes, up to 135 folds magnified images on the 19" monitor are available.

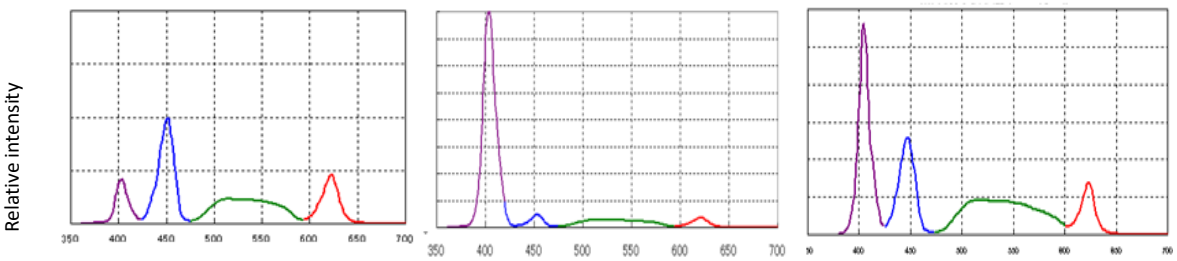
The white light mode (WLE) is similar to conventional endoscopy, using a Xenon lamp.

Blue Light Imaging technique

Blue Light Imaging (BLI) is an imaging technology that is based on light absorption characteristics of haemoglobin and scattering characteristics of mucosa. BLI has a peak wavelength of 410nm±10nm (Fig 1). This wavelength is more likely to be absorbed by hemoglobin and to be scattered in the surface mucosa than other wavelengths. It can therefore clearly distinguish the microvasculature in the surface of the mucosa from the blood vessels in the deep mucosa.

Linked Color Imaging technique

Linked Color Imaging (LCI) is a new image enhanced technology. It is developed to enhance color difference in the mucosa. The post-processing of the image makes the strong red-tint color more red and the pale red-tint color more pale, so that eventually the discrimination in red colors becomes more noticeable (Fig 1).



Wave length White light mode Wave length BLI mode Wave length LCI mode

Fig. 1 Spectral power distributions of each mode achieved by 7000 system respectively

Endoscopic procedure

All endoscopic procedures will be performed by expert endoscopists (JB, RB, AM, HN, OP, TP) with extensive experience in the use of advanced imaging techniques and endoscopic treatment of early Barrett's neoplasia. The procedure will be performed according to the standard clinical practice, with the addition of obtaining multiple images using the different modes of the HDTV 7000 endoscopy system (Fujifilm® Corporation, Tokyo, Japan).

All patients that will be included are referred for first endoscopic imaging for the work-up and treatment of HGDN/EAC as part of the standard guideline for work-up of Barrett neoplasia.

Patients will be consciously sedated by intravenous administration of Propofol or Midazolam (2.5-15 mg) supplemented with Fentanyl (0.1-0.2 mg) or Pethidine (25-50 mg) if necessary.

The esophagus will be examined in overview and in detail (magnification) with white light endoscopy (WLE) using the EG-760Z endoscope (Fujifilm® Corporation, Tokyo, Japan) and the length of the Barrett segment will be recorded according to the Prague-classification system(2). Then, the BLI and function of the endoscope is used to inspect the lesion again in overview and in detail. The location (distance from the incisors and endoscopic quadrant), diameter and lesion type according to the Paris classification will be recorded on a standardized CRF. A still image will be obtained with WLE and BLI of the lesion in overview. The WLE and BLI images in overview are obtained without the use of a distal attachment cap and are obtained with the endoscope in the same position. Subsequently, the endoscope is removed and a transparent cap is attached to the end of the endoscope. The lateral margins of the lesions are then inspected in detail and still images in magnification (>40) are obtained of 2 areas showing different parts of the lateral margin of the lesion. These areas should ideally be chosen in such a way that a) the neoplastic lesion encompasses between 25-75% of the mucosal surface area depicted (*i.e.* the demarcation line should be oriented more or less in the middle of the endoscopic screen); b) the magnified images can later be indicated on the still images obtained in overview. The selection of these 2 areas is performed with WLE and/or BLI to the discretion of the endoscopist. Of each area, the corresponding WLE and BLI magnified still images are obtained without changing the position of the endoscope or the scale of magnification. Finally, the lesion is demarcated by electrocoagulation markers using WLE and/or BLI to the discretion of the endoscopist. Once demarcation is completed, a still image in overview is obtained with WLE and BLI as described above, preferably with the endoscope in the same position and orientation. These images may be used as a reference at a later stage but will initially not be formally evaluated. The demarcated lesion is resected using EMR/ESD (resection/dissection technique is left to the discretion of the endoscopist) such that the lesion and all demarcation markers are removed. A still image in overview post EMR/ESD is obtained with WLE and BLI

Histological analysis

Histological analysis will be performed according to standard protocol. All resection specimens will be embedded in paraffin, cut, and stained with haematoxylin and eosin (H&E). All slides will be routinely evaluated by an expert Barrett pathologist, who will record the presence, grade and distribution of inflammation and intestinal metaplasia and neoplasia according to the WHO classification for gastrointestinal tumours: no-dysplasia, indefinite for dysplasia, LGD, HGD or invasive cancer(3). For the purpose of this study no central pathology review will be performed.

Assessments of WLE and BLI images

A group of 6 Barrett's experts will assess the images obtained from all lesions as follows:

- There will be multiple assessments separated by a wash-out period of 2-4 weeks.
- These assessment will be performed using a proprietary online scoring and delineation module.
- Assessors will be required to log in and to complete the assessment in a single session.
- Images will be locked after being assessed: the assessor cannot go back to earlier images.
- The order of images is randomized between endoscopists and between assessment rounds.
- The estimated time required for each assessment is less than one hour.

In total six assessments will take place:

1. WLE images of the lesion in overview (no BLI images shown in this assessment).
2. BLI images of the lesion in overview (no WLE images to be shown in this assessment).
3. WLE and corresponding BLI images of the lesion in overview (side-to-side).
4. Detailed WLE images of part of the lateral margin of the lesion together with the overview WLE images (no BLI images to be shown in this assessment).
5. Detailed BLI images of part of the lateral margin of the lesion together with the overview BLI images (no WLE images to be shown in this assessment).
6. Detailed WLE and corresponding BLI images of the lateral margin (side-to-side) together with the overview WLE and BLI images.

For assessments 1-3 the following items will be scored by all experts:

- Macroscopic appearance (Paris classification).
- Visual analogue scale (VAS): how well can you assess the Paris classification and surface relief on WLE/BLI and which technique is better for this purpose?
- Delineate the lesion on the image (delineation software will allow this to be done on screen).

- VAS: how well can you delineate the lesion with WLE/BLI and which technique is better?
- In assessment 3 the lesion has to be delineated on the preferred image (either WLE or BLI).
- There is a 2-4 weeks wash-out between assessments.

For assessments 4-6 the following items will be scored by all experts:

- Draw the delineation line (delineation software will allow this to be done on screen).
- VAS: how well can you delineate the lesion with WLE/BLI and which technique is better?
- In assessment 6 the lesion has to be delineated on the preferred image (either WLE or BLI).
- 2-4 weeks wash-out between assessments.

Statistical analysis

Statistical analysis will be performed with SPSS 20 Software for Windows. For descriptive statistics mean (±SD) will used in case of a normal distribution of variables, and median (IQR) for variables with a skewed distribution. For differences between experts for VAS scores and between VAS scores for WLEvs. BLI the paired Student t-test or Wilcoxon test and McNemar test will be used.

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