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Evaluation of a novel infra-red endoscopy system in the assessment of early neoplasia in Barretts esophagus: Pilot study from a single center.

Authorship:
Dr Jacobo Ortiz-Fernández-Sordo and Prof Krish Ragunath were involved in substantial contributions to manuscript concept and design.
Dr Jacobo Ortiz-Fernández-Sordo performed data collection, analysis and interpretation.
Dr J. Ortiz-Fernández-Sordo , Dr Sarmed Sami, Dr Rodrigo Mansilla-Vivar, Dr Venkat Subramanian, Dr Jayan Mannath, Dr Emmanoulis Telakis and Prof Krish Ragunath participated in drafting the article, revising and approval of content for final version.

Institution:
Nottingham Digestive Diseases Centre and NIHR Biomedical Research Unit, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK.

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Corresponding Author:
Dr Jacobo Ortiz-Fernández-Sordo
NIHR Nottingham Digestive Diseases Biomedical Research Unit
Queens Medical Centre campus, Nottingham University Hospitals NHS Trust
Nottingham NG7 2UH
Tel: +44 (0) 115 8231039
jacobo.ortizfernndezsordo@nottingham.ac.uk
jacobo.ortizfernandez-sordo@nuh.nhs.uk

SUMMARY

Evaluation of a novel infra-red endoscopy system in the assessment of early neoplasia in Barretts esophagus: Pilot Study from a single center.

Infrared endoscopy (IRE) has been shown to be useful in detecting submucosal (SM) invasion in early gastric cancer. Its role in the endoscopic assessment of Barrett's neoplasia has not been reported to date. We aimed in this study to evaluate the role of IRE in the detection and characterization of early neoplastic lesions within BE. The secondary aim was to explore its usefulness for the assessment of the presence of submucosal invasion in these early neoplastic Barrett's lesions.

We included in the study patients with dysplastic Barrett´s esophagus (BE) who were referred to our institution for endoscopic therapy of a previously diagnosed early Barrett's neoplasia.
An examination with white light High Resolution Endoscopy (HRE) and near infrared endoscopy (IRE) after intravenous injection of Indocyanine green was performed for all patients using an Infrared endoscope prototype. Staining on IRE and correlation with final histological staging by EMR/surgery or histological diagnosis on mapping biopsies was analyzed.

A total of 23 patients were enrolled in our study; 17 of them with 19 visible lesions and 6 patients with flat BE and no lesions. Staining on IRE was noted in 18 cases; 17 (94%) had at least HGD. No stain was noted in 7 cases; final histology was <HGD in 5 (71%) and ≥HGD in 2 (29%). There was statistically significant difference between cases with no stain and any staining on IRE with regard to the presence of ≥HGD [2/7 (29%) vs. 17/18 (94%) p=0.0022]. Stain was reported as faint in 12 and dense in 6. All 6 cases with dense staining had at least HGD.

We concluded that IRE can provide additional information to the currently available white light endoscopy for detecting early neoplastic lesions within BE. IRE also allows detecting HGD and most advanced histology in BE. Usefulness of IRE to detect submucosal involvement in early Barrett's neoplastic lesions needs to be assessed further in larger cohort studies.

Evaluation of a novel infrared endoscopy system in the assessment of early neoplasia in Barrett's esophagus: Pilot study from a single center.

BACKGROUND

Endoscopic therapy is now the standard of care for early neoplasia in Barrett's esophagus (BE) confined to the mucosa layer (1-3). Accurate staging of tumor depth is mandatory before considering curative endoscopic treatment.

Endoscopic imaging has undergone a great technological evolution over the last decade and advanced imaging techniques are now widely used in the surveillance of BE and assessment of Barrett's neoplasia (4).

Angiogenesis plays a relevant role in the carcinogenesis process (5). The microvasculature of neoplastic lesions differs from that in normal mucosa, and its characterization is useful for the diagnosis of early neoplasia (4, 5). It has also been suggested that vascular patterns may be different in superficial neoplasia compared to more invasive lesions and would be useful to differentiate between mucosal and submucosal involvement.

Infrared Endoscopy (IRE)

Infrared light is an invisible electromagnetic radiation with longer wavelengths than visible white light and penetrates deeper into the tissue (6).

Indocyanine green (ICG) is used as a contrast medium to improve visualization of the vascular patterns, increasing contrast between vessels and the surrounding tissue (6).

The dual-wavelength infrared endoscope system emits two different infrared rays by the light source at a different wavelength. Red and green channels of the rotary filter pass the light at 790-820 nm, and the blue channel at 920-960 nm. ICG in the submucosal vessels absorbs near infrared light maximally at 805 nm, corresponding to red and green channels of the endoscope, and reflects infrared light at 920-960 nm, corresponding to blue channel of the endoscope and vessels therefore appear blue on the monitor (6).

Infrared and near infrared endoscopy using ICG as a fluorescence marker allows visualization of the vessels in the gastrointestinal tract and has showed to be useful to assess the depth of invasion in early gastric cancer (8-11).

The potential role of IRE in the endoscopic assessment of early Barrett's neoplasia has never been studied previously.

AIMS

The primary aim was to evaluate the role of IRE in the detection and characterization of early neoplastic lesions in BE. The secondary aim was to explore its usefulness for the assessment of submucosal invasion in early neoplastic lesions.

PATIENTS AND METHODS

Study Design

This is a prospective single-center pilot study in a tertiary university hospital setting conducted at the Queens Medical Centre, Nottingham University Hospitals NHS trust, United Kingdom. Informed consent was obtained from every participant and the study was approved by the National Research Ethics Service (NRES) Committee East Midlands - Nottingham 1 (REC Ref 10/H0403/36).

Participants

All patients over 18 years old with a previous diagnosis of early Barrett's neoplasia referred for endoscopic therapy to our institution were invited to participate.

Procedure

All subjects enrolled in the study underwent consecutive examinations performed during the same endoscopic procedure with white light and near infrared light using an Infrared endoscope prototype (GIF-RQ260Z; Olympus, Tokyo, Japan).

An initial assessment was performed using white light high-resolution endoscopy (HRE, Depth of viewing 7 mm-100 mm (WIDE position) and 1.5 mm-3mm (TELE position) and 85x zoom magnification). ICG was then administered intravenously at a dose of 2 mg/kg and light mode was switched to near infrared light by pressing a button located on the endoscope handle. Few seconds after ICG injection a careful examination was performed under near IRE mode. Depending on the length of the Barrett's segment and the presence or absence of any superficial visible lesions diagnostic examination ranged from 10 to 15 minutes. Both examinations were carried out by a single experienced endoscopist (KR).

The Barrett's segment was assessed and reported as per Prague Classification criteria (12) defined by C=circumferential length of the Barrett's segment and M=maximum length. Distance from the incisors and location at o'clock position was recorded for any identified visible lesions. Endoscopic appearances following the Paris Classification (13) for superficial neoplastic lesions were also described: 0-Ip=Pedunculated, 0-Is=Sessile, 0-IIa=Flat-elevated, 0-IIb=Flat, 0-IIc=Depressed, 0-III=Ulcerated or any combination of these.

Under IR light the neoplastic lesions within the Barrett's segment were visualized as deep blue areas

compared to the non-neoplastic tissue. IRE findings were classified as 1) No stain: no areas of increased dye accumulation compared to the surrounding mucosa; 2) Faint stain: area of minimal diffuse increased dye accumulation and 3) Dense stain: area of dense increased dye accumulation (Figures 1-3). These findings were recorded per patient if no VL was present and per lesion when a macroscopic lesion was identified.

Random four quadratic mapping biopsies following the Seattle protocol were obtained from flat Barrett's segment in all patients. Endoscopic Mucosal Resection (EMR) was performed for all VL if appropriate. Patients were referred surgical treatment if the lesion was deemed not to be suitable for endoscopic resection.

All biopsy samples and ERM specimens were reviewed by an expert pathologist highly experienced in BE. Final histology after random esophageal biopsies and any subsequent staging by EMR or surgery were included for analysis. Correlation between IRE findings and final histology was analyzed.

Study Outcomes

The primary end point was to evaluate the role of IRE in the detection and characterization of early neoplastic lesions within BE.

Secondary endpoint was to explore the usefulness of the IRE in predicting submucosal invasion in early Barrett's neoplasia.

Statistical Analysis

Microsoft Excel and SPSS statistical software was used. To establish the differences between the groups, the Chi square test was used for categorical variables. The means with SD of primary and secondary end points was compared between two groups using unpaired T test and two tailed p value of 0.05 as statistically significant.

Diagnostic performance of the IRE identifying early Barrett's neoplasia was also assessed and accuracy, sensitivity, specificity and negative predictive value were calculated and compared with the currently recommended quality standards.

RESULTS

A total of 23 patients agreed to participate in the study and were included for analysis (median age 69 years, 87% men). Initial histology from previous random or target biopsies was LGD in 3 patients, HGD in 16 and IMC in 4. Baseline characteristics are summarized in Table 1.

6 of 23 patients had no macroscopic lesions and a total of 19 VL were identified in the remaining 17 patients; two patients had two different lesions. The endoscopic appearance of the lesions according to the Paris Classification was: 0-Is=2; 0-IIa=9; 0-IIa+c=2; and 0-IIb=6. Three 0-IIb lesions of the 19 reported could not be identified on white light HRE but were detected on IR; final staging for all 3 was ≥HGD (HGD=2 and IMC=1).

EMR was performed in 15 patients for 17 macroscopic lesions; three patients underwent surgery. Final histology based on the endoscopic resection or surgical specimens is summarized in Table 2.

Staining characteristics on IRE after ICG injection, median dose 160 mg, range 120-262 mg, were reported per patient when no VL was noted and per lesion when a macroscopic lesion was present. IRE findings and its correlation with final histology are summarized in Tables 3 and 4. No adverse events were reported after intravenous injection of ICG.

No stain was noted in 7 cases; final histology was <HGD in 5 (71%) and ≥HGD in 2 (29%). Staining was noted in 18 cases; 17 (94%) had at least HGD (HGD=9, IMC=5, SMC=3). There was statistically significant difference between cases with no stain and those with any staining on IRE with regard to the presence of at least HGD [2/7 (29%) vs. 17/18 (94%), respectively, p=0.0022].

Stain was reported as faint in 12 cases and dense in 6. All 6 cases with dense staining had at least HGD (HGD=1, IMC=4 and SMC=1). There was no statistically significant difference between cases with faint and dense staining on IRE with regard to the presence of submucosal invasion [2/12 (17%) vs. 1/6 (17%) p=1].

Up to 89% (17/19) of cases with ≥HGD on final histology (table 2) showed staining on IRE and no staining was noted in 84% (5/6) of cases with <HGD on final histology.

Diagnostic accuracy, sensitivity, specificity and negative predictive value on IRE in identifying HGD or more advanced histology was 88%, 90%, 83% and 71% respectively.

Discussion

This is the first study reporting clinical usefulness of the IRE in the pre-therapeutic assessment of early Barrett's neoplasia.

In this feasibility study we found that IRE is useful to detect and delineate early neoplasia within BE. IRE allowed to identify three 0-IIb lesions not detected on WLE. Moreover, IRE was also useful in the detection of dysplastic areas within the BE segment. The majority (94%) of cases with any grade of staining on IRE contained ≥HGD and all those classified as dense stain had ≥HGD on final histology.

Our results showed that the presence of staining on IRE correlated with histology grade. We decided to use the presence of HGD on final staging as a cut-off because the presence of HGD in Barrett’s esophagus is a well-established indication for treatment (3).

Previously published small-scale retrospective single-center studies have reported a global accuracy >80% of IRE in diagnosis of the depth of gastric cancer invasion, allowing to distinguish between mucosal and submucosal or more invasive gastric cancers (8-11). Some studies also showed correlation between staining and tumor differentiation grade (10,11).

Main limitation of our study was the low prevalence of submucosal lesions not allowing adequate evaluation of the potential role of IRE in detecting invasion into the submucosa layer in Barrett’s neoplastic lesions. Final staging after EMR/surgery was ≥T1b in only 3 of 19 lesions. All 3 lesions

showed staining under IR light but it was faint in 2 and dense in 1.

Advanced imaging techniques including conventional and virtual chromoendoscopy have shown to significantly increase the diagnostic yield of early Barrett's neoplasia (14). The American Society of Gastrointestinal Endoscopy (ASGE) has recently published a systematic review and meta-analysis assessing the quality standards for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus to replace the random biopsy protocol (15). In our study, most of the diagnostic performance results of the IRE in identifying at least HGD reached the quality standards recommended by the ASGE, which stated that a new technology should have a sensitivity of >90%, specificity of >80%, and negative predictive value (NPV) >98%. Only NPV was below the recommended value. But we have to mention this is a pilot study in a small cohort and all diagnostic performance results need to be validated in larger multicenter studies.

Comparing IRE with other advanced imaging modalities was not the aim of this pilot study and larger cohort studies are needed for this purpose. Our results in terms of diagnostic performance, with sensitivity of 90%, specificity 83% and NPV 71%, in identifying HGD or more advanced histology are slightly lower compared to the previously reported for other virtual chromoendoscopy modalities. NBI has been widely assessed and there are results available from a previous meta-analysis (16) and the recently published systematic review and meta-analysis by the ASGE Technology Committee (17). They reported a sensitivity ranging from 91% to 94%, specificity between 95% and 97.5% and NPV 94% for NBI discriminating lesions with HGD (16,17).

There are limited data on other electronic chromoendoscopy techniques such as I-SCAN or FICE, which have been only evaluated in a few small studies (17-19) and their results were not included in the recent meta-analysis carried out by the ASGE Technology Committee. A recently published international multicenter study leaded by University College London reported an accuracy of 83% analyzing the dysplasia detection with I-SCAN magnification and acetic acid (17).

We also need to mention as potential limitations the possibility of a selection bias as all subjects were referred with a previous diagnosis of dysplastic BO and the endoscopist was not blinded to the initial histological diagnosis. There was also the possibility of an investigator bias, as both WLE and IRE were performed by a single endoscopist. One of the potential relevant limitations of the new advanced imaging techniques is a high inter-observer variability. Due to the just mentioned limitation with a single endoscopist performing all procedures, the inter-observer agreement for IRE could not be assessed in this study and needs to be addressed in larger cohort studies.

Despite the proven statistically significant difference between cases with no stain and those with any staining on IRE with regard to the presence of at least HGD, two patients with a final diagnosis of HGD had no staining on IR. This is suggesting that the sensitivity of IRE in the diagnosis of early Barrett's neoplasia might be low and will need to be evaluated further in larger cohort studies.

In conclusion, IRE can provide additional information to the currently available white light endoscopy for detecting early neoplastic lesions within BE. IRE also allows detecting HGD and more advanced histology in BE. Usefulness of IRE to detect submucosal involvement in early Barrett's neoplastic lesions needs to be assessed further in larger cohort studies.

Competing Interests:

Prof Krish Ragunath has received research support, educational grants, speaker honoraria, and consultancy fees from Olympus Keymed, Pentax, Cook Medical, Covidien and Boston Scientific

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TABLES

Table 1. Demographics and Barrett's segment characteristics	
Patients	N=23
Mean Age (years)	69 (range 49-85)
Gender (M/F)	20/3
Barrett's type	
Short Segment	3 (13%)
Long Segment	20 (87%)
Median Barrett's length (cm)	5 (range 1-16)
Visible Lesions	
Yes	17 (74%)
No	6 (26%)
Initial Histological Diagnosis	
LGD	3
HGD	16
IMC	4
Treatment	
EMR	15
Surgery	3*
RFA	2**
No treatment***	4

**One patient underwent surgery after EMR due to T1b tumour. One patient with a 0-Is lesion not suitable for endoscopic resection was referred to surgery. One patient with no VL and persistent IMC on mapping biopsies was also referred to surgery; final staging was T1sm1.*

*** One patient with no VL and one patient with a 0-IIb lesion and HGD on target biopsies succesfully underwent eradication treatment with RFA.*

****All 4 patients had ≤LGD on final histology*

Table 2. Final Histopathological staging.	
Negative for Dysplasia	1 (4%)
Indefinite for Dysplasia	1 (4%)
Low Grade Intraepithelial Neoplasia	4 (16%)
High Grade Intraepithelial Neoplasia	9 (36%)
Intramucosal adenocarcinoma (T1a)	7 (28%)
≥Submucosal adenocarcinoma (T1b)	3 (12%)

Table 3. Infrared findings and final histological diagnosis		
	No Stain (n=7)	Stain (n=18)
Histology		
<HGIN	5 (83%)	1 (7%)
HGIN	1 (10%)	9 (90%)
IMC	1 (7%)	5 (83%)
≥SMC	0	3

Table 4. Infrared findings and final histological diagnosis		
	Stain (n=18)	
	Faint (n=12)	Dense (n=6)
Histology		
<HGIN	1	0
HGIN	8 (89%)	1 (11%)
IMC	1 (20%)	4 (80%)
≥SMC	2	1

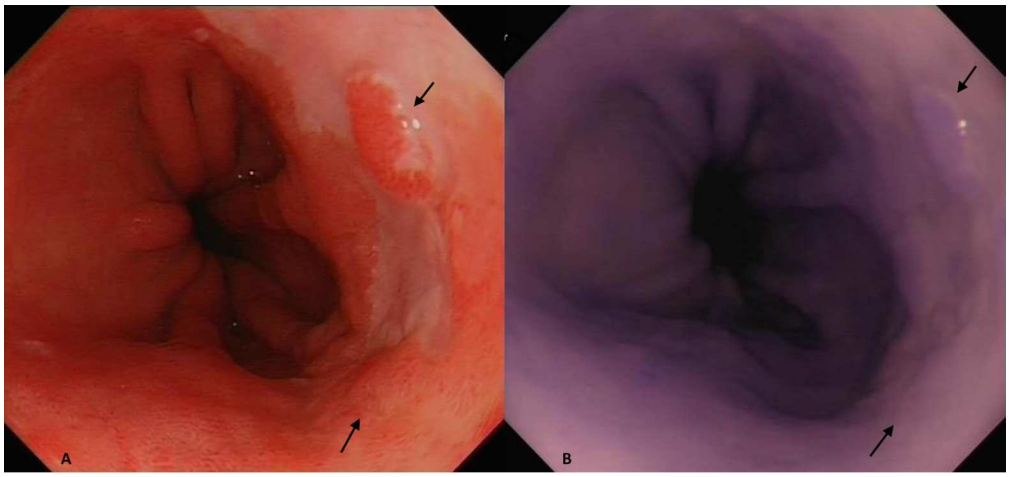

Fig_1._0-IIa_lesion_with_No_Stain_on_Infrared_Endoscopy.WLE (A)_and_IRE (B)

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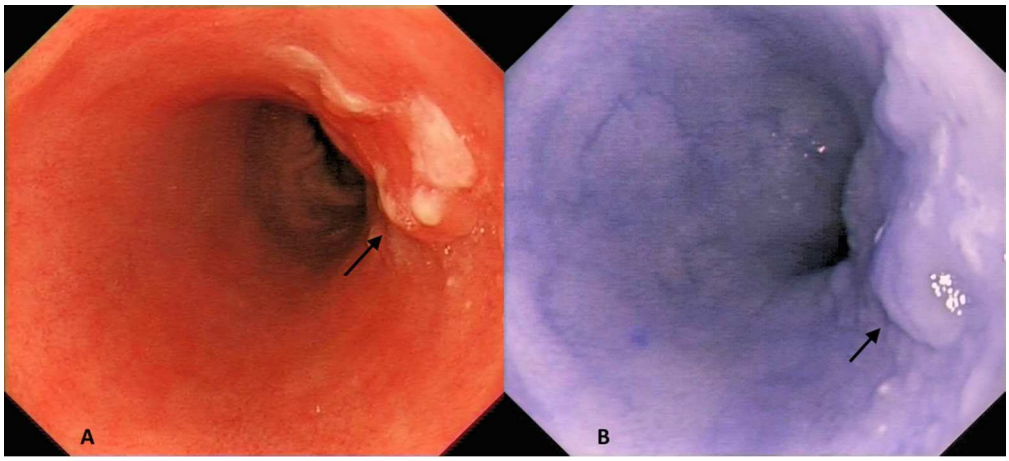

Fig_2._0-IIa_lesion_with_Faint_stain_on_Infrared_Endoscopy.WLE (A)_and_IRE (B)

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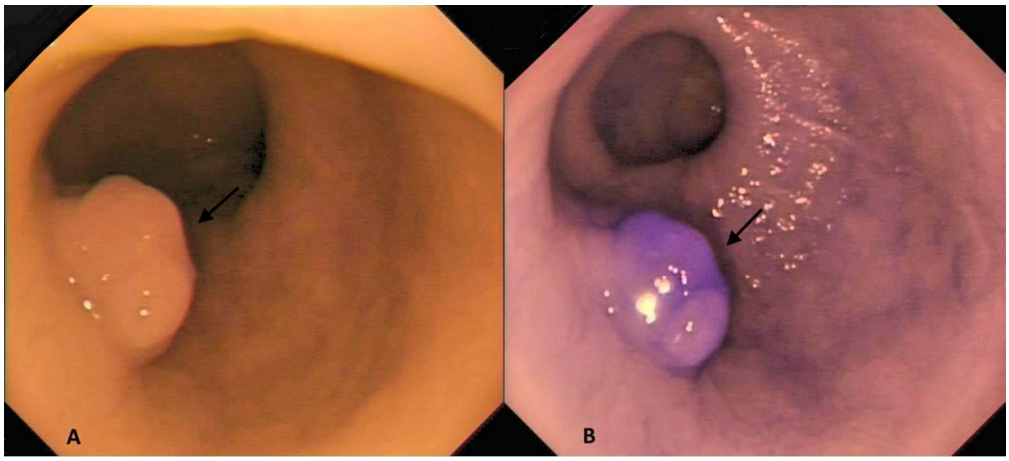

Fig._3._0-Is_lesion_with_Dense_stain_on_Infrared_Endoscopy._WLE (A)_and_IRE (B)

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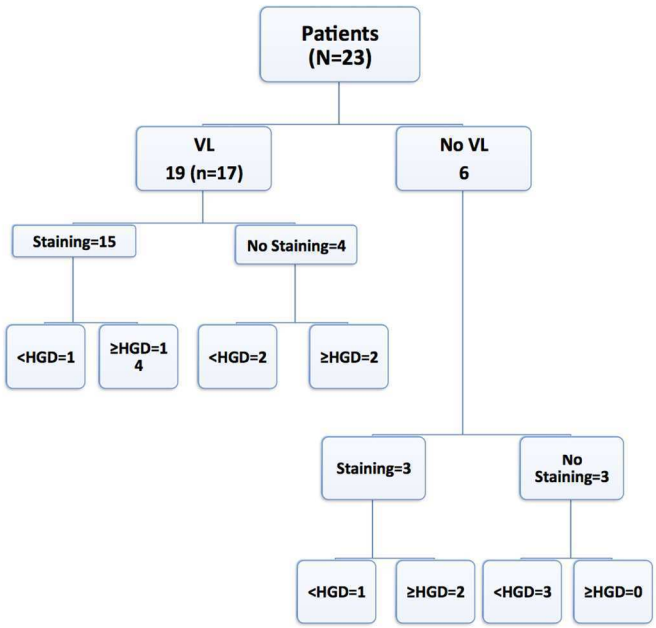

Fig 4. Barrett's characteristics of patients included in the study. IRE findings and correlation with final histology.

209x297mm (150 x 150 DPI)