Evaluation of a novel infra-red endoscopy system in the assessment of early neoplasia in Barretts oesophagus.

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Background

Patients with Barrett's oesophagus (BO) are recommended to undergo regular endoscopic surveillance to detect neoplastic lesions at an early stage (1). Endoscopic therapy is now the standard of care for mucosal neoplasia in Barrett's oesophagus (BO) (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 BO and assessment of Barrett's neoplasia, although we are yet to see any definitive advantage of one over the other (4).

In gastrointestinal cancers, including Barrett's neoplasia, angiogenesis plays a relevant role in the carcinogenesis process (5). The microvasculature of neoplastic lesions differs from that in normal mucosa, and as a result, the characterisation and detection of these abnormal vascular patterns 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 (700 nm-300 μm) than visible white light. It therefore penetrates deeper into the tissue due to its limited scattering and low absorption by water (6). The near infrared light, with wavelength between 700-1000 nm, is the most frequently used in clinical practice.

The haemoglobin absorbs near-infrared light more than the surrounding tissue, allowing a clear visualization of the vessels in the gastrointestinal tract when infrared light is used as the light source for endoscopy. An intravascular injection of Indocyanine green (ICG) has been used as a contrast medium, in order to improve visualization of the vascular patterns by increasing contrast between vessels and the surrounding tissue (6)

ICG 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 of wavelength, corresponding to blue channel of the endoscope. Submucosal vessels are then displayed in a deep blue colour in the monitor (6).

ICG has a negligible uptake by the peripheral tissue. Within 1-2 seconds after intravenous injection, ICG binds to α1-lipoproteins. It is eliminated almost entirely via the liver with the bile, and after 10 minutes, only a small fraction of the injected volume is detectable in the blood (7).

IRE and near IRE 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 of this feasibility study was to evaluate the role of IRE in the detection and characterisation of early neoplastic lesions in BO. The secondary aim was to explore its usefulness for the assessment of submucosal invasion in early neoplastic lesions.

Patients and methods

Patients with dysplastic BO referred for endoscopic therapy to our institution were invited to participate in the study. The study was approved by the National Research Ethics Service (NRES) Committee East Midlands - Nottingham 1 (REC Ref 10/H0403/36).

All subjects underwent sequential examinations with white light high-resolution endoscopy (HRE), followed by near IRE after ICG injection. A total dose of 2 mg/kg of ICG was intravenously administered immediately before the IRE examination. All procedures were performed by a single experienced endoscopist (KR) using an Infrared endoscope prototype (GIF-RQ260Z; Olympus, Japan).

The Barrett's segment was assessed and reported as per Prague Classification (12) and endoscopic appearances of all visible lesions (VL) according to the Paris Classification (13) were recorded.

Neoplastic lesions within the Barrett's segment were visualised as deep blue areas under IR light compared to the non-neoplastic surrounding 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 according to the Seattle Protocol were obtained from flat Barrett's segment. EMR was performed for all VL if appropriate using the multiband resection

technique (Duette, Cook Medical, Limerick, Ireland) or the cap assisted resection technique (Olympus Keymed, Southend-on-Sea, United Kingdom).

Final histology after random oesophageal biopsies and any subsequent staging by EMR or surgery were included for analysis. Correlation between IRE findings and final histology was analysed.

Results

A total of 23 patients with BO agreed to participate in the study and were included for analysis (median age 69 years, range 49-85, 87% men). The median Barrett's length was 5 cm (range 1-16 cm). Initial histology from previous mapping and/or target biopsies was LGD in 3 patients, HGD in 16 and IMC in 4. Baseline and demographic 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 was: 0-Is=2; 0-IIa=9; 0-IIa+c=2; and 0-IIb=6.

EMR was performed in 15 patients for 17 macroscopic lesions; final histology is summarized in Table 2.

The median dose of ICG was 160 mg (range 120-262 mg) 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.

Per patient analysis (n=23)

No stain was noted in 7 patients (<HGD in 5 (71%) and ≥HGD in 2 (29%)), while in the remaining 18 patients staining was noted (17 (94%) had ≥HGD (HGD=9, IMC=5, SMC=3). There was a significant difference in the yield of dysplasia (HGD or more) between cases with no stain and those with any staining on IRE [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 ≥HGD (HGD=1, IMC=4 and SMC=1). There was no 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].

Per biopsy analysis (n=25)

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 patients and lesions with <HGD. Three 0-IIb lesions of the 19 reported VL's could not be identified on white light HRE but were detected on IRE. Final staging for all 3 was ≥HGD (HGD=2 and IMC=1).

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 BO. 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 BO segment. The majority (94%) of patients with staining on IRE contained ≥HGD and all those classified as dense stain had ≥HGD on final histology. Staining on IRE also 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 oesophagus is a well-established indication for treatment (3). We found no correlation between the degree of staining on IRE and risk of submucosal invasion, however, these results are limited by the small number (n=3) of patients who had this outcome of interest.

Our results are comparable to previous published studies evaluating IRE in the assessment of early gastric cancer. Small-scale retrospective single-centre studies have reported a global accuracy for IRE of >80% in diagnosis of the depth of cancer invasion, allowing to distinguish between mucosal and submucosal or more invasive gastric cancers regardless of the presence of ulcerative changes.

Iseki et al. reported their experience in 37 patients with a previous diagnosis of gastric cancer, all lesions without stain under IR light were confined to the mucosal layer (8). Very similar results were reported by Ishihara et al. after analysis of 30 patients with depressed gastric cancer lesions. 21 of 23 (91%) intramucosal and superficial submucosal lesions (>1000 μm) were no stain or faint stain tumours; all cancers deeper than 1000 μm into the submucosa showed dense staining (9).

Mataki et al. also found that presence of staining indicates deep invasion; all submucosal lesions were positive on IRE compared to only 36% of mucosal cancers. In this study staining also correlated with differentiation grade, no staining was observed in well-differentiated lesions and it was present in all moderately and poorly differentiated cancer (10).

Bit less promising results were found by Kimura et al. using Infrared fluorescence endoscopy (IRFE) in 23 patients with a previous diagnosis of early gastric cancer. 25% of well-differentiated lesions were positive compared with 71% of poorly differentiated cancer, but differences were not statically significant. Regarding depth of invasion, none of the superficial mucosal lesions were positive under IR light vs. 80% of the submucosal or deeper cancers (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. This may be explained because of the presence of inflammation and hyper vascularization within the Barrett's making difficult the correct visualization of submucosal vessels.

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

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TABLES

Table 1. Demographics and Barrett's segment characteristics	
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*

***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

IMAGES

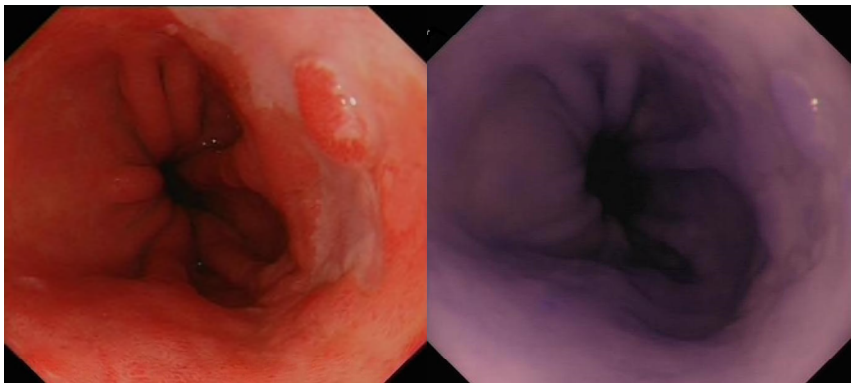

Fig 1. 0-IIa lesion with No Stain on Infrared Endoscopy. Final staging LGD.

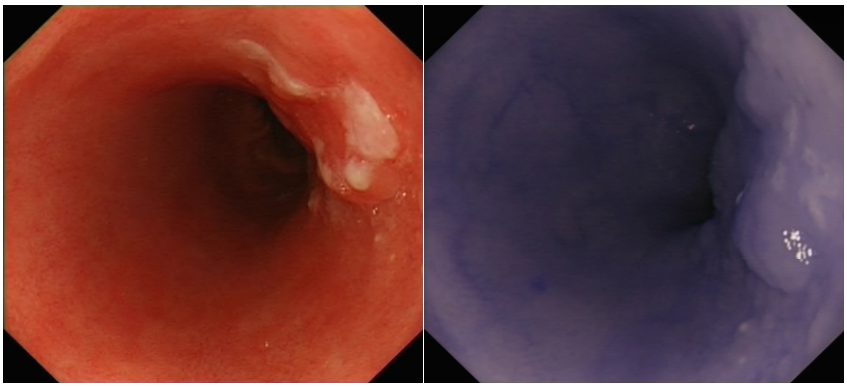

Fig 2. 0-IIa lesion with Faint stain on Infrared Endoscopy

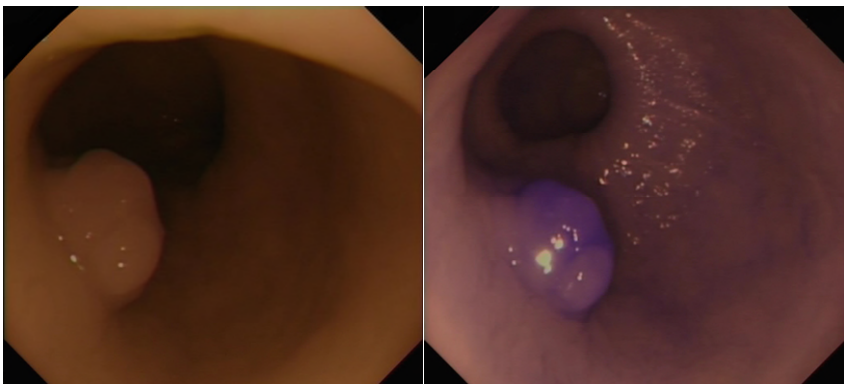

Fig. 3. 0-Is lesion with Dense stain on Infrared Endoscopy. Final staging IMC (T1m3)