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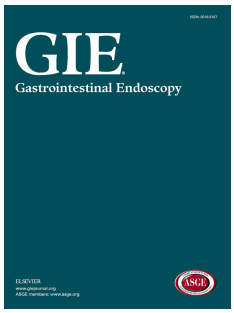

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Virtual chromoendoscopy using optical enhancement improves the detection of Barrett's esophagus–associated neoplasia

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Abstract

Background and Aims

The Seattle protocol for endoscopic Barrett's esophagus surveillance samples a small proportion of the mucosal surface area – risking a potentially high miss rate of early neoplastic lesions. We assess if the new iScan Optical Enhancement system (OE, Pentax) improves the detection of early BE associated neoplasia compared with high definition white light endoscopy (HD-WLE) in both expert and trainee endoscopists to target sampling of suspicious areas. Such a system may both improve early neoplasia detection and reduce the need for random biopsies.

Methods

41 patients undergoing endoscopic BE surveillance from Jan 2016-Nov 2017 were recruited from 3 international referral centers. Matched still images in both HD-WLE (n=130) and iScan OE (n=132) were obtained from endoscopic examinations. Two experts, unblinded to the videos and histology, delineated known neoplasia, forming a consensus criterion standard. 7 expert and 7 trainee endoscopists marked one position per image where they would expect a target biopsy to identify dysplastic tissue. The same expert panel then reviewed magnification images and using a previously validated classification system attempted to classify mucosa as dysplastic or non-dysplastic based on the mucosal and vascular patterns observed on magnification endoscopy. Diagnostic accuracy, sensitivity, specificity, NPV, and PPV were calculated. Improvements in dysplasia detection in HD-WLE vs OE and interobserver agreement (IA) were assessed by multilevel logistic regression analysis and Krippendorff's alpha, respectively. Improvements in diagnostic performance were expressed as an odds ratio between the odds of an improvement in OE, compared with the odds of an improvement in WLE

Results

Accuracy of neoplasia detection was significantly higher in all trainees using OE versus WLE (76% vs 63%) and in 6 experts (84% vs 77%). OE improved sensitivity of dysplasia detection compared with WLE in 6 trainees (81% vs 71%) and 5 experts (77% vs 67%). Specificity improved in 6 trainees using OE vs WLE (70% vs 55%) and in 5 experts (92% vs 86%). PPV improved in both an expert and trainee cohort but NPV only improved significantly in trainees. Using the MV classification and OE magnification endoscopy compared with HD-WLE, we demonstrated improvements in accuracy (79.9% vs 66.7%), sensitivity (86.3% vs 83.4%) and specificity (71.2% vs 53.6%) of dysplasia detection. PPV improved (62% to 76.6%), as did NPV (67.7% to 78.5%).Interobserver agreement also improved using OE from 0.30 to 0.55.

Conclusion

iScan OE may improve dysplasia detection on endoscopic imaging of BE, as well as the accuracy of histology prediction compared with HD-WLE, when using OE magnification endoscopy in conjunction with a simple classification system in both expert and non-expert endoscopists

Introduction

Barrett's esophagus (BE) is a known precursor to esophageal adenocarcinoma (OAC), a cancer with a dismal 5-year survival of around 17.9%[1]. Early neoplastic lesions arising in BE and confined to the mucosa are amenable to endoscopic eradication therapy (EET), with high cure rates[2–5], avoiding the need for esophagectomy. To facilitate the early detection of these lesions patients with histologically confirmed BE, should be enrolled into an interval surveillance program[6]. The Seattle protocol (SP)[7] requires that after examination of the BE segment by HD-white light (HD-WLE) endoscopy, visible abnormalities are target biopsied, then random quadrantic biopsy specimens are taken at 1 to 2 centimeters through the remaining segment.

Early dysplastic lesions are often subtle and focal and so are easily missed on endoscopic surveillance examinations. Inherent limitations of the Seattle protocol and the sensitivity of HD-WLE may impair the detection of early neoplasia. Visrodia et al[8] estimate up to 25.3% (95% CI,16.4%-36.8%) of new adenocarcinoma diagnoses follow a normal surveillance endoscopy in the preceding year. Less than 5% of the Barrett's epithelium is sampled during a typical endoscopy with SP biopsies and adherence to the protocol worsens with increased segment length[9]. Furthermore, SP biopsies generate a large number of biopsy samples with a low reported sensitivity for dysplasia detection, ranging from 28% to 85%[10]. Because early neoplasia is subtle, improved identification of areas suspicious for such changes to facilitate targeted biopsies is vital, both to improve early detection and to reduce procedure times and number of unnecessary biopsy specimens taken.

Enhanced visualization of the BE mucosa, using advanced endoscopic imaging systems, may improve the detection of dysplasia, which may be recognized based on mucosal and vascular

abnormalities[11–13]. However, most studies to date have validated these classification systems in expert endoscopists working in high-volume Barrett's referral centers; as such they may not be a true reflection of a general population of endoscopists in smaller centers performing routine Barrett's surveillance.

The iScan Optical Enhancement (OE) system (Pentax Hoya, Japan) is an alternative and novel advanced imaging technology with a range of clinical applications in upper and lower gastrointestinal endoscopy[14]. The OE platform uses both novel pre- and post-processing technologies to provide surface enhancement of the superficial structures of the mucosa, as well as improving the visibility of the mucosal microvasculature. Using a new optical filter, OE delivers specific wavelengths of light, which correspond with the main absorption spectrum of human haemoglobin (415 nm, 540 nm, and 570 nm) at high light intensities, thereby highlighting the microvasculature within the most superficial layers of mucosa (figure 1). The use of magnification endoscopy coupled with OE also facilitates closer interrogation, at up to 136x resolution, of the microstructures of the mucosa and its vasculature

A recent study by our working group has validated the use of the previous iScan systems (contrast, surface and tone enhancement or iScan 1/2/3) in the detection of BE dysplasia using a simple classification system based on mucosal and vascular patterns[13]. A further improvement was demonstrated with application of the chromo-endoscopic agent acetic acid to the mucosa; although clinically this may lengthen procedure times. The latest iteration of the Pentax system, iScan Optical Enhancement (OE), may confer an additional improvement in dysplasia detection without the additional use of acetic acid.

We aim to assess the clinical utility of iScan OE in the endoscopic detection of early BE neoplasia in a group of trainee and expert endoscopists. This represents the first study to assess the role of OE in BE associated neoplasia detection and compare the outcomes in both trainee and expert endoscopists. We have regarded trainee endoscopists in our study as surrogates for non-expert endoscopists at low-volume centers. This may be representative of the improvements that may be derived by endoscopists in low volume centers who have less experience with advanced imaging modalities. Secondly, we aim to validate a previously published consensus driven magnification endoscopy classification system for use with OE compared with HD-WLE in expert endoscopists[13].

Methods

Patient recruitment, inclusion and exclusion criteria

Patients attending 1 of 3 European referral centers for either endoscopic surveillance or therapy of at least C1M2 BE were enrolled between Feb 2016 and Oct 2017. Patients were excluded if they had received previous endoscopic eradication therapy for BE neoplasia. Patients with active esophageal ulceration or varices were also excluded. The study had ethical approval and was registered with ISRCTN (Registration: 58235785)

Endoscopic procedures and image acquisition

All endoscopic examinations were undertaken by endoscopists with extensive expertise in the assessment and management of dysplastic BE (R.J.H., R.B.). Mucous was removed from the esophageal mucosa using a solution of simeticone and water. The endoscopist then slowly withdrew the endoscope from the GOJ to the proximal extent of the BE segment, described as a "pull-through" (figure 2). All examinations were recorded in HD-WLE and iScan OE, before biopsy or endoscopic resection of suspicious areas. All videos were recorded using a Pentax EG-2990Zi MagniView endoscope with *i*-Scan EPK-i7010 high-definition video processor.

Tissue acquisition for histologic analysis

The borders of areas identified as suspicious for neoplasia were marked by electrocautery snare. In the majority of cases tissue was then resected by EMR or alternatively were sampled by forceps biopsy. Biopsies of suspected non-dysplastic areas were taken in accordance with the Seattle protocol. Histologic samples were affixed to cork board with pins and placed in formalin, by nursing staff experienced in handling resection specimens. Samples were then embedded in paraffin in the histopathology lab and cut to give serial levels. All histopathology samples containing dysplasia were reviewed and the diagnosis confirmed by 2 expert GI pathologists and the protocol for sample processing was identical at all sites.

Image pre-processing and analysis

Images were extracted as single frames from high-definition video recordings and saved in the high-quality .png format. Images were taken throughout the distal, middle, and proximal BE segment to simulate the normal "pullthrough" maneuver performed during BE surveillance (figure 2). All videos were assessed by a study member for blurring, clarity, and to ensure they were representative of informative "real life" endoscopic images. Videos were also excluded if the location of histological samples taken at the time of endoscopy could not be established on the recorded video (eg, if the resection margins on EMR were not clearly visualized due to blood or mucus in the recording or the biopsy locations were not clearly visualized/recorded at the index endoscopy due to peristalsis). A range of pathological lesions were selected including LGD, HGD, and OAC as well as videos of normal BE segments, in order to replicate the early lesions typically encountered in clinical practice. Matched images using HD-WLE and iScan OE were selected where possible. A total of 262 images were included for analysis (130 HD-WLE and 132 OE, mean, and median 3 images per patient, range 1-5)

Establishing an expert consensus

Two endoscopists who recorded the endoscopic examinations (R.J.H., R.B.), performed the biopsies of suspicious areas or the EMR of dysplastic lesions, then reviewed images or videos of the complete lesion, EMR resection margins or biopsy locations before delineating neoplastic areas seen on the images used in this study. For both HD-WLE and OE images,

each expert assessed each image and delineated areas that represented histologically confirmed dysplastic tissue using the GNU image manipulation program (GIMP V2.8.22). These delineations were performed after the 2 experts had reviewed the videos of the index endoscopy and assessed the resection margins of dysplastic tissue taken at that time. Both expert delineations were used to generate an overlay on the original image to define the area deemed positive for dysplasia, which was also very closely correlated, as described above, to histologically proven dysplasia. The area where both expert's delineations overlapped was deemed positive for dysplasia (figure 3).

Evaluation of images by trainees and expert endoscopists

A second group of 7 experts and 7 trainee endoscopists were asked to individually assess each image. Experts were defined as clinicians who had completed their formal advanced endoscopic training and work in high-volume referral centers specializing in the assessment and management of BE associated neoplasia, with local appraisal and clinical audit validating high quality outcomes. Trainees were defined as those who had not yet completed formal training but had at least 3 years of endoscopy experience, previous exposure to BE surveillance endoscopy but with no formal training using OE. All endoscopists were blinded to histology, the initial endoscopy video and the resection margins of lesions depicted. Study participants reviewed the images of lesions alone, using high definition (HD) screens. Participants were required to review all HD-WLE images first, followed by all OE images. To simulate the selection of a site to target biopsy in the clinical setting endoscopists were instructed to place a single marker on each image over the area that they felt was most likely to yield a biopsy with BE neoplasia. A positive result was recorded when an endoscopists target biopsy fell within the consensus area delineated by the expert endoscopists (figure 5).

Assessing the role magnification endoscopy using HD-WLE and OE for recognition of dysplastic tissues at potential resection margins

As the second part of the study, magnification endoscopy was used to produce matched images of the mucosal surface at up to 136x zoom in both HD-WLE and OE of normal and abnormal areas of BE (figure 7A and B). In this part of the study only the experts were asked to classify images as dysplastic or non-dysplastic based on the MV classification previously validated for use with the iScan system (figure 6). This decision was made as currently magnification endoscopy is typically only used in high-volume referral centers to assist not only with lesion recognition but also demarcation and endoscopic resection planning so it was felt not relevant to non-expert endoscopists. All experts had prior knowledge and training in the use this classification system from previous studies [13].

Statistical analysis

All statistical analysis was undertaken by an independent medical statistician. Dysplasia detection accuracy, sensitivity, specificity, positive and negative predictive values were calculated per endoscopist, on a per-image basis. To allow for the non-independence of the data (due to multiple measurements of images from the same patient), multilevel logistic regression was used for the analysis of diagnostic performance, using a cross-classified structure, in which individual measurements were nested within both patients and observers.

Improvements were reported as an odds ratio (odds of an improvement using OE compared with odds for an improvement using WLE)

Only images deemed positive for dysplasia were included in the analysis of sensitivity, those deemed negative for dysplasia were included in the analysis of specificity. PPV analyses were restricted to images where the observer indicated neoplasia was present, NPV analyses were restricted to images where the observer indicated neoplasia was absent.

Agreement between observers was measured for each imaging method using the kappa statistic. The K values and their standard errors were used to perform a z-test to examine if the agreement varied statistically between modalities. A modified Likert scale developed by Landis and Koch was used to interpret K values (poor <0.20; fair =0.21-0.40, moderate =0.41-0.60, substantial =0.61-0.80; very good =0.81-1.00).

Sample size calculation

A previous study by our group demonstrated dysplasia detection accuracy using HD-WLE of 76%[13]. Our study was powered to detect an improvement in accuracy to 82% with the addition of OE. Images were produced using each modality; the sample size calculations are based on comparing between 2 independent groups; we acknowledge that the images results may not be independent of each other due to multiple measurements per patient. Using a 5% significance level and 80% power, we calculated that 723 individual measurements per modality are required. The degree of clustering between repeat measurements from the same patient is unknown, to allow for non-independence of the data we propose to double the calculated sample size based on independent observations. 1446 measurements for each of the 2 modalities are required. Assuming a mean of 3 images per modality per patient were acquired, this would yield a total 42 images per modality per patient (3 images x 14 endoscopists). This implies that 35 patients are required for the study

Results

Patient characteristics

80 patients were recruited to the study. Videos were excluded if they were deemed to be of poor quality (blurred, bleeding mucosa or the pullthrough was out of focus etc), or matched histology corresponding to the imaged mucosa was not retrieved at the index endoscopy – (for example, patients in whom the resection site was neither documented clearly or recorded on video). 262 images from 41 patients were included after quality control (figure 4). 62/130 HD-WLE images contained visible dysplasia and 69/132 OE images contained visible dysplasia. The histology of the lesions assessed within our patient cohort are summarized in table 1.

Dysplasia detection rates in expert and trainee endoscopists using iScan OE

The accuracy of dysplasia detection improved in all trainees from 63% using HD-WLE compared with 76% using OE (OR, 2.00; 95% CI, 1.61 - 2.49; P<0.001). Sensitivity improved in 6 of 7 trainees from 71% with HD-WLE to 81% when using OE (OR, 1.93; 95% CI, 1.33 - 2.81; P=0.001). The use of OE also improved specificity in 6 of 7 trainees from 55% to 70% (OR, 2.12; 95% CI, 1.58 - 2.85; p<0.001). PPV improved from 59% to 75% (OR, 2.07; 95% CI,1.58 - 2.71; p <0.001) as did NPV from 68% to 77% (OR, 1.60; 95% CI, 1.17 - 2.20; P <0.004) when using OE compared with WLE.

The accuracy of dysplasia detection improved in all experts when using OE compared with WLE 85.6% versus 76.8% (OR, 1.74; 95% CI, 1.34 - 2.25; p<0.001) Sensitivity improved in 6 of 7 experts from 67% with WLE to 77% in OE (OR, 2.26; 95% CI, 1.55 - 3.29; P<0.001). Specificity improved in 5 of 7 experts when using OE compared with WLE, to 92% from 86% (OR, 2.13; 95% CI, 1.34 - 3.39; P=0.001). PPV improved from 81% to 91% (OR, 2.37; 95% CI, 1.51 - 3.73; P<0.001). However, NPV did not improve; from 74% to 78% (OR, 1.27; 95% CI, 0.95 - 1.69; p=0.10). Table 2 summarises the pooled diagnostic performance for trainee endoscopists, expert endoscopists and all endoscopists combined.

Validating MV classification system for lesion characterization using OE-ME

The second part of our study was to explore a previously validated and published mucosal and vascular classification with magnification endoscopy and show its performance with OE. Such a system for use with ME would facilitate the delineation of resection margins when planning EET for early neoplastic lesions.

63 HD-WLE and 90 OE still images of magnified mucosa from 54 patients were obtained. Where possible mucosal images were matched between both imaging modalities and there was a non-significant difference in the proportion of images in each group containing dysplastic tissue (29/63 vs 49/90).

Using the MV classification, our panel of experts correctly classified tissue as dysplastic or non-dysplastic with 66.7% (95% CI, 62.7% - 70.8%) accuracy using HD-WLE; this improved to 79.9% (95% CI, 77.8% - 82%) using iScan OE, where significantly more correct diagnoses were made (p <0.001). The sensitivity of dysplasia detection also improved from 82.4% (95% CI, 76.5% - 88.3%) using HD-WLE to 86.3% (95% CI, 81.5% - 91%) using OE. Specificity improved using OE; increasing from 53.6% (95% CI, 43.5% - 63.7%) in HD-WLE to 71.2% (95% CI, 67.5% - 74.8%) using iScan OE (table 3).

We demonstrated an improvement in interobserver agreement between experts when classifying BE mucosa as dysplastic or nondysplastic based on our proposed MV classification. Overall interobserver agreement was fair using HD-WLE (0.30), improving to moderate agreement using OE (0.53). The use of OE to classify either mucosal features or vascular features in isolation also improved interobserver agreement compared with HD-WLE, as shown in table 4.

Discussion

Inherent limitations of Barrett's surveillance using the Seattle protocol raises the potential for early, treatable, esophageal cancers to be missed. Up to 36% of early lesions are not detected through endoscopic surveillance in the year preceding diagnosis[8]. Advanced endoscopic imaging platforms may improve the early detection of such lesions.

Our study examines 2 main concepts. First, can virtual chromoendoscopy with iScan OE improve dysplasia detection during the endoscopic assessment of BE. Second, could we validate a previously proposed classification system, based on mucosal and vascular patterns, for use with OE magnification endoscopy. A system with sufficient accuracy, sensitivity and specificity could both improve neoplasia detection and change how biopsy specimens are taken during BE surveillance from random to a more targeted approach. We envisage that abnormal areas could be detected on withdrawal of the endoscope through the BE segment, with abnormal areas and potential resection margins interrogated further with magnification endoscopy. A more targeted approach could potentially reduce procedure times and streamline workflow in endoscopy suites and pathology departments.

We show that the use of iScan OE improves the diagnostic accuracy of both trainee and expert endoscopists performing endoscopic surveillance of Barrett's esophagus. We demonstrate a significant improvement in trainee endoscopists accuracy in identifying early neoplasia when using OE compared with HD-WLE (63% vs 76%). A similar improvement in the accuracy of dysplasia detection was also observed in a panel of expert endoscopists when using OE compared with WLE (77% vs 84%). Interestingly the use of optical enhancement imaging by trainees improved accuracy to a level comparable with those of expert endoscopists. We propose that trainees in our high-volume center could be considered a surrogate for non-expert endoscopists who have completed training but work in low-volume centers. The use of this advanced imaging modality, therefore, shows promise if it were used within the training environment or in a secondary care setting where caseloads of early Barrett's neoplasia might be lower compared with the centers used in this study.

We have also validated a previously proposed magnification endoscopy classification system for use with the iScan OE platform[13]. The MV classification system, in combination with OE magnification endoscopy, confers a significant improvement in accuracy of dysplasia detection using OE compared with WLE, with accuracy improving from 66.7% to 79.9%. Sensitivity improved from 83.4% to 86.3% with OE. Improvements were also seen in specificity, PPV and NPV, as well as a favorable interobserver agreement (k=0.53 vs 0.30). We have also shown improved agreement using both criteria for of our classification individually, indicating that they should be used in combination.

Our study compares favorably with other published work in this field. A large, well-designed trial validated a similar classification system for use with NBI magnification endoscopy. The BING classification identified dysplasia with 85% accuracy, 80% sensitivity and specificity, PPV and NPV of 88%, 81%, and 88%, respectively[11]. Although the OE system has better sensitivity, specificity, PPV, and comparable accuracy in this study, our NPV was lower (78%).

A follow-up study by Nogales et al[15] using a larger number of images for testing demonstrated accuracies for dysplasia detection of 81.1% using the BING criteria, comparable with our result of 84%. In our study OE attained higher sensitivities than NBI (77% vs 48.4%), but lower NPV. Comparison of our results suggest that OE may improve the detection of dysplasia compared with NBI but remains a modality with lower negative predictive value.

Previous work from our group assessing the previously used iScan 1,2, and 3 for BE neoplasia detection suggests that OE may be a preferable modality. Lipman et al[13] reported accuracy, sensitivity and specificity of dysplasia detection using the MV classification of 77%, 81%, and 74%, respectively[13]. We report 79.9% accuracy, 86.2% sensitivity, and 71.3% specificity. The accuracy of dysplasia detection on endoscopic pullthrough using OE was greatly improved at 84% compared with detection accuracy of 76% reported in the iScan 1 study; furthermore, we demonstrate higher detection accuracy without the addition of acetic acid.

Our current results do not meet Preservation and Incorporation of Endoscopic Innovations (PIVI) guidelines for the incorporation of new technologies into endoscopy[16]. These are defined as sensitivity, NPV, and specificity for dysplasia detection of >90%, >98%, and >80%, respectively. The sensitivity of dysplasia detection using OE approaches this for magnification endoscopy (86.3%), but the technology is not specific enough. We note that NBI has also not consistently exceeded PIVI thresholds, nor does HD-WLE in this study. We therefore suggest that although OE should not routinely replace HD-WLE for use in BE surveillance, it may serve as a useful adjunct to improve the early detection of neoplastic tissue in trainee endoscopists, and endoscopists who have completed formal training but may not perform Barrett's surveillance regularly.

The primary limitation of our study is that it used still images rather than real time videos, a more artificial and controlled situation than might be expected in clinical practice. To mitigate this, we have used sequential still images throughout the BE segment to mimic the withdrawal procedure performed in clinical practice. Further studies using this platform should focus on assessing dysplasia detection using videos. The prevalence of early neoplasia in our cohort introduces a potential bias, our cohort is an enriched population with around 50% of our subjects exhibiting early neoplasia. This is in line with other studies and logistically it would be difficult to achieve a sufficiently powered study with a cohort prevalence reflective of day to day practice.

All clinicians, both experts and trainees, practice within academic or referral centers and so potentially may have more expertise in the assessment and management of early BE associated neoplasia than clinicians practicing in a more general setting. The utility of OE and our MV classification system should therefore be assessed in a wider range of settings by clinicians with more varied experience.

In summary, we have demonstrated that iScan OE improves the accuracy of both trainee and expert endoscopists for the detection of BE associated neoplasia. We have also developed a novel, consensus driven, and internally validated classification designed to facilitate the accurate prediction of BE mucosal histology using iScan OE magnification endoscopy. Our classification is intuitive and, if externally validated, offers a potential system for routine clinical use.

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TABLES

Lesion characteristics		
Histology	NDBE	15
	LGD	2
	HGD	11
	M1-3 adenocarcinoma	12
	≥ SM1 adenocarcinoma	1

Table 1: Summary of lesion histology for patients recruited

Performance measure	WLE	OE	Odds ratio (95% CI)	*P* value
Trainees				
Sensitivity	71% (309/434)	81% (379/469)	1.93 (1.33 - 2.81)	**0.001**
Specificity	55% (261/476)	70% (301/427)	2.12 (1.58 - 2.85)	**<0.001**
PPV	59% (309/524)	75% (379/505)	2.07 (1.58 - 2.71)	**<0.001**
NPV	68% (261/386	77% (301/391)	1.60 (1.17 - 2.20)	**0.004**
Accuracy	63% (570/910)	76% (680/896)	2.00 (1.61 - 2.49)	**<0.001**
Experts				
Sensitivity	67% (291/434)	77% (360/469)	2.26 (1.55 - 3.29)	**<0.001**
Specificity	86% (407/476)	92% (393/427)	2.13 (1.34 - 3.39)	**0.001**
PPV	81% (291/360)	91% (360/394)	2.37 (1.51 - 3.73)	**<0.001**
NPV	74% (407/550)	78% (693/502)	1.27 (0.95 - 1.69)	0.10
Accuracy	77% (698/910)	84% (753/896)	1.74 (1.34 - 2.25)	**<0.001**
All				
Sensitivity	69% (600/868)	78% (739/938)	2.03 (1.57 - 2.63)	**<0.001**
Specificity	70% (668/952)	81% (694/854)	2.10 (1.64 - 2.70)	**<0.001**
PPV	68% (600/884)	82% (739/899)	2.14 (1.70 - 2.69)	**<0.001**
NPV	71% (668/936)	78% (694/893)	1.41 (1.13 - 1.74)	**0.002**
Accuracy	70% (1268/1820)	80% (1433/1792)	1.84 (1.56 - 2.18)	**<0.001**

Table 2: Diagnostic performance measures in OE compared with HD-WLE for dysplasia detection in both a trainee cohort, expert cohort and combined cohort. Odds ratio expressed as the odds for an improvement in diagnostic performance using OE compared with the odds for an improvement in diagnostic performance in HD-WLE

Observer	WLE accuracy (%)	OE accuracy (%)	WLE sensitivity (%)	OE sensitivity (%)	WLE specificity (%)	OE specificity (%)	WLE PPV	OE PPV	WLE NPV	OE NPV
1	69.8	75.6	79.3	75.6	61.8	73.0	63.9	79.2	77.8	71.1
2	65.6	77.9	70.0	79.6	61.7	75.7	63.9	81.3	70.0	73.7
3	68.3	79.1	83.0	81.6	54.6	75.7	62.5	81.6	78.3	75.7
4	65.0	79.1	82.8	91.8	50.0	62.2	58.5	76.3	77.3	85.2
5	76.2	83.7	79.3	89.8	73.5	73.7	71.9	81.5	80.7	84.9
6	63.5	81.4	96.6	91.8	35.3	67.6	56.0	79.0	92.3	86.2
7	58.7	82.6	85.7	91.8	38.2	70.3	53.3	80.4	76.5	86.7
Mean (±SD)	66.7 (±5)	79.9 (±2)	83.4 (±8)	86.3 (±6)	53.6 (±13)	71.2 (±2)	61.4 (±6)	79.9 (±2)	79.0 (±6)	80.5 (±7)

Table 3: Performance measures for the classification of BE as NDBE or DBE using the MV classification

	Overall assessment (NDBE v DBE) (95% CI)	M classification (95% CI)	V classification (95% CI)
WLE	0.30 (0.10-0.49)	0.33 (0.13-0.52)	0.38 (0.20-0.56)
OE	0.53 (0.34-0.70)	0.50 (0.33-0.66)	0.52 (0.35-0.68)

Table 4: Interobserver agreement for dysplasia detection, mucosal pattern assessment and vascular pattern assessment using HD-WLE compared with OE.

FIGURE LEGENDS

Figure 1: Schematic diagram of the image pre and post processing technology incorporated by the iScan OE technology.

Figure 2: Representative example of how images were generated throughout the BE segment by carrying out a steady "pull through" sequence to simulate the normal endoscope withdrawal manoeuvre performed during BE surveillance endoscopy. Top row iScan OE, bottom row HD-WLE.

Figure 3: Representative example showing how the gold standard delineation *(yellow, right)* was generated from the two expert delineations shown in the middle column *(red and blue)* of a suspicious area seen here in iScan OE

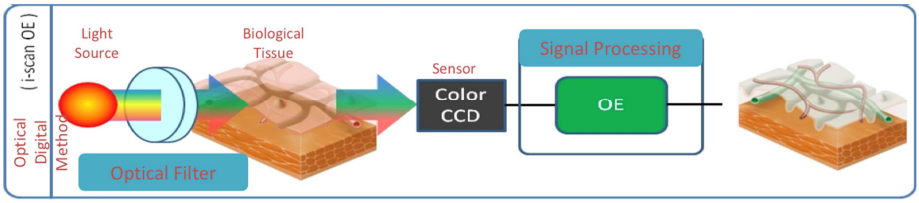
Figure 4: Schematic illustrating patient recruitment and exclusion from this study.

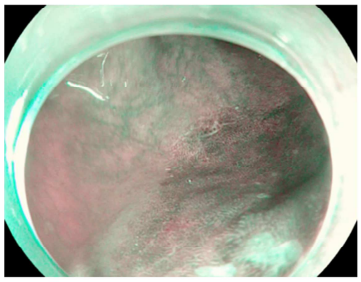
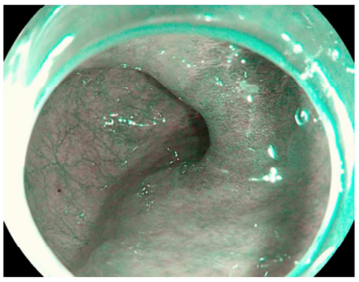
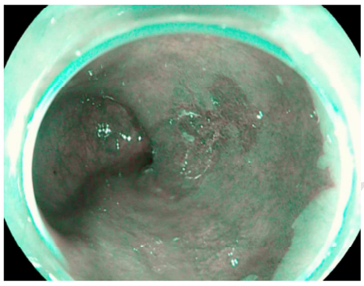
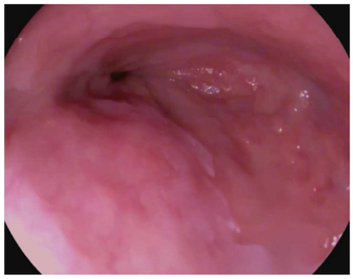
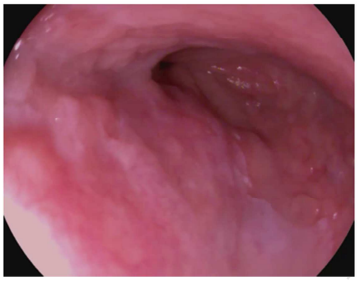
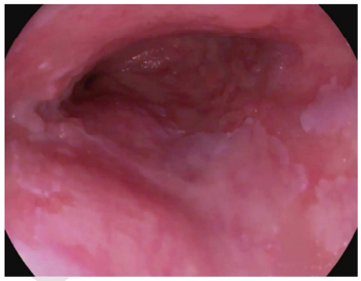
Figure 5: Illustrative example of expert delineated consensus area considered positive for dysplasia. Assessor biopsy sites considered a true positive *(white)* and false negative *(black).*

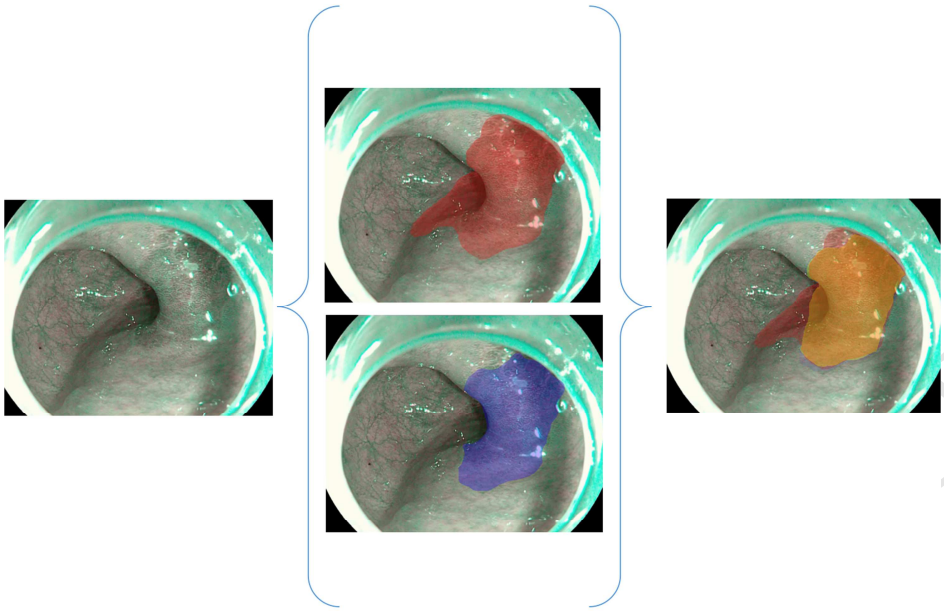
Figure 6: Summary of MV classification for HD WLE and OE magnification endoscopy (ME).

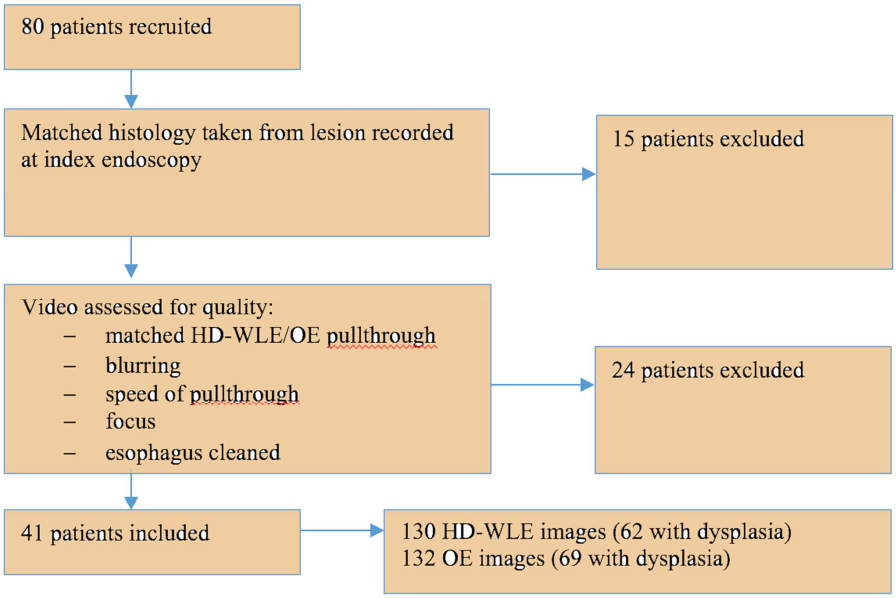
Figure 7A: Representative examples of normal and abnormal areas of BE mucosa on HD-WLE magnification endoscopy.

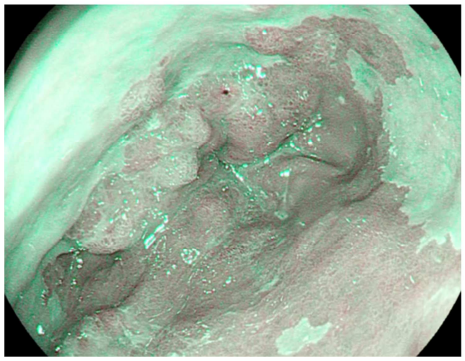
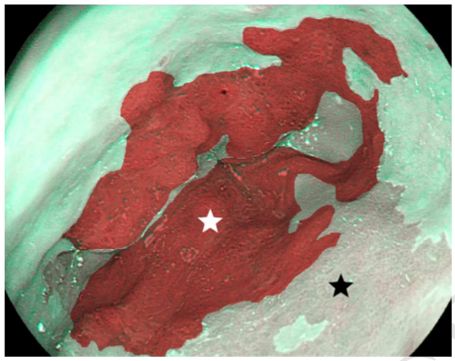
Figure 7B: Representative examples of normal and abnormal areas of BE mucosa on OE magnification endoscopy.



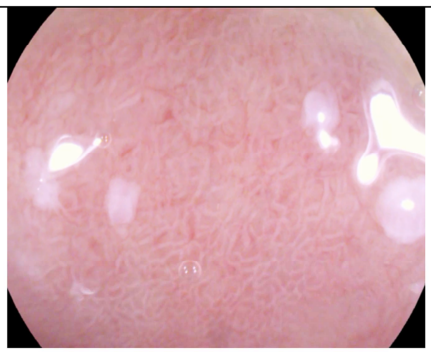
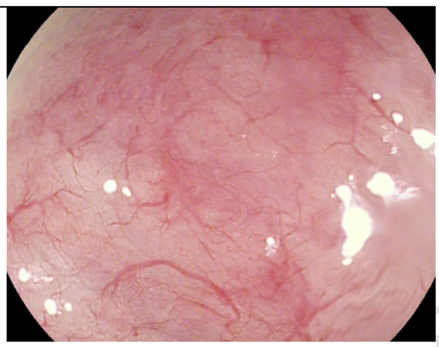
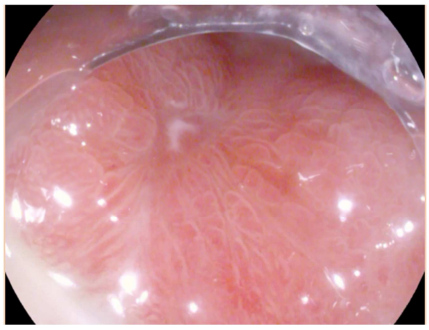
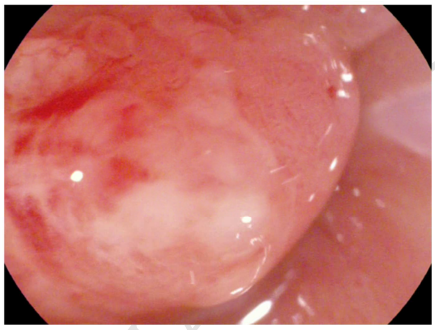
Distal segment	Mid-segment	Proximal segment
		
		

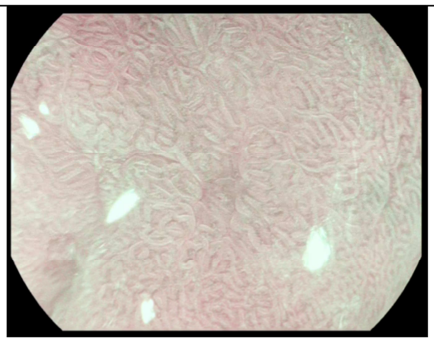
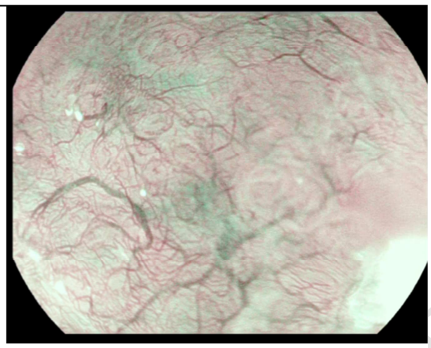
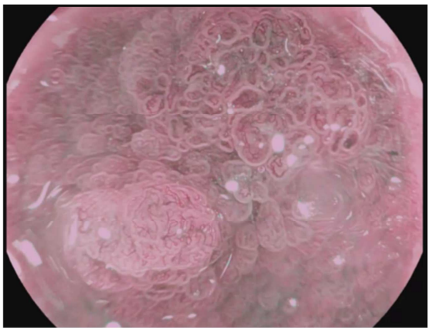
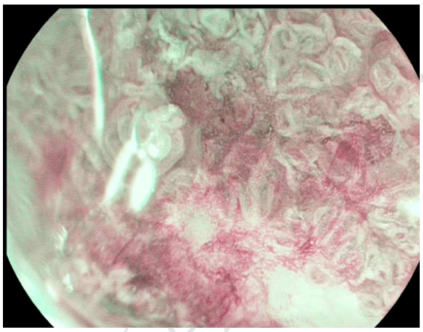




OE image	Expert consensus
	

	Mucosal features (M)	Vascular features (V)
1	Regular, gyric pit pattern	Regular, fine-caliber vessels between pits
2	Irregular, disordered pit pattern or featureless mucosa	Irregular, tortuous or dilated vessels not confined by pits

	V1	V2
M1		
M2		

	V1	V2
M1		
M2		

BE – Barrett's oesophagus
OAC – Oesophageal adenocarcinoma
EET – Endoscopic eradication therapy
SP – Seattle Protocol
HD-WLE – High definition white light endoscopy
OE – Optical Enhancement
LGD – Low grade dysplasia
HGD – High grade dysplasia
NDBE – Non dysplastic Barrett's oesophagus
DBE – Dysplastic Barrett's oesophagus

HD-WLE		TRAINEES Was correct overall diagnosis made per patient?						
Patient number	**Dysplasia present**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	N	Y	Y	N	N	Y	N	N
2	Y	Y	N	Y	Y	Y	Y	Y
3	N	Y	N	N	N	N	N	N
4	Y	N	Y	Y	N	N	Y	N
5	Y	Y	Y	Y	Y	Y	Y	Y
6	N	Y	N	N	N	N	N	N
7	Y	N	Y	Y	N	N	N	Y
8	N	Y	N	N	N	N	N	N
9	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	N	Y	Y	Y	Y	N
11	Y	N	Y	Y	Y	Y	Y	N
12	N	Y	N	N	N	N	N	N
13	N	Y	N	N	N	N	Y	N
14	Y	N	Y	Y	Y	Y	Y	Y
15	N	Y	N	Y	N	N	N	N
16	N	N	N	N	N	N	N	N
17	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	N	Y	Y	Y	Y	Y
19	Y	N	N	Y	N	Y	N	Y
20	Y	Y	Y	N	N	N	N	N
21	Y	N	N	Y	Y	Y	Y	Y
22	N	Y	N	Y	N	N	N	N
23	Y	Y	Y	Y	Y	Y	Y	Y
24	Y	Y	Y	Y	Y	N	Y	Y
25	Y	Y	Y	Y	Y	Y	Y	Y
26	Y	N	N	Y	N	Y	Y	Y
27	N	Y	Y	N	N	N	N	N
28	Y	Y	N	Y	Y	Y	Y	Y
29	Y	Y	Y	Y	Y	Y	Y	Y
30	N	Y	Y	N	Y	N	Y	N
31	Y	N	Y	Y	Y	Y	Y	Y
32	Y	N	Y	Y	Y	Y	Y	Y
33	Y	Y	Y	Y	Y	Y	Y	Y
34	N	N	N	N	N	N	N	Y
35	N	N	Y	N	N	N	Y	N
36	N	Y	Y	N	Y	N	N	N
37	Y	Y	N	Y	Y	Y	Y	Y
38	N	Y	N	N	N	N	N	N
39	Y	Y	N	N	Y	N	N	N
40	Y	Y	Y	Y	Y	Y	Y	Y
41	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary table 1: depicts whether each patient had histologically confirmed dysplasia within their images and the number of correct diagnoses made by trainee endoscopists using HD-WLE

OE		TRAINEES Was correct overall diagnosis made per patient?						
Patient number	**Dysplasia present**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	N	Y	Y	Y	Y	N	Y	N
2	Y	Y	Y	Y	Y	Y	Y	Y
3	N	Y	Y	Y	N	Y	N	N
4	Y	N	Y	Y	N	N	N	N
5	Y	Y	Y	Y	Y	Y	Y	Y
6	N	Y	N	N	N	Y	N	N
7	Y	N	Y	Y	Y	Y	Y	Y
8	N	Y	N	Y	N	N	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	N	Y	Y	N	Y	Y	Y
11	Y	N	Y	Y	Y	Y	Y	Y
12	N	Y	N	N	Y	Y	N	N
13	N	Y	Y	N	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y
15	N	Y	N	N	N	N	N	N
16	N	Y	N	N	N	Y	Y	N
17	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	Y	Y	Y	N	Y	Y	Y
20	Y	Y	Y	Y	N	N	Y	Y
21	Y	N	N	Y	Y	N	Y	Y
22	N	N	Y	N	N	N	N	N
23	Y	Y	Y	Y	Y	Y	Y	Y
24	Y	Y	Y	Y	Y	Y	Y	Y
25	Y	Y	Y	Y	Y	Y	Y	Y
26	Y	Y	Y	Y	Y	Y	Y	Y
27	N	Y	N	N	Y	N	Y	Y
28	Y	Y	Y	Y	N	Y	Y	Y
29	Y	Y	Y	Y	Y	Y	Y	Y
30	N	N	N	N	Y	N	N	N
31	Y	Y	Y	Y	Y	Y	Y	Y
32	Y	Y	Y	Y	Y	Y	Y	Y
33	Y	Y	Y	Y	Y	Y	Y	Y
34	N	N	N	N	N	N	N	N
35	Y	N	Y	Y	Y	Y	Y	Y
36	N	N	N	N	Y	Y	N	N
37	Y	Y	Y	N	Y	Y	Y	Y
38	N	Y	Y	N	Y	Y	N	N
39	Y	N	N	Y	N	N	Y	Y
40	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary table 2: depicts whether each patient had histologically confirmed dysplasia within their images and the number of correct diagnoses made by trainee endoscopists using OE

HD-WLE		EXPERTS Was correct overall diagnosis made per patient?						
Patient number	**Dysplasia present**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	N	N	N	Y	Y	Y	Y	N
2	Y	Y	N	Y	Y	Y	Y	Y
3	N	N	Y	Y	Y	N	Y	N
4	Y	Y	Y	N	N	Y	Y	N
5	Y	Y	Y	N	Y	Y	Y	Y
6	N	Y	Y	Y	Y	N	N	N
7	Y	Y	Y	Y	N	Y	Y	Y
8	N	Y	Y	Y	Y	Y	N	Y
9	Y	Y	Y	Y	Y	N	Y	Y
10	Y	Y	Y	N	N	N	N	N
11	Y	Y	Y	Y	N	Y	N	Y
12	N	N	Y	Y	Y	Y	Y	N
13	N	Y	Y	Y	Y	Y	Y	Y
14	Y	Y	Y	N	Y	Y	Y	Y
15	N	N	Y	Y	N	N	N	N
16	N	N	Y	Y	N	Y	Y	N
17	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	N	N	N	N	N	N	Y
20	Y	Y	Y	N	Y	N	Y	Y
21	Y	Y	N	N	N	N	N	N
22	N	N	Y	N	N	Y	Y	N
23	Y	Y	Y	Y	Y	N	Y	Y
24	Y	Y	Y	Y	Y	Y	Y	Y
25	Y	N	Y	Y	Y	Y	N	Y
26	Y	N	N	N	N	N	N	Y
27	N	N	Y	Y	Y	Y	N	Y
28	Y	Y	Y	Y	Y	Y	Y	Y
29	Y	Y	Y	Y	Y	Y	Y	Y
30	N	Y	Y	Y	Y	Y	Y	N
31	Y	Y	Y	N	Y	N	Y	Y
32	Y	Y	N	N	Y	N	Y	Y
33	Y	Y	Y	Y	Y	Y	Y	Y
34	N	Y	Y	Y	Y	Y	Y	Y
35	N	Y	Y	Y	Y	Y	Y	Y
36	N	Y	Y	Y	Y	Y	Y	Y
37	Y	Y	Y	Y	Y	Y	Y	Y
38	N	Y	Y	Y	Y	Y	Y	Y
39	Y	N	N	N	Y	Y	Y	Y
40	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary table 3: depicts whether each patient had histologically confirmed dysplasia within their images and the number of correct diagnoses made by expert endoscopists using HD-WLE

OE		EXPERTS Was correct overall diagnosis made per patient?						
Patient number	**Dysplasia present**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	N	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y
3	N	Y	Y	Y	Y	Y	Y	N
4	Y	Y	Y	Y	N	Y	Y	N
5	Y	Y	Y	Y	Y	Y	Y	Y
6	N	N	N	N	N	N	N	N
7	Y	Y	Y	Y	Y	Y	Y	Y
8	N	Y	Y	Y	N	Y	Y	N
9	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	N	Y	N	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y
12	N	Y	Y	Y	Y	N	Y	Y
13	N	Y	Y	Y	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	Y	Y	N	Y	N	N
16	N	Y	Y	Y	N	Y	Y	N
17	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	Y	N	Y	N	Y	Y	Y
20	Y	N	N	N	Y	Y	N	N
21	Y	N	Y	N	Y	N	N	Y
22	N	Y	Y	N	Y	N	N	N
23	Y	Y	Y	Y	Y	N	Y	Y
24	Y	Y	Y	Y	Y	Y	Y	N
25	Y	Y	Y	Y	Y	Y	Y	Y
26	Y	Y	Y	Y	Y	N	N	Y
27	N	Y	Y	Y	Y	Y	Y	Y
28	Y	Y	Y	Y	Y	Y	Y	Y
29	Y	Y	Y	Y	Y	Y	Y	Y
30	N	Y	Y	N	Y	Y	Y	Y
31	Y	Y	Y	Y	Y	N	Y	Y
32	Y	N	N	Y	Y	Y	Y	Y
33	Y	Y	Y	Y	Y	Y	Y	Y
34	N	Y	Y	Y	N	N	N	Y
35	Y	Y	Y	N	Y	N	N	N
36	N	Y	Y	Y	Y	Y	Y	N
37	Y	Y	Y	Y	Y	Y	Y	Y
38	N	Y	Y	Y	Y	Y	Y	Y
39	Y	Y	Y	N	Y	N	Y	Y
40	Y	Y	Y	Y	Y	Y	Y	Y

Supplementary table 4: depicts whether each patient had histologically confirmed dysplasia within their images and the number of correct diagnoses made by expert endoscopists using OE