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ABSTRACT

Background & Aims: Prediction of histology of small polyps facilitates colonoscopic treatment. We aimed 1) to develop a simplified polyp classification system 2) to evaluate its performance in predicting polyp histology 3) to reproduce the classification by trainees using multiplatform endoscopic systems.

Methods: Eight international electronic chromoendoscopy experts participated in the development. In phase 1, a new simplified endoscopic classification for polyps (Simplified Identification Method for Polyp Labeling during Endoscopy - SIMPLE) was created using OE-iSCAN. In phase 2, the accuracy, level of confidence and inter-observer agreement to predict polyp histology before and after training and univariable/multivariable analysis of the endoscopic features were performed. In phase 3 reproducibility of SIMPLE by trainees using different endoscopy platforms was evaluated.

Results: Using the SIMPLE, the accuracy of experts for prediction of polyp was 83 % (95% CI: 77- 88) before and improved to 94% (95% CI: 89 - 97; p=0.002) after training. The sensitivity, specificity, PPV, NPV, after training were 97%, 88%, 95%, 91%. The inter-observer agreement of polyp diagnosis improved from 0.46 (95% CI: 0.30-0.64) to 0.66 (95% CI: 0.48-0.82) after training. The trainees demonstrated that the SIMPLE classification is applicable across endoscopy platforms, with similar post training accuracies: (0.69 (95% CI: 064-0.73) for narrow band imaging (NBI) and 0.71 (95% CI: 0.67-0.75) for SIMPLE.
Conclusions: Using the OE- iSCAN system, the new SIMPLE classification demonstrated a high degree of accuracy for adenoma diagnosis, meeting the ASGE PIVI recommendations. We demonstrated that SIMPLE may be used with either OE-iSCAN or NBI.

Abbreviations:

OE = Optical enhancement
SIMPLE= Simplified identification method for polyp labeling during endoscopy
NBI= Narrow banding imaging
HP= Hyperplastic polyp
SSA= Sessile serrated adenoma
NPV= Negative predictive value
CI= Confidence interval
PPV= Positive predictive value
NICE= NBI international colorectal endoscopic
ICE= i-scan classification for endoscopic diagnosis for colorectal polyp prediction
FICE= Fujinon intelligent chromo endoscopy
HD= High definition
DVI= Digital visual interface
CHREB= Conjoint health research ethics board
AVI= Audio video interleave
USB= Universal serial bus
ASGE= American Society for Gastrointestinal Endoscopy
PIVI= Preservation and incorporation of valuable endoscopic innovations
DVI = digital visual interface

BACKGROUND

Colonoscopy is the gold standard for detection of colonic polyps and colorectal cancer. [1,2] Novel endoscopic enhancement by virtual electronic chromoendoscopy such as narrow-band imaging [NBI, Olympus, Japan], Fuji Intelligent Chromo Endoscopy [FICE, Fujifilm, Japan], i-scan [Pentax, Japan], and confocal laser endomicroscopy techniques have been developed to aid endoscopists to better characterize the mucosal and vascular pattern of colonic polyps and predict histology [3-5] thus facilitating the adoption of the new paradigm of resect and discard i.e. the PIVI-ASGE strategy resulting in cost savings and avoidance of complications in patients. [3]

The ability of NBI to predict polyp histology has been most evaluated using the standardised NICE polyp classification. [6] A recent meta-analysis showed that the sensitivity and specificity of NBI for differentiating neoplastic from non-neoplastic polyps were 92% and 83%, respectively. Subgroup analysis also indicated that the NPV was greater than 90% for academic medical centres (91.8%; 95% CI, 89-94), for experts (93%; 95% CI, 91-96), and when the optical biopsy assessment was made with high confidence (93%; 95% CI, 90-96). This confirms that the threshold criteria of the ASGE PIVI for real-time endoscopic diagnosis for "resect and discard" strategy were met for assessment of the histology of diminutive polyps, when experts used NBI as an optical biopsy [3] However, detection and differentiation of small and diminutive colonic polyps is still difficult in "real time" in community gastroenterology practice even with advanced endoscopic techniques [7]

Education and training using computerised modules will have to be developed to train endoscopists to predict polyp histology during colonoscopy with a high level of confidence and acceptable level of accuracy before the strategy of "resect and discard" policy may be adopted. [8-11] However, an additional challenge in implementing "characterise, resect, and discard" is how to monitor quality metrics

and the sustainability of optical diagnostic performance in polyp detection and characterisation. [12]

The new OE-iSCAN system (7010 EPKi, Pentax, Japan) is a recently introduced technology, which enhances and characterises in detail the surface and vessel architecture. It incorporates optical enhancement for vessel characterisation and digital post–processing for detection and mucosal pattern characterisation. [13-14]

The aims of this study were 1) to develop a simplified endoscopic colorectal polyp classification system to differentiate non neoplastic (hyperplastic polyps) from neoplastic polyps (SSA/P and adenoma) by consensus of an international expert group using OE-iSCAN platform 2) to evaluate the performance of the simplified classification system by international experts to predict polyp histology as neoplastic or non-neoplastic. Though we initially devised the SIMPLE classification using OE-iSCAN, we aimed for it to be applicable to multiple endoscopic platforms (OE-iSCAN and NBI) and hence-3) To reproduce the simplified classification system by trainee gastroenterologists using videos from different endoscopic systems creating a multiplatform classification.

METHODS

The Conjoint Health Research Ethics Board (CHREB) of the University of Calgary, Alberta, Canada approved the study in 2015. (REB15-2311)

Participants

International experts

Eight endoscopists from Europe and North America with experience in virtual electronic chromoendoscopy (NBI, iscan and/or FICE), but *without prior experience* in the novel i-scan OE colonoscope (OE-iSCAN 7010 EPki, Pentax) participated in the study. The endoscopists involved in the study were in practice for a median of 15 years and had performed a median of 9500 colonoscopies in practice and all of them were familiar and experienced with NBI or i-SCAN, and two with FICE.

Trainees Gastroenterologists

Six trainee gastroenterologists from UK previously exposed to NBI and one on iSCAN but none of them have experience of optical diagnosis and in the OE-iSCAN system took part in the external validation of SIMPLE classification. They were considerably less experienced (median years in practice 4 years; median of number of colonoscopies 350).

Optical Enhancement–iSCAN &NBI videos

All patients provided informed consent for their videos being used anonymized for this study. Each video clip had a duration of 90 to 120 seconds. The videos showed the polyps being detected under high definition white light iSCAN 1 followed by activation of iSCAN, 2 and 3, and subsequently of OE in normal view and then a closer view with the OE-iSCAN system, and NBI in normal white light high definition view and then closer view for the Olympus EVIS LUCERA ELITE CF-HQ290. The video images focused on the polyp surface to visualise the mucosal, vascular and colour pattern. The polyps were all resected and sent to the pathologist who was blinded to the endoscopic optical characteristics for

histological examination and were assessed according to the revised Vienna classification [15]. In our institution with central accredited histopathology laboratory, all polyp specimens were reviewed by a second pathologist before the final report. The videos were saved in audio video interleave (AVI) format. Twenty-one high definition video clips of small polyps (<10 mm) were selected from an existing library in a first phase of the study and 80 video clips in a second phase of the study. The anonymized library has been collected by two investigators (MI, CT) during colonoscopy for colon cancer screening using the 7010 EPKi OE-iSCAN colonoscopy and the Olympus EVIS LUCERA ELITE CF-HQ290.

Of the twenty one polyp videos in phase 1, 7 were sessile serrated adenomas (SSA), 7 were hyperplastic polyps and 7 were tubular adenomas.The videos did not reveal the anatomic location of the polyps in the colon. Of the 80 videos for the external validation 30 were NBI and 50 OE-iSCAN (40 adenoma, 10 SSA and 30 HP). All the polyps recorded were either small (6-9mm) or diminituive (1-5 mm) in size.

The new OE-iSCAN system enables capturing of high definition (HD) video files through a Universal Serial Bus (USB) storage device. We used a dedicated EPKi-7010 video processor with digital visual interface (DVI) output to the procedure monitors, S-video output to endoPRO legacy (MPS Motion Picture Studio) standard definition image capture (video) in MPEG3 format, DVI output to external USB300 MediCapture recording device High definition image capture (video) in MPEG4 format. Our HD image capture system used the 1280X1024 MPEG4 format. The Olympus IMH-20 Image Management Hub, which provides full High Definition (HD) images, was used to record NBI colonic polyps videos with Olympus EVIS LUCERA ELITE CF-HQ290.

Clinical research form A structured clinical research form was created for the participants to assess all the endoscopic features and to enter their responses. [

Appendix 1]. The international experts also scored a second form that included only the endoscopic findings selected for the SIMPLE classification (Figure 1).

The structure of the consensus included introduction to current colonic polyps classification (NICE, ICE, Hazewinkel's criteria, 19-21), followed by presentation of the new OE-iSCAN OE system and design of the new 'SIMPLE (Simplified Identification Method for Polyp Labeling during Endoscopy) classification using a package of videos and slides of small and diminutive polyps using OE-iSCAN system. Subsequently an independent set of videos were used pre-training and post-training to determine the operating characteristics of the new classification, with a teaching module in between using a different set of images. The post-training test was performed on a second day to minimise recall bias. The details are as follows [Appendix 2]:

Phase 1

Development and derivation of the SIMPLE classification

In phase 1 of the study the international consensus group reviewed all the polyp characterization criteria and selected diagnostic characteristics through a modified Delphi consensus process to be included in the new classification system. A panel of international experts, through interactive roundtable discussion and in stepwise feedback fashion (to ensure equal participation), in a modified Delphi method to achieve consensus, defined endoscopic signs of the SIMPLE classification using international nomenclature and literature (NICE, ICE, Paris endoscopic classification, Kudo pit-pattern classification and Hazewinkel criteria for diagnosis of sessile serrated polyps) (12,17,19-21). We used only endoscopic Hazewinkels's criteria predictors of SSA/P histology (clouded surface, indistinctive border, irregular shape, dark spot inside the crypts and Kudo pit pattern modified IIO). We did not consider the colour criteria, which is specific to the NICE classification.

Phase 2

 Internal validation of the SIMPLE classification by the expert panel

In Phase 2, performance accuracy, level of confidence and inter-observer agreement for predicting polyp histology before and after a training module were evaluated between international experts.

First day (Pre-test)

All participants were provided with the pre-test slides and instructed to view the video clips and enter their responses in the forms provided. (Appendix 1 and table 1) A total of 21 video clips were projected to the participants who completed standardized forms which were handed over to the principal investigator. The participants did not consult with each other and could ask for a replay of the entire clip once but not rewind in the middle of the clip.

Teaching module

A PowerPoint teaching module was presented by two endoscopists (MI and JRS) with experience in imaged enhanced endoscopy including NBI and i-scan. The presentation included both slides and videos and had duration of 45 minutes (50 images and videos, distinct from pre- and post-test package). The contents of the module included an introduction to Paris classification, Kudo pit pattern, NBI and NICE polyp classification [6,12, 16-19]. i-SCAN ICE classification, Hazewinkel criteria for SSA/Ps [20,21]. The NBI and i-SCAN patterns of hyperplastic polyps, adenomatous polyps and sessile serrated adenoma (SSA/Ps) polyps were reviewed by showing several endoscopic images that illustrated the different mucosal and vascular pattern criteria for endoscopic differentiation of each polyp subtype during the presentation in a stepwise fashion. Representative slides from the training module and a video are shown in Figures 1 - 4 with video. The same teaching module was presented to the trainee gastroenterologists but also

included images and videos collected with the NBI Olympus EVIS LUCERA
ELITE CF-HQ290.

The training was designed to reflect the entire spectrum of Kudo pit pattern, the
colour, mucosal and vessel pattern of the NICE classification, and Hazewinkel
criteria. The participants' ability to categorize the polyps into a particular category
before and after the training (validation) was determined. [6,16-21]

Second day (Post-test)

A   stepwise feedback in a round table discussion with 10 new videos
representative of different lesions adenomas, HP and SSA were projected the
second day of the consensus before the post test videos scoring by the experts
group.

After the teaching module presentation, a post-test with the same videos clips
played in a different random order was provided to all the participants, who
viewed the videos and recorded their responses on the forms. The post-test was
done on the second day, which minimized recall bias. All endoscopist raters were
blinded to clinical history, clinical activity and number of videos in each category.

Each endoscopist individually scored each of the criteria in the endoscopic form
provided and the SIMPLE classification (surface pattern, vessel pattern and
border lesion), predicted histology as adenoma, sessile serrated polyp and
hyperplastic polyp, and assigned a level of confidence to the prediction degree of
confidence (high vs. low). [Appendix 1, Table1]. High confidence was considered
> 90% of confidence in the diagnosis with histology as reference.

All the responses were then transferred to a REDCap (Research Electronic Data
Capture) database and exported to Stata Version 13.1 for further analysis.

Phase 3 (External validation)

External validation of the SIMPLE classification by trainee gastroenterologists was done using both iSCAN-OE and NBI systems. External validation and reproducibility of SIMPLE classification applied to multiplatform systems, using videos recorded by NBI and iSCAN-OE systems were performed by 6 trainee gastroenterologists in UK. The participants in the pre- and post training in a randomized order scored 80 videos clips. The same power point teaching module used by international experts was presented to the trainee gastroenterologists but also included images and videos collected with the new NBI Olympus EVIS LUCERA ELITE CF-HQ290. Each trainee scored each of the criteria of NICE and the SIMPLE classification (surface pattern, vessel pattern and border lesion), predicted histology as adenoma, SSA/P and hyperplastic, and assigned a level of confidence to the prediction. (High vs. low)

Statistical analysis

All data were collected and managed using REDCap electronic data capture tools (Research Electronic Data Capture, REDCap consortium hosted by Vanderbilt, open access) hosted at the University of Calgary. REDCap is a secure, web-based application designed to support data capture for research studies.

The diagnostic performance of the endoscopists was calculated according to the histopathology of the polyp. Sensitivity, specificity, PPV, NPV, and accuracy with their 95% confidence intervals were calculated pre- and post- training using STATA 13.1 for Mac (Stata Corp LP, College Station, TX). We converted the histology to neoplastic (adenoma and SSA/P) and non-neoplastic (hyperplastic). The histology report was used as the reference standard. Estimates of sensitivity, specificity, positive and negative predictive value, and accuracy were created from the 2x2 table created by the endoscopic predictions and reference standard

as histology. These estimates, along with 95% exact confidence intervals were reported. Neoplastic was considered a positive result and non-neoplastic was considered a negative result. SSA/P were analysed as "neoplastic." Sample size was based on determination of accuracy and 168 observations (21 videos, 8 reviewers) had power to differentiate 90% accuracy from 80% accuracy with type 1 error of 0.05 and type 2 errors of 0.10. *Kappa* statistic was used to determine inter-observer agreement in polyp video classification during the training session. 168 observations had the ability to detect 0.20 points of *Kappa* statistics difference with type 1 error of 0.05 and type 2 of 0.02. [22-25]

Fisher's exact test was used to compare diagnostic accuracy before and after training   and it did not take into account the correlated observations. Univariable and multivariable analysis with bootstrapping of the endoscopic features of polyps was performed to determine the strength of endoscopic predictors of neoplastic vs. non-neoplastic diagnosis. We used univariable logistic regression and then, of those variables that were significant at the univariable stage, we used multivariable logistic regression.

For the reproducibility with trainee gastroenterologists, 80 videos for the external validation provided 80% power to detect a kappa agreement difference from (0.40 to 0.60) (moderate –good agreement using a two—sided significance level of 0.05). The inter-observer agreement was calculated by using the Fleiss kappa coefficients (6 observers; >3 categories). Eighty videos provided substantial inter-observer agreement (Fleiss kappa coefficient: 0.80, 95% CI, 0.70-0.90) in order to predict lesion histology [22-25]. A sensitivity analysis by excluding the endoscopist who recorded videos and developed training module was evaluated to reduce bias.

RESULTS

Participants

In phase 1 of the study, a new simplified endoscopic classification system for colorectal polyps was created using expert consensus opinion in a stepwise fashion. The Simplified Identification Method for Polyp Labeling during Endoscopy - SIMPLE classification was developed after a briefly introduction to virtual chromoendoscopy, optical diagnosis and the new characteristics of iSCAN-OE [Table 1.]

Diagnostic accuracy

Table 2a shows the overall performance for polyp diagnosis by using the SIMPLE classification before and after the teaching module. The overall accuracy in prediction of polyp histology was 83% (95% CI: 77-88) before training and increased to 94% (95% CI: 89- 97; p=0.0002) after training. The overall sensitivity, specificity, PPV and NPV of the SIMPLE classification were 84%, 80%, 91%, 67% before training and 97%, 88%, 95% and 91%, respectively after training. About 70% of predictions were made with high confidence in pre- and post training. For polyp diagnosis with high confidence the accuracy was 87% (95% CI: 82 - 91) before training and 91% (95% CI: 86-95; p=0.11) after training (Table 3). Details of high and low confidence diagnosis are presented in table 3. A sensitivity analysis without the principal investigator (MI) is shown in table 2b and did not affect the results.   The performance characteristics for each rater are shown in Appendix 2a and 2b. Of note, individual rater accuracy increased in all participants after training, being ≥ 90% in all cases, and 5 out of 8 endoscopists achieved an NPV >90% for adenoma diagnosis.

Similar diagnostic characteristics were achieved when SSA/P polyps were removed from data analysis (Table 4). Individual rater accuracy increased in all participants after training, being > 90% in 8/8 cases (ranged from 81.2% to 100%) and 5/8 endoscopists achieved an NPV > 95% for adenoma diagnosis.

Diagnostic agreement

The interobserver agreement of polyp histology diagnosis using the SIMPLE classification improved from 0.46 (95%CI: 0.30-0.64) at baseline to 0.66 (95%CI: 0.48-0.82) after training. However, the interobserver agreement for polyp histology diagnosis when using all the endoscopic criteria of NBI, ICE and *Hazewinkel* indicated in the endoscopic form did not improve between baseline 0.42 (95%CI: 0.27-0.57) and after training 0.40 (95% CI: 0.30-0.49).

Univariable and multivariable analysis of individual and combination criteria to predict polyp histology

Univariable analysis showed that the endoscopic criteria used to predict polyp histology (colour, surface and vessel pattern) were predictive of an adenoma diagnosis. The odds of adenoma diagnosis were 1.8 (95% CI: 0.7-4.6) when using surface pattern alone and 4.6 (95% CI: 2.3-9.4) when using vessel pattern alone. The odds of adenoma diagnosis were 4.7 (95% CI: 2.17-11.5) when using color and 5.9 (95% CI: 2.17-11.5) when using border characterization.

Table 5 shows the diagnostic values for combinations of different endoscopic criteria at multivariable analysis. The combination of two of the three criteria, (surface patter, vascular pattern and color of the lesion) significantly increased adenoma histological prediction by using i-scan OE.

Reproducibility of SIMPLE classification by trainee gastroenterologists using multi-platform videos

Six trainee gastroenterologists demonstrated that SIMPLE classification could be applied to both NBI and iSCAN endoscopic platforms. The trainee gastroenterologists showed an improvement in the sensitivity, accuracy, and proportion of high- confidence performance diagnoses of colonic polyps using

SIMPLE classification in a multiplatform systems (NBI and iSCAN-OE) in the post training compared with the pre training (Table 6).

As the trainee gastroenterologists had exposure to NBI but not OE-iSCAN, the pre-test operating characteristics were somewhat better with NBI, but the trend to improvement was seen post-test with both platforms (Table 6). The SIMPLE classification appeared more sensitive but less specific than the NICE classification in trainee gastroenterologists (table 7). The performance of accuracy to predict colonic polyps histology was similar in the post training when used NICE 0.69 (95% CI: 064-0.73) and SIMPLE 0.71 (95% CI: 0.67-0.75) classifications (Table 7). Inter-observer agreement of the trainee gastroenterologists when used NICE classification was good but did not improve from the pre-training (kappa =0.40, 95% CI: 0.29- 0.50) to post training (kappa = 0.34, 95% CI: 0.25-0.43).

DISCUSSION

We developed a simplified classification system for optical diagnosis of small and diminutive adenomas, SSA/Ps and hyperplastic polyps using the newly introduced OE-iSCAN system which achieved a high degree of diagnostic accuracy for small/diminutive polyp diagnosis. Furthermore, we showed that a training module on SIMPLE classification resulted in an overall NPV of 91.3%. This user-friendly classification system can be used by experienced and non-experienced gastroenterologists on multiple endoscopy imaging platforms to differentiate neoplastic from non-neoplastic polyps.

A workshop involving an international group of endoscopists met in Boston, USA and developed the SIMPLE classification to predict histology of colonic small/diminutive polyps. By consensus this group (international group of the Boston consensus) selected and decided to include only a few endoscopic criteria such as surface, vessels architecture and border from the previous validated endoscopic classification systems of diagnosis and characterisation of small/diminutive polyps [3,12, 19-21.]

Repici *et al* [26] recently demonstrated that the application of the NICE classification to the FICE digital chromoendoscopy system resulted in suboptimal accuracy and only moderate inter-observer agreement. In our study, among the three individual NICE criteria, surface and vessel features appeared to be significantly more accurate predictors than the colour criterion alone, which in turn was associated with a poor sensitivity for the prediction of adenoma. Particularly, the odds ratio for adenoma detection was 3.4 (95% CI, 1.8-6.3) and 4.0 (95% CI, 2.1-7.5) by using surface and vessels patterns alone, as compared with the colour criterion (we used odds ratio rather than risk ratio as we used logistic regression with multivariable analysis. However odds ratio should not be interpreted as relative risk). Therefore colour as an endoscopic feature predictive of polyp histology was not included in the SIMPLE classification. However, in the

univariable analysis the colour was predictive. In our opinion colour is correlated with the endoscopic system (reddish, green or brown) and could also be interpreted differently by different observers. Our aim was to develop a simple user- friendly classification, easy to be adopted by everyone, experienced and non-experienced gastroenterologists amongst all the endoscopic systems available.

The newly developed OE-iSCAN system is a unique combination of optical imaging, similar to NBI, with digital post-processing incorporated into one endoscopic system. This combination of both techniques might explain why the colour criterion alone or in combination with surface and vessels criteria performed well in our study to predict diagnosis of adenoma and SSA/P vs. hyperplastic polyps.

Similar to other recent studies, our data confirm that a short training module increased the optical diagnostic accuracy of small/diminutive polyp histological prediction. [9-11,27.] Individual rater accuracy increased in all participants after training, being ≥ 90% in all cases, and 5 out of 8 endoscopists achieved an NPV > 90% for neoplastic lesion diagnosis. Patel *et al* recently showed that with standardized training, academic gastroenterologists without prior expertise in NBI were able to meet the negative predictive value and surveillance interval thresholds set forth by the ASGE. Performance improved with time, but most endoscopists require on-going audit of performance. [12]

Optical diagnosis remains an attractive paradigm because of the potential for reducing costs and streamlining care. In our study the overall NPV of 91% meets the ASGE PIVI benchmark for the "characterise, resect, and discard" strategy in diminutive polyps. However, currently optical diagnosis cannot yet be recommended for use in routine clinical practice. The largest multicentre diagnostic study in this field, the DISCARD 2 study, demonstrates that NBI-assisted optical diagnosis cannot currently be recommended for routine use

outside of expert academic centers. Accuracy, both at polyp and patient level, was substantially below recommended levels. [7]

We have showed that SIMPLE classification performed well to predict colonic polyp histology amongst non-experienced gastroenterologists and can be applied in a multiple –platform systems. Interestingly, the accuracy of performance of trainees was similar and when using NBI improved from 72% in the pre-test to 78% in the post-test and with OE-iSCAN improved from 58% in the pre–test to 68% in the post-test (Table 6-7). Our results are in line with Lee *et al* [28] who has showed that NBI and i-SCAN displayed similar diagnostic accuracy to predict colonic polyp histology.

The main strength of our study was that international experts in novel endoscopic technologies developed a SIMPLE classification system and assessed the diagnostic performance of this classification system using the new OE-iSCAN system. We showed that this simplified classification system covers the endoscopic findings to predict adenoma and SSA/P using any of the image-processing platforms. In fact, a third of the polyps evaluated were SSA/P.

Furthemore, we accomplished the third phase of the study as we have validated the SIMPLE classification with less experienced trainee gastroenterologists. In future we plan to study the real-life operating characteristics of this score using multiple electronic chromoendoscopy platforms in a multicentre setting (Table 6-7). The performance of the SIMPLE classification system meets the criteria of the ASGE PIVI policy, though our study included both diminutive and small polyps.

This study has a number of potential limitations. First, the performance of SIMPLE classification in "real life "clinical practice was not assessed. However video clips were chosen instead of still photos because these more closely simulate live endoscopy. The sample size estimate was based on our calculated sample size estimate for accuracy. [9, 21] We used Fisher's test for comparing

accuracy between pre- and post test but it did not take into account correlated observations due to sample size and complexity. In our study also the same video sequences were used for pre-training and post-training tests, albeit in a different random order and the different day to minimize recall bias. We did not use an independent set of videos post-training as a different range of polyps may affect the final observation regarding the effect of training module. A generalisation to more than 2 categories was needed in order to obtain our results about multilevel non-dichotomous ratings. [22.] We did not formally study polyps 1 cm or more in size as the challenges in optical characterisation are most for small /diminutive polyps - we developed the SIMPLE classification system for polyps less than 1 cm, similar to the NICE. Our study included both diminutive 1-5 mm (as in NICE) as well as small 6-9 mm polyps. However, it is likely that the classification will hold for $\geq$ 1cm polyps where the patterns are easier to observe in details.

In conclusion, a new endoscopic simplified classification system, SIMPLE to predict polyp histology was developed by an international expert consensus group. Using the OE-iSCAN system, the SIMPLE classification achieved a high degree of accuracy for neoplasia diagnosis in small polyps. The overall NPV of 91.3% meets the ASGE PIVI benchmark (for diminutive polyps) for the "characterise, resect, and discard" strategy. Univariable and multivariable analyses showed that the criteria used in the SIMPLE classification were predictive of a neoplastic diagnosis. External validation also demonstrated that SIMPLE may be used by trainee gastroenterologists and with either NBI or iSCAN optical diagnosis system. However, we believe that before adoption of the "resect and discard" strategies for diminutive polyps, standardised training module are required to achieve adequate competency and it is imperative that training in endoscopic imaging is incorporated as a part of gastrointestinal education in the future.

Figure Legends
Figure 1: SIMPLE (Simplified Identification Method for Polyp Labeling during Endoscopy) Classification

Figure 2: Example of training module computerized slide: hyperplastic polyp using the different modes of i-scan OE (i-scan 2 and i-scan OE)

Figure 3: Example of training module computerized slide: adenoma polyp using the different modes of i-scan OE (i-scan 2 and i-scan OE)

Figure 4: Example of training module computerized slide: SSA using the different modes of i-scan OE (i-scan 2 and i-scan OE)

Figure 5: Example of training module computerized slide using the 3 different modes of i-scan OE (i-scan 1, i-scan2 and i-scan OE)

Video clip: Representative video of SSA scored by the international experienced endoscopists in scoring. The video showed a small SSA polyp using the different modes of i-SCAN OE (i-SCAN 1, i-SCAN 2 and OE)

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Table 1a. Comparison of the overall performance for polyp diagnosis (non neoplastic hyperplastic vs. neoplastic Adenoma, SSA/P) by using the SIMPLE classification before and after training

	Before training (95% CI)	After training (95% CI)	p Value
Sensitivity	84% (77-90)	97% (91-99)	0.002
Specificity	80% (67-89)	88% (74-94)	0.424
PPV	91% (84-95)	95% (89-98)	0.358
NPV	67% (54-78)	91% (78-98)	0.006
Accuracy	83% (77-88)	94% (89-97)	0.002

Table 1b. Comparison of the overall performance for polyp diagnosis (non neoplastic hyperplastic vs. neoplastic Adenoma, SSA/P) by using the SIMPLE classification before and after training without the rater MI as sensitivity analysis

	Before Training (95% CI)	Post training (95% CI)	P value
Sensitivity	82% (74-88)	96%(89-98)	0.002
Specificity	77% (62-87)	85% (70-94)	0.439
PPV	90% (82-94)	94% (87-97)	0.362
NPV	63% (50-75)	90%(75-96)	0.007
Accuracy	80%(74-86)	93%(87-96)	0.002

Table 2. Diagnostic Accuracy performance according to the level of confidence using all the endoscopic criteria of NICE, ICE and *Hazewinkel*

Pre vs. Post training Polyp Diagnosis Compared to Histology			
	Before Training	**After Training**	**p Value**
Sens	91%(85-95)	93%(86-96)	0.83
Spec	77%(64-87)	87%(74-94)	0.30
PPV	91%(84-95)	94%(88-97)	0.36
NPV	79%(65-88)	84%(70-92)	0.71
Accuracy	87%(82-91)	91%(86-95)	0.31
% High Conf.	74%(67-80)	74 %(63- 77)	0.49
High Confidence vs. Low Confidence Before training			
	High	**Low**	**p Value**
Sens	92%(84-96)	90%(73-97)	1
Spec	83%(67-93)	64%(38-84)	0.22
PPV	94%(87-97)	82%(64-92)	0.08
NPV	79%(63-90)	78%(48-94)	1
Accuracy	90%(83-94)	81%(66-90)	0.17
High Confidence vs. Low Confidence After training			
	High	**Low**	**p Value**
Sens	95%(87-98)	88%(73-96)	0.37
Spec	94%(79-99)	69%(38-89)	0.06
PPV	97%(90-99)	88%(73-96)	0.12
NPV	89%(73-96)	69%(38-89)	0.21
Accuracy	94%(88-97)	83%(69-92)	0.03

Table 3. Overall performance for predicting adenoma vs. hyperplastic histology by using the SIMPLE classification			
	Before training	**After training**	**p Value**
Sensitivity	91% (76-97)	94% (84-98)	0.821
Specificity	74% (56-87)	88% (74-95)	0.209
PPV	80.8% (66-90)	91% (80-96)	0.215
NPV	87% (68-96)	91% (78-97)	0.793
Accuracy	83% (72-90)	91% (84-95)	0.163

Table 4. Multivariate analysis of performance characteristics of individual and in combination endoscopic criteria to predict polyp histology

Individual Criteria	OR	OR Lower Bound	OR Upper Bound	p value
Colour	4.73	2.178	11.52	0.0002
Vessels	4.56	2.309	9.445	0.0002
Surface	1.78	0.660	4.592	0.2362
Individual in Combination				
Colour +Vessels	4.90	2.183	12.59	0.0003
Colour + Surface	4.33	1.988	10.54	0.0004
Vessels +Surface	4.73	2.373	9.954	0.0001
Border +Colour	8.96	4.33	19.90	0.0001
Border +Vessels	9.57	4.74	20.12	0.0001
Border+ Surface	4.87	1.40	19.32	0.0001
Any 3 of 4	6.05	2.69	15.51	0.0001
Any 4 of 4	4.61	2.052	11.854	0.0005
Overall				
All Predictions	2.80	2.02	3.91	0.0002

Table 5.Diagnostic performance of SIMPLE classification by the trainees gastroenterologists using NBI and OE-iSCAN systems (Optical characterisation as neoplastic (adenoma or SSA/P) or non-neoplastic referenced against gold standard of histology (neoplastic –adenoma or SSA/P; non-neoplastic –hyperplastic)

SIMPLE			
Pre vs. Post training - NBI			
	Pre	Post	p-value
Sensitivity	0.81 (0.72-0.88)	0.89 (0.81-0.94)	0.149
Specificity	0.56 (0.43-0.69)	0.59 (0.45-0.72)	0.850
Accuracy	0.72 (0.64-0.78)	0.78 (0.71-0.84)	0.186
High Confidence	0.69 (0.61-0.76)	0.78 (0.70- 0.84)	0.092
Pre vs. Post training - iSCAN			
	Pre	Post	p-value
Sensitivity	0.65 (0.58-0.71)	0.75 (0.68-0.80)	0.032
Specificity	0.43 (0.34-0.53)	0.56 (0.47-0.65)	0.066
Accuracy	0.57 (0.52-0.63)	0.68 (0.63-0.73)	0.004
High Confidence	0.64 (0.59- 0.70)	0.76 (0.72- 0.81)	0.0007

Note: True Positive = Optical diagnosis of neoplastic matches histology of neoplastic.

True Negative= optical diagnosis of non-neoplastic matches histology of non-neoplastic.

False Positive = optical diagnosis of neoplastic and histology of non-neoplastic.

False Negative= optical diagnosis non-neoplastic and histology of neoplastic.

Table 6: Comparison of diagnostic performance by the trainees gastroenterologists using NICE vs. SIMPLE classifications in the post test training

NICE vs. SIMPLE – POST TRAINING			
	NICE	SIMPLE	p-value
Sensitivity	0.66 (0.60-0.71)	0.79 (0.74-0.84)	0.0002
Specificity	0.74 (0.66-0.80)	0.57 (0.49-0.64)	0.0015
Accuracy	0.69 (0.64-0.73)	0.71 (0.67-0.75)	0.395
High Confidence	0.73 (0.69- 0.77)	0.77 (0.73- 0.80)	0.229