A review of image enhanced endoscopy (IEE) in the evaluation of colonic polyps

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Word count: 6789

Conflicts of interest: none

Summary

The practice of colonoscopy has changed considerably over the last decade. The growth of image enhanced endoscopy (IEE) have altered our concepts of how we perform colonoscopy. This article examines the evidence base behind these techniques and looks at where future research needs to be directed.

Key words

Colonic polyp, NBI, FICE, i-scan, indigo carmine

Expert commentary

Paradigms in our understanding of how colonoscopy should be performed are shifting. Image enhanced endoscopy using both dye based chromoendoscopy and electronic imaging are providing us with methods of improving lesion detection and characterization beyond what we previously thought possible. Traditional views that the neoplastic potential of a lesion can only be determined by the pathologist are being challenged, and it is likely that the era of protocol guided mapping biopsies for surveillance of conditions such as ulcerative colitis are nearing an end. However, these technologies are not without limitations, and although they are all trying to achieve similar goals there are significant differences between them. Perhaps the biggest challenge that we now face will be to understand both how to train in these techniques effectively, and how to translate the large body of published research into routine clinical practice.

Five year view

There will be a growth in the publication of guidelines from the World endoscopy societies setting standards for the use of image enhanced endoscopy in place of conventional approaches of mapping biopsies and histological examination. Training tools will emerge to enable structured training programmes to be developed, as will strategies for auditing success in application of these techniques to clinical practice. Initially the techniques will be adopted by experts in tertiary referral centres, but dissemination to the wider community will occur as the practical difficulties of adoption of these approaches are solved.

Key issues

- Indigo carmine or methylene blue chromoendoscopy increases adenoma detection during routine colonoscopy

- Indigo carmine or methylene blue Chromoendoscopy is the method of choice for the surveillance of patients with ulcerative colitis

- Indigo carmine or methylene blue Chromoendoscopy is an effective tool for *in-vivo* histology prediction of colonic polyps

- NBI and FICE have no role in polyp detection in a surveillance population. The position with i-scan is less clear. There is very little evidence in a high risk population, with a small selection of studies on NBI and i-scan suggesting they may be of some benefit in increasing the polyp detection rate

- There is a lack of evidence to recommend NBI, FICE or i-scan for surveillance of ulcerative colitis

- There is good evidence for the use of NBI, FICE and i-scan for the *in-vivo* histology prediction of colonic polyps

- The adoption of a 'resect and discard' policy for colonic polyps may well be a very cost effective measure with minimal clinical consequences in expert hands

Introduction

There have been considerable advances in the endoscopic examination and treatment of colonic neoplasia with the development of techniques for performing image enhanced endoscopy (IEE), including chromoendoscopy and electronic imaging. It is important to understand what can and cannot be achieved with these emerging technologies. This article reviews the evidence behind these new endoscopic enhancement techniques, and discusses where this field is likely to be moving in the future

Background

A key role of colonoscopy is lesion detection and characterization. Colorectal cancer accounts for an estimated 550,000 deaths worldwide [1], with poor outcomes for advanced disease. Colorectal cancer develops from adenomatous polyps through the adenoma-carcinoma sequence [2,3]. Therefore detection of adenomatous polyps before they turn into cancer and polypectomy is important, and was shown to reduce colon cancer mortality. However, small hyperplastic polyps, accounting for one third of all polyps, have negligible malignant potential, especially if located in the left side of the colon.

It has been traditionally felt that hyperplastic polyps cannot be separated clinically from adenomas or polyp cancers. For this reason all polyps are removed. However, polypectomy is associated with significant risks [4],

results in an immediate cost in processing the samples, increases the workload for pathologists, and increases the procedure time. However, It is becoming recognized that *in-vivo* characterization of lesions is possible, with the ASGE recently proposing standards for *in-vivo* assessments [5].

Image enhanced endoscopy in the colon

IEE can help in two ways:

1) Improved lesion detection
2) Improved lesion characterization

There are many emerging technologies which can impact on both of these areas. These include high resolution (HD) colonoscopy and electronic imaging techniques including narrow band Imaging, FICE and i-scan, chromoendoscopy and novel devices including cap assisted colonoscopy and confocal endoscopy. This article will focus on chromoendoscopy and electronic imaging. To understand how these technologies can impact on lesion detection and characterization it is necessary to broadly understand how they work and the principles behind their use.

Chromoendoscopy

Chromoendoscopy involves application of a dye to the gastrointestinal tract. The techniques were pioneered in Japan where initial experience was in the use of the vital stain crystal violet to characterize colonic neoplasia. Crystal

violet irreversibly binds to cellular structures, highlighting surface patterns in great detail. It was with this dye that the first attempts were made at *in-vivo* histology prediction for colonic polyps. It cannot be used for lesion detection but is very effective for lesion characterization. However, it poses a number of problems. Vital stains are inconvenient to use. They have to be dripped onto the lesion surface and allowed to fix for several minutes, followed by washing prior to evaluation. This is time consuming and subjective. For this reason it is generally accepted that vital stains are not practical for daily use outside of a research setting. This led to a search for alternative dyes.

Indigo carmine, generally used at a concentration of 0.2%, is a blue dye which does not bond to or react with human tissue. It simply sits on the surface of tissues, highlighting surface patterns. For this reason it is very safe. Furthermore, it is easier to use than crystal violet as the results are instant. As it does not bind to tissues, excess dye can be sucked away. Indigo carmine can be used for two purposes; to find polyps or to characterize neoplasia. Methylene blue is a similar blue dye. It differs however from indigo carmine in that it binds to tissues and therefore carries a theoretical risk of DNA damage. In practice it can be used in a very similar way to indigo carmine.

Pan-chromoendoscopy for lesion detection in a surveillance population

A Cochrane meta-analysis concluded that chromoendoscopy with indigo carmine enhances the detection of neoplastic polyps [6]. The review examined five randomized controlled trials, excluding polyposis or colitis

patients [7-11], representing 1059 patients. Chromoendoscopy significantly increased both the number of patients with at least one polyp detected (OR 2.22) and the number of patients with at least one dysplastic lesion detected (OR 1.67). The predominant increase was in the number of diminutive adenomas detected. Four other randomized controlled trials were not included in the meta-analysis [12-15]. All but one of these studies [14] demonstrated improved lesion detection with indigo carmine. Methylene blue has shown similar results [102].

Pan-chromoendoscopy for lesion detection in a high risk population

Chromoendoscopy is potentially of benefit in hereditary syndromes by enhancing detection of subtle lesions. Indigo carmine chromoendoscopy has been studied in Familial adenomatous polyposis (FAP), attenuated FAP, and hereditary non-polyposis colorectal cancer (Lynch syndrome).

Chromoendoscopy may help in making a diagnosis by revealing additional lesions required to meet a diagnostic criteria. A very small study has suggested that indigo carmine can help distinguish between attenuated FAP and classical FAP (>100 adenomas) [16]. Likewise, the diagnosis of hyperplastic polyposis syndrome is dependent on identification of a specific number of polyps, and chromoendoscopy may help in meeting the criteria [17].

Chromoendoscopy may be beneficial in the surveillance of polyp syndromes. back-to-back studies in Lynch syndrome suggest that polyp detection may be improved [18,19,20]. Dye-spray increases polyp detection in FAP surveillance [21]. Whether this is of any clinical value is unclear as most true FAP patients are treated with colectomy rather than surveillance. There are no studies published in hyperplastic polyposis syndrome or Peutz-Jeghers syndrome.

Pan-chromoendoscopy in inflammatory bowel disease

There is growing evidence that chromoendoscopy using indigo carmine is the optimum method for performing colitis surveillance. There are two randomized controlled trials and several large cohort studies comparing the technique to conventional mapping biopsies [22-30]. All of these trials have demonstrated improved neoplasia yields with pan-chromoendoscopy. A meta-analysis [31] examining these studies showed a 44% increase in detection of neoplasia with the majority of them being flat. The meta analysis also demonstrates a dramatic reduction in number of biopsies taken per patient from 40 with the conventional strategy to 11 with chromoendoscopy directed targeted biopsies. Studies with methylene blue have yielded similar results [103]. Recent ECCO guidelines recommends this as the strategy for ulcerative colitis surveillance. It should be noted that pan-chromoendoscopy is only of value when the patient is in remission. In the presence of active inflammation there is little to be gained through the application of dye spray, as ulceration, mucous and pus interferes with the assessment of surface patterns and makes such evaluations unreliable.

There is good evidence that pan-chromoendoscopy improves lesion detection in a routine surveillance population. However, pan-colonic dye spray, where indigo-carmine is applied to the entire colon using a spray catheter, has not become routine practice. There are a number of reasons for this. Dye spraying is time consuming messy and inconvenient. The colon has to be clean and free of debris and this remains a big challenge as bowel preparation in western settings is not perfect in all patients. Practically most western units would find the practice of pan-chromoendoscopy very challenging. Furthermore, there is a lack of data to support whether this increase in lesion detection results in a long term reduction in cancer risk.

Chromoendoscopy for lesion characterization

There has been considerable work evaluating the use of chromoendoscopy in characterizing colonic lesions. The initial work with indigo carmine for *in-vivo* diagnosis was conducted in Japan by Kato et al. who retrospectively analysed 4445 lesions using magnifying endoscopy with indigo carmine dye spray. All of the lesions were less than 5mm in size and assessed by evaluating surface patterns [32]. These patterns were originally described using vital stains (crystal violet) by Professor Kudo and have formed the cornerstone of most of the subsequent *in-vivo* diagnostic studies [33,34]. All of the lesions were assessed *in-vivo,* with the predicted diagnosis correlated with the histopathological diagnosis. The findings suggested that a sensitivity for adenoma of 98% and specificity of 52% could be achieved. The excellent sensitivity was achieved by compromising the specificity, resulting in a large

proportion of hyperplastic polyps being overcalled as adenomas. The data was dependent on 100x magnification with a magnifying endoscope.

Further work was conducted in Japan [35] which investigated the differences between indigo carmine with and without magnification in the examination of small (<10mm) polyps. The results were encouraging, with a sensitivity for neoplasia of 93.1% and specificity of 76.1% being achieved. However, there was improvement with magnification. This suggested that in appropriately skilled hands, *in-vivo* diagnosis was possible without the need for magnification endoscopy or vital stains. There were further Japanese studies looking at magnification endoscopy with indigo carmine for *in-vivo* histology prediction which showed similar results [36-38]. See figure 1.

There has been work from outside of Japan using magnifying chromoendoscopy with indigo carmine. Tischendorf et al in Germany conducted a prospective cohort study of neoplastic vs non neoplastic polyps using both narrow band imaging and indigo carmine with magnifying endoscopy. A sensitivity of 91.7% and specificity of 90% was achieved for indigo carmine using Kudo pit pattern analysis [39]. A large German study compared indigo carmine and the electronic imaging modality FICE in the assessment of polyps <10mm. The primary aims of this study were lesion detection. However a sub-group of 280 lesions were assessed using indigo carmine for histology prediction. A sensitivity for neoplasia of 87.6% and specificity of 62.0% was achieved [40]. High definition endoscopes were used

without optical magnification. There was a further German study by a different group examining indigo carmine with high resolution endoscopes. This study investigated 273 lesions <5mm, with a sensitivity of 94%, specificity of 64% and accuracy of 83% [41]. This study differed from the other studies described in that it only examined rectosigmoid polyps. Further similar studies [42-46] are summarized in tables 1 and 2.

It should be noted that methylene blue has also been studied for lesion characterization. The results have been excellent, and it is widely accepted that it can be used in the same way as indigo carmine [102].

A notable point observed in most of the published studies is the trade off between adenoma sensitivity and specificity. Many of the studies with the highest sensitivity have a low specificity, typically between 60-70%. Whilst this is the safest approach to *in-vivo* diagnosis, it is not ideal. The ultimate goal for diminuitive polyps <5mm in size would be to have the ability to confidently leave small hyperplastic polyps, reducing the risks posed by polypectomy. To achieve this, sensitivity and specificity both need to be very high.

High definition colonoscopes are becoming an industry standard and it is important to know if they improve lesion characterization. A recent study published from the United Kingdom has suggested that diagnostic accuracy, sensitivity and specificity of assessment of colonic polyps <10mm in size was not affected by the resolution of the colonoscope used [47]. This was a single centre, single endoscopist study, but is the only study in this field. However, it is encouraging as standard resolution endoscopes are still in widespread use

and still being marketed and sold by most of the major endoscope manufacturers. HD endoscopes are more expensive and require updated processor and display screen which all come at extra cost and do improve the quality of image. However, clinicians can draw comfort from the above study that if they are using indigo carmine for *in-vivo* assessments then even standard definition endoscopes can produce comparable accuracy.

Because of growing interest in the use of *in-vivo* diagnosis The American Society for gastrointestinal endoscopy (ASGE) has produced PIVI guidelines, setting standards a technique or technology needs to achieved to be used for *in-vivo* diagnosis [5]. This includes standards which need to be met for setting rescope intervals and for leaving small rectosigmoid hyperplastic polyps *in-vivo*. Most of the indigo carmine studies are from the pre-PIVI era so do not report on PIVI standards but a recent study looked at the PIVI standards that can be achieved with indigo carmine [48]. This study used indigo carmine without optical magnification. The results were encouraging, with indigo carmine meeting both the requirements for rescope intervals and for leaving polyps in situ. It should be noted that the assessments were made after first assessing using the electronic imaging modality FICE. Indigo carmine did improve the negative predictive value of assessment, enough to meet the PIVI standard for leaving small left sided hyperplastic polyps in situ, although the change in accuracy, sensitivity and specificity was not statistically significant. See table 2. We can conclude from this study that indigo carmine when used after FICE will improve the negative predictive value to a standard that will let

us implement 'do not resect' policy for diminuitive rectosigmoid polyps <5mm in size.

There has been some work examining magnifying chromoendoscopy in the evaluation of sessile serrated polyps. A paper from Japan has suggested that, using a modified form of the Kudo pit pattern classification system, it is possible to identify sessile serrated adenomas with 83.7% sensitivity and 85.7% specificity [101]. More work is needed in this field.

Chromoendoscopy has been shown to be an effective tool in predicting depth of sub-mucosal invasion of early cancers in the colon [96-97], with accuracy between 71% and 91%. This requires magnifying endoscopes and highly skilled endoscopists. Furthermore, whilst some of the published work has used indigo carmine [97] the majority of assessments have used vital staining with crystal violet. The data has come from specialist centres in Japan and it is unclear whether such techniques could currently be used in a western setting. However, with the growth of EMR and ESD as the standard for removal of large benign colonic polyps it is possible that endoscopists will become more confident in their diagnostic abilities and that skills in this area will improve.

Electronic imaging

Some endoscopists have been critical of chromoendoscopy, claiming that it is a messy time consuming process. Furthermore, it physically colours the mucosa, requiring extensive washing if the endoscopist decides that he or she wants an unstained view. This has led to the development of push button

'virtual chromoendoscopy' techniques. These will be referred to collectively as 'electronic imaging' for the purposes of this article.

Narrow band imaging

The first commercially available system came from Olympus, known as narrow band imaging (NBI). The concept of NBI is to improve visualization of mucosal vascular patterns. It is based on the principle of variable penetration of light depending on its wavelength. Red light penetrates deep into the submucosa but doesn't help with surface pattern assessment. Blue and green light at a wavelength range of 415-540nm does not penetrate deep but enhances mucosal vessel patterns. Blue light displays superficial capillary networks whilst green light highlights subepithelial vessels. The result is a high contrast image which makes the interpretation of surface vascular patterns possible. NBI uses a physical filter to block red light and to narrow the bandwidth of the blue and green light, hence improving visualisation of surface patterns.

Narrow band imaging for lesion detection

Early studies suggested that there was some improvement in lesion detection using NBI [49-50]. This was not however repeated in later investigations [51,52,53]. The overall conclusions were that the gains seen in the preliminary studies were largely due to inexperienced endoscopists, still on a steep

section of the polyp detection learning curve. However, NBI did help improve polyp detection skills. When used by experts, who already had high adenoma detection rates, there was no gain [52] [54]. There has been a tandem endoscopy published which suggested that the adenoma miss rate may be lower in the proximal colon. Furthermore, a significantly higher number of small lesions <5mm were found using NBI compared to white light imaging in this study [94]. It is likely therefore that if there is any gain from NBI in lesion detection that it is small.

Narrow band imaging in familial polyp syndromes

There is limited evidence for use of NBI in any of the polyp syndromes. Due to profound differences between the syndromes it is difficult to consider them as a single group. The greatest evidence base is in hyperplastic polyposis, where a randomized controlled trial has been conducted [58]. This is perhaps unsurprising, as the key clinical aim in this condition is to identify adenomas amongst a sea of hyperplastic lesions, and there is evidence to suggest that electronic imaging is effective in differentiating hyperplastic from adenomatous polyps. There is some evidence in Lynch syndrome, but this is from small cohort studies and it is questionable whether these were adequately powered. Of the studies examining lynch syndrome it would appear there may be benefit from NBI, but there is a greater gain from chromoendoscopy.

There has been one cohort study examining NBI in the assessment of familial adenomatous polyposis (FAP). This involved analysis of images captured at live endoscopy [55]. In total thirteen patients with FAP were examined. Colonoscopic images were obtained using white light colonoscopy, autofluorescence imaging, NBI, and chromoendoscopy, with all images captured at equivalent angles and distances from the colorectal mucosa. Chromoendoscopy detected the greatest number of lesions at all sites. NBI depicted more lesions than white light. Autofluorescence imaging appeared superior in the rectum. The authors concluded that chromoendoscopy was the optimum imaging modality, and superior to white light colonoscopy, autofluorescence imaging, and NBI for detection of diminutive colorectal lesions in adenomatous polyposis. However, NBI was better than white light alone.

There have been three published studies examining narrow band imaging in Lynch syndrome. A cohort study from the United Kingdom [56] examined 62 patients from Lynch syndrome families, all diagnosed using the Amsterdam II or genetic criteria as part of a colonoscopic surveillance programme. All patients were examined twice from caecum to sigmoid-descending junction, first with high definition white light and then after a second pass with NBI in a back-to-back fashion. Initial adenoma detection in the proximal colon with white light was 17/62 (27%). 26/62 (42%) patients had at least one adenoma detected after NBI, with an absolute difference of 15% (95% CI 4-25%), p=0.004 versus white light alone. The authors commented that the proportion of flat adenomas detected in the NBI pass (9/21 (45%)) was higher than in the

white light pass (3/25 (12%)) p=0.03, suggesting that the principal gain was in the detection of flat adenomas in the proximal colon.

A cohort study from Germany [57] examined 109 patients with HNPCC. In 47 patients, standard colonoscopy was followed by chromoendoscopy with indigo carmine, and In 62 patients NBI was performed first followed by chromoendoscopy. 128 hyperplastic and 52 adenomatous lesions were detected in total. 0.5 lesions/patient were identified by standard colonoscopy and 1.5 lesions/patient by chromoendoscopy (P < 0.001). 0.7 lesions/patient were detected by NBI. At least one adenoma was detected in 15 % of patients by both standard and NBI colonoscopy compared with 28 % of patients by chromoendoscopy. The authors concluded that chromoendoscopy detected significantly more adenomatous lesions than standard white light colonoscopy or NBI.

There has been one randomized controlled trial [58] investigating NBI for the assessment of patients with hyperplastic polyposis syndrome. In total 22 patients was identified. Patients underwent tandem colonoscopy with high resolution white light and NBI, in randomized order with removal of all detected polyps. 209 polyps were detected (27 with normal histology, 116 hyperplastic polyps, 42 sessile serrated adenomas, and 24 adenomas). Among patients assigned to white light first (n = 11) a total of 78 polyps was detected; subsequent NBI added 44 polyps. In patients examined with NBI first, 78 polyps were detected and subsequent white light added 9. Polyp miss rates of white light and NBI were 36% and 10% (OR 0.21; 0.09-0.45). Again,

in a similar fashion to the Lynch syndrome studies, flat polyp shape was independently associated with increased miss rate. The authors concluded that NBI significantly reduces polyp miss rates in hyperplastic polyposis patients.

Narrow band imaging in inflammatory bowel disease

Because of the success of chromoendoscopy in colitis surveillance, the question was asked whether narrow band imaging could achieve similar results. Three randomized controlled trials have attempted to answer this question [59-61], with all of these trials giving negative results.

Two randomized controlled trials compared NBI to conventional chromoendoscopy. One of these trials [30] demonstrated a considerably higher miss rate with NBI compared to pan-chromoendoscopy (31.8% vs 13.6%). The second trial [62] (which used methylene blue as the dye) showed comparable neoplasia detection rates. The position is therefore uncertain whether NBI can be used as an alternative to chromoendoscopy for colitis surveillance. However, it cannot be recommended as a suitable technique at present.

Narrow band imaging for lesion characterization

There have been numerous publications investigating the potential for *In-vivo*

histology prediction using NBI [63-70], with several classification systems validated specifically for use with NBI [99,100]. Similar results have been achieved to those seen with indigo carmine. Several publications have concentrated on non-magnifying endoscopes, perhaps most notable being the DISCARD study [68]. This was however a general study of *in-vivo* diagnosis, and the use of indigo carmine was allowed. Whilst the authors argued that this was only needed in a minority of cases, it is difficult to ascertain the efficacy of NBI on its own. Another study compared the accuracy of NBI with and without magnification [71]. This showed no statistically significant difference with or without magnification. However, the polyps were not assessed *in-vivo*. Pictures were taken and then reviewed after the procedure by two endoscopists. Therefore the results have to be interpreted with caution.

NBI certainly appears very promising and provides accuracy close to histology. With the new validated classification systems it is ready for use in expert hands. However, acquiring competence may be challenging. Recent data has shown that, despite training, NBI was not that good in the hands of general endoscopists compared to the results obtained in expert centres, failing to meet the key standards laid down in the ASGE PIVI [74]. Similar issues have been raised in other, similar studies [93]. Whilst there are published studies suggesting that NBI can be taught relatively easily [101], this raises a concern about the widespread applicability of NBI / *in-vivo* diagnostic techniques outside of expert centres. This is an area needing further research. There has been a study published which has suggested that,

with appropriate training, high magnification NBI can increase the diagnostic skill of less experienced endoscopists to that of highly experienced endoscopists [95]. It may be that when learning to perform *in-vivo* assessments the greater clarity of patterns seen with magnification is highly beneficial, but that this becomes less important as experience increases. This should form the basis for future studies.

Unlike the studies into indigo carmine dye spray, where Japanese research predominates, the work into NBI have come from a larger range of countries. This perhaps reflects the reluctance of western endoscopists to embrace dye spray. It should be noted however that the largest NBI study (1473 polyps) comes from Japan [69].

Of all vascular enhancement techniques the biggest evidence base exists for NBI. It is a tool where classification systems and assessment techniques have been developed specifically for use with it. Data has been produced from more than one centre, suggesting the techniques are reproducible in expert hands. Unfortunately all of the data has been produced using high definition equipment and it is necessary to assume, at present, that this is a prerequisite for *in-vivo* diagnosis. See table 3. Most studies have reported sensitivity between 82-95% and specificity of 75-90%. See figure 2 and table 3.

There has been some work examining the use of narrow band imaging with optical magnification in examining depth of invasion of early colorectal cancers [98]. The early data was promising, suggesting that thick and severely irregular microvessels were diagnostic of sub-mucosal invasion. This

Flexible spectral imaging color enhancement (FICE)

FICE is a post processor technology found on Fujifilm endoscopes. Unlike NBI, which utilizes a physical filter, FICE uses the charged coupled device (CCD) in the endoscope to capture spectral reflectance data. This is sent to a spectral estimation matrix processing circuit contained in the video processor. The reflectance spectra of corresponding pixels that make up the conventional image are mathematically estimated. From these spectra, a virtual image is reconstructed of a single wavelength. Three such single-wavelength images can be selected and assigned to the red, green, and blue monitor inputs to display a composite colour enhanced multi band image in real time. This can be used like narrow band imaging to remove data from the red part of the waveband and narrow the green and blue spectra. However, the system is flexible. It has 10 pre set digital filter settings with the ability to program more.

FICE is a technically more complex than NBI, and therefore potentially more flexible. This can prove off putting to clinicians who can find the multitude of settings confusing.

FICE for lesion detection

In a similar position to NBI, a multicenter randomized controlled trial investigating FICE for lesion detection in a surveillance population has concluded that FICE was no more effective than white light for lesion detection [40]. These results have been repeated in several further studies [75,76] with the same negative results. It would therefore appear that FICE has no role in improving polyp detection rates in the colon. There is no published data for FICE in high risk patient groups.

FICE for lesion characterization

Several studies into the *in-vivo* histology prediction of colonic polyps come from Germany. A prospective study of 150 polyps <2cm was compared to indigo carmine dye spray with low (50x) and high (100x) magnification using high resolution endoscopes (650,000 pixel CCD). The study was performed by taking static pictures of each polyp and reviewing them by 3 different readers after the procedure [77]. An accuracy of 83% and 90%, sensitivity of 89.9% and 96.6% and specificity of 73.8% and 80.3% could be achieved with low and high magnification respectively. The results were essentially the same with Indigo carmine with no statistically significant difference between the two modalities. There are some important criticisms to note about this study. As it is based on static images it is unclear whether the results are directly transferrable to *in-vivo* diagnosis. Furthermore, as lesions over 1cm were allowed, it is unclear whether these results could be achieved with

smaller polyps which are arguably harder to assess. High definition (650,000 pixel CCD) endoscopes were used and the results cannot be applied to standard definition equipment.

The same team went on to conduct a further prospective randomized study with the primary aim to investigate the impact of FICE on adenoma detection rates (ADR) [40]. In this study lesion characterization was a secondary end point. It demonstrated that FICE was able to differentiate adenomas from hyperplastic polyps<10mm in size with a sensitivity of 93% and specificity of 61.2%. Accuracy was 84.7%. This was comparable but not superior to that of indigo carmine, with no statistically significant difference between the two techniques (p=0.44). Specificity was sacrificed to achieve adequate sensitivity. Whilst safe, this approach limits the cost benefit position of *in-vivo* diagnosis. Lesions were assessed using Kudo's pit patterns which are not validated for FICE. Furthermore, the primary end point of the study was not lesion differentiation, but lesion detection.

There has been a Japanese study looking at histology prediction using FICE. This study was small, examining 107 polyps <5mm in size and utilizing optical magnification with high definition scopes. With high magnification (100x) a sensitivity of 93% specificity of 70% and accuracy of 87% was achieved. There was a small drop in accuracy with low (50x) magnification (87%) [37]. Again Kudo's patterns were used for the assessments performed by Japanese experts.

Not all studies support these findings. There was a study in which five endoscopists assessed 144 pictures of 19 polyps to establish the diagnostic accuracy of WLI, FICE and indigo carmine in making a histology prediction for polyps <10mm in size. The results were disappointing, with a mean diagnostic accuracy for WLI of 57%, FICE without magnification of 58.9% and IC without zoom of 70.5% [78]. The methodology of this study could be criticized in many ways. The number of lesions was extremely small and it was picture based. Furthermore, It is unclear how experienced the endoscopists were in making an *in-vivo* diagnosis. They achieved similar (poor) results with indigo carmine which is out of keeping with previous studies. The Sano classification was used to assess the lesions with FICE. This is a system designed for Narrow band imaging [72]. Practically, the appearances are different with FICE to NBI, and the Sano classification has never been validated for use with FICE. See figure 3.

A study from Brazil has described a surface pattern system which is not dissimilar to Kudo pit pattern classification but describing the vascular patterns seen with FICE [79]. The study enrolled 309 lesions ranging in size from 1-50mm, with 242 lesions <5mm in size. Again only high definition endoscopes were used and no attempt to examine without magnification was made. The authors commented that they felt optical magnification was essential for analysis of vascular patterns. An accuracy of 98.3% sensitivity of 99.2% and specificity of 94.9% was achieved. The advantage of including larger lesions was that 22 cases of colorectal cancer could be examined, enabling a classification system to be validated. However, it does mean that

the very high sensitivity and specificity cannot be directly compared to the other studies looking at much smaller lesions. The authors did not attempt to analyze accuracy on the basis of lesion size.

A further study has attempted to validate a more simple classification system for use with FICE, known as N.A.C.[92]. This classification system makes use of vascularity, vascular patterns and surface patterns. It is designed for use without optical magnification and makes use of both the white light and FICE enhanced images. The details of this system are shown in table 5.

A recent study has examined FICE in a U.K. bowel cancer screening population, as has compared results to the ASGE PIVI standard [48]. The study suggested that FICE meets the PIVI standards for adopting a resect and discard strategy, but could not produce a negative predictive value sufficient for leaving recto-sigmoid hyperplastic polyps in situ. The same team went on to examine the impact of colonoscope resolution on diagnostic accuracy [80]. This study demonstrated an improvement in lesion characterization with a high resolution colonoscope, with greater accuracy for setting rescope intervals using ASGE and British Society of Gastroenterology (BSG) guidelines. It clearly demonstrated that if electronic imaging like FICE is to be used for *in*-vivo diagnosis then HD scopes are a must as they improve the accuracy to a level that all PIVI standards are comfortably met. This raises an important concept; whereas indigo carmine based assessments appear to be independent of colonoscope resolution, the same cannot be said for FICE. Whilst it is not clear whether the same issues apply to NBI or i-scan it should

be noted that all of the research on these systems has been performed using high resolution equipment. Therefore it is safest to assume that, until studies have been performed to prove or refute the position, that all electronic imaging assessments are best made using high resolution colonoscopes. See table 4.

i-scan

The most recent introduction to vascular enhancement has come from Pentax. In some ways i-scan is a similar technology to FICE. It is a post processor reconstruction from spectral reflectance data. However, in addition to vascular enhancement it can also enhance surface patterns, increasing the contrast between edges without reducing the brightness of images. At present high definition 1.3 million pixel CCD endoscopes are available which have been marketed for use with this system. These are not equipped with optical magnification.

An early study using i-scan has suggested that increased lesion detection can be achieved using the surface pattern enhancement setting [81]. This is in stark contrast to results seen with NBI and FICE. The argument has been made that the surface pattern enhancement features are fundamentally different from the vascular enhancement of NBI and FICE, which explains the difference. However, these results were not replicated in a subsequent trial [82] and this is an area requiring further research.

There has been a study examining i-scan in hereditary polyp syndromes (83). This study used the tone enhancement (TE) capacity of i-scan in Lynch syndrome. In total 49 patients underwent back-to-back colonoscopy with two imaging modalities, randomized into 2 groups. Group 1 (25 patients) underwent High definition white light (HDWL) first followed by i-scan, group 2 (24 patients) i-scan first followed by High definition white light. The lesion detection rate was 0.73 for i-scan and 0.36 for HDWL (p=0.095). In group 1, 14 lesions were detected with HDWL first and 15 with subsequent i-scan. In group 2, 21 lesions were detected with i-scan first and 4 with subsequent HDWL. The miss rate for endoscopic lesions was 52% and 16% respectively and was significantly different in favor of i-scan (p<0.01). The authors concluded that In patients with Lynch syndrome the miss rate for polyps is significantly reduced during colonoscopy performed with i-scan in comparison to high definition white light.

i-scan for lesion characterization

The previously described study examining i-scan for lesion detection [81] also examined the role of i-scan in lesion characterization. *in-vivo* histology prediction was made on 145 polyps <10mm with a sensitivity of 98%, specificity of 100% and accuracy of 98.6%. Kudo pit patterns were used for assessment. The most recent study from the United Kingdom called the Hi-scope trial suggested similar results for i-scan [85]. However, this study was unique in comparing the high resolution white light diagnosis to the i-scan diagnosis. The authors found no significant difference in accuracy rates between high definition white light and i-scan. This is in sharp contrast with

other similar studies comparing white light to enhanced imaging such as NBI or FICE. Of note the white light accuracy was excellent, with much better results achieved than those seen in previous studies where white light was used for histology prediction [48]. It should be noted that Pentax colonoscopes have a higher resolution than the other endoscope manufacturers. The authors argued that such high accuracy with high definition white light could be due to high levels of expertise and high definition colonoscopes. It is quite likely that in the past publications and investigations could have been biased in favour of enhanced technologies like NBI, etc. and has undervalued the role of high definition white light. It is also possible that the endoscopists involved in the Hi-scope trial have improved their *in-vivo* diagnostic skills over the years with the aid of enhanced imaging techniques and chromoendoscopy and now they can make very accurate diagnoses even with high definition white light. These results need to be replicated by other investigators. See figure 4.

The cost effectiveness of *in-vivo diagnosis*

An important aspect of all *in-vivo* diagnostic techniques is what value they add to clinical assessment. We feel such assessments have several functions. In larger polyps it is essential to correctly identify potential areas of invasive cancer, as it can affect whether to undertake endoscopic resection or refer for surgery. Assessment can also help target the correct area for biopsy to achieve accurate histological confirmation. In contrast, in small polyps the key

is distinguishing neoplastic from non-neoplastic polyps. This can allow the endoscopist to practice strategies like 'resect and discard' and 'do not resect' small hyperplastic polyps in the rectosigmoid. This could reduce complications associated with unnecessary polypectomy and result in a reduction in costs and burden to histopathology departments. Finally, it can enable surveillance intervals to be set accurately at the time of endoscopy.

The cost effectiveness of *in-vivo* diagnosis has been examined in 5 papers. The first study from the United Kingdom [68] introduced the concept of resect and discard and made cost calculations, suggesting savings of $169 per patient undergoing colonoscopy. Rescope intervals could be set accurately 98% of the time using BSG guidelines.

A study based upon a Markov model examined potential cost and clinical implications of applying resect and discard policy to the United States of America screening population [87]. The authors concluded that an annual undiscounted saving of $33 million /year could be made ($25/person) with a negligible impact on rescope intervals or screening efficacy. A further cross sectional analysis of American surveillance colonoscopy [88] examined data from a single-institution tertiary referral centre. A Decision analysis model examined the effects on surveillance intervals, costs and clinical outcomes of two strategies for polyp assessment; conventional histological examination of all polyps and *in-vivo* diagnosis of diminuitive lesions <5mm in size. It calculated up-front cost savings which could be achieved from forgoing conventional histological assessment and assessed the frequency of incorrect

surveillance intervals based on errors in both histological and endoscopic *in-vivo* assessment. It also assessed the number needed to cause harm from adoption of an *in-vivo* assessment strategy, based on published sensitivity and specificity data of endoscopic assessments using NBI, FICE and i-scan. The model predicted that pathology set surveillance intervals incorrectly in 1.9% of cases, and that this would increase to 11.8% of cases if an *in-vivo* assessment was used instead. The annual up-front cost savings from *in-vivo* diagnosis would exceed a billion dollars. Less than 10% of this would be offset by downstream costs and consequences of forgoing pathology. The number needed to harm would be over 11,000. This study includes data on all of the main diagnostic systems but did not include any papers where chromoendoscopy with indigo carmine was used, although such papers were referenced. Given that most studies have suggested at least equal efficacy from chromoendoscopy this paper would effectively be relevant to such models for *in-vivo* diagnosis as well.

The fourth study came from the United Kingdom which looked at *in-vivo* diagnosis in the UK Bowel Cancer Screening Programme (BCSP) [48]. This single centre study included polyps less than 10mm in size. Calculations for cost effectiveness were based on histology costs alone. It suggested a total saving of £678,253 (€762,767) could be made per annum within the programme (which was at its infancy), or £55 (€62) per patient undergoing colonoscopy, with a negligible impact on rescope intervals. The UK BCSP uses Faecal occult blood tests prior to colonoscopy, hence polyp detection rates in this population were high, making the potential savings higher than in

the US screening population. The proposed cost savings from this should, if applied to the current screening programme, result in a several fold higher cost savings than initially proposed due to the increase in the number of patients undergoing colonoscopy in the porgramme. The most recent work on cost effectiveness is an American retrospective multicentre study [89]. The authors suggest an even larger saving of $309 per patient screened could be made, with assessments meeting the standards set in the ASGE PIVI.

A flaw with all of the cost effectiveness studies is the assumption that endoscopists reach the required level of expertise quickly and easily. None of the studies take into account the cost of training to achieve this, which may be significant. This has not been studied and should form the focus for future work.

Summary

There is a growing body of literature demonstrating what can and cannot be achieved by image enhanced endoscopy. It would appear that the greatest role lies in lesion characterization, where all of the available techniques have demonstrated effectiveness in expert hands. It is an essential skill for all endoscopists involved in resection of large and challenging polyps but is becoming increasingly recognized as an effective technique for the assessment of small polyps. Such techniques may one day be able to replace conventional histology in selected patient groups. The role of lesion detection is more controversial. Whilst indigo carmine is effective, challenges in its

usage have prevented its widespread adoption. Electronic imaging does not seem adequate for this purpose, although the picture is less clear with i-scan where more work is needed. The role in high risk patient groups is less clear, with most of the studies small with varying objectives. Chromoendoscopy is the technique of choice for surveillance of inflammatory bowel disease. Data is lacking with electronic imaging for this purpose and large studies will be required to answer this question. What has become very evident is that advanced imaging techniques have challenged the way we detect and evaluate polyps. Lesion identification has become a priority, and the endoscopist is no longer perceived as simply a tissue retrieval technician but an integral part of the diagnostic process. We feel that literature from expert centres has proven the potential of these imaging technique but generalizing of these techniques outside the expert centres still remains to be proven. This is an area for future research and we remain optimistic.

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Figure 1: Adenomatous polyp after indigo carmine dye spray

Figure 2: Adenomatous polyp viewed with Narrow band imaging

Figure 3: An adenomatous polyp viewed with FICE on setting 4

Figure 4: Adenomatous polyp viewed with i-scan setting 3

Author	Country	Journal	Year	Size	Dye	No polyps	Sensitivity	Specificity	Accuracy
Togashi (13)	Japan	Dis Colon Rectum	1999	All size	Ingigo carmine	923	92%	73.3%	88.4%
Kato (32)	Japan	Endoscopy	2001	<5mm excluded No max size	Indigo carmine	4445	94%	75%	NR
Tung (36)	Taiwan	Am J Gastro	2002	<10mm	Indigo carmine	175	93.8.%	64.6%	80.1%
Fu (35)	Japan	Endoscopy	2003	<10mm	Indigo carmine	206	96.3%	93.5%	95.6%
Konishi (45)	Japan	Gastrointestinal endoscopy	2003	<10mm	Indigo carmine	405	97%	100%	93%
Su (90)	Taiwan	Dig Dis Sci	2004	<10mm	Indigo carmine	270	95.1%	86.8%	91.9%
Hurlstone (44)	UK	Gut	2004	Any size	Indigo carmine and crystal violet	1008	98%	92%	NR
Palma (43)	Italy	World Gastroenterology J	2006	<5mm	Indigo carmine	240	97.5%	94.3%	95.4%
Sonwalker (46)	UK with Japan	Endoscopy	2007	Any size	Indigo carmine	709 (513<10mm)	91%	87%	90%
Tiscendorf (39)	Germany	Endoscopy	2007	Any size	Indigo carmine	200 (100 with IC)	91.7%	90%	NR
Pohl (77)	Germany	American Journal of Gastroenterolog	2008	<20mm	Indigo carmine (picture)	150	95.5%	73.8%	87.7%
Togashi (37)	Japan	Gastrointestinal endoscopy	2009	<5mm	Indigo carmine	107	90%	74%	86%

Table 1: Summary of publications stating accuracy, sensitivity and specificity of chromoendoscopy with optical magnification (NR=not reported).

Author	Country	Journal	Year	Size	No polyps	Sensitivity	Specificity	Accuracy
Eisem (42)	USA	Gastrointestinal Endoscopy	2002	<10mm	520	82%	82%	82%
Fu (35)	Japan	Endoscopy	2003	<10mm	206	96.3%	93.5%	95.6%
Konishi (45)	Japan	Gastrointestinal endoscopy	2003	<10mm	405	97% 86%	100% 61%	68% 93%
Apel (41)	Germany	Gastrointestinal endoscopy	2006	<5mm	273	94%	64%	83%
Pohl (40)	Germany	Gut	2009	<10mm	280	87.6%	62.0%	NR
Longcroft-Wheaton (47)	UK	UEG journal	2013	<10mm	237	91% SD 96% HD	87% SD 84% HD	89% SD 92% HD
Longcroft-Wjeaton (48)	UK	Eur J Gastrohep	2011	<10mm	232	94%	84%	91%

Table 2: Summary of publications stating accuracy, sensitivity and specificity of chromoendoscopy with indigo carmine on polyps<10mm without optical magnification (NR=not reported)

Author	Country	Journal	Year	Modality	Endoscope	No	Sensitivity	Specificity	Accuracy
Machida (54)	Japan	Endosc	2004	NBI	Zoom	43	100%	75%	NR
Chiu (65)	Taiwan	Gut	2007	NBI (pictures)	Zoom non zoom	180	82-86% 87-95%	59-83% 71-88%	81-82% 87-90%
Rastogi (50)	USA	GIE	2008	NBI	HD [1]	123	86-92%	86-92%	NR
Rogart (66)	USA	GIE	2008	NBI	Zoom	265	80%	81%	80%
East (56)	UK	Endosc	2008	NBI	HD+zoom	116	88%	91%	89.6%
Ragstogi (67)	USA	Am J Gastro	2009	NBI	HD without magnification	236 all size	96%	NR	93%
Ignjatovic (68)	UK	Lancet Onc	2009	NBI with IC	HD	278	94%	89%	93%
Sano (72)	Japan	GIE	2009	NBI	HD+zoom	150	96.4%	92.3%	95.3%
Wada (70)	Japan	GIE	2009	NBI (pictures)	HD+zoom	617	90.9%	97.1%	NR
Henry (73)	USA	GIE	2010	NBI (retrospective pictures)	Uncertain	126	93%	88%	91%
Wada (69)	Japan	Dig Endosc	2010	NBI	Uncertain	1473	88.9%	98.9%	98.2%
Tischendorf (71)	Germany	Endosc	2010	NBI (pictures)	HD with and without zoom	200	87.9% 92.1%	90.5% 89.2%	NR
Van Den Broek (91)	The Netherlands	Clinical Gastro and Hepat	2009	Trimodal imaging	HD + zoom	208	99%	35%	63%

Table 3: Accuracy, sensitivity and specificity for narrow band imaging (NBI), auto fluorescence imaging (AFI) and trimodal imaging. IC= indigo carmine, HD= high definition NR= not reported

Author	Country	Journal	Year	Modality	Endoscope	No	Sensitivity	Specificity	Accuracy
Pohl (77)	German	Am J Gastro	2008	FICE (picture)	HD low and high magnification<20mm	150	89.9% 96.6%	73.8% 80.3%	83% 90%
Pohl (12)	German	Gut	2009	FICE (subgroup analysis)	HD non zoom<10mm	321 <10 mm	93%	61.2%	84.7%
Togashi (37)	Japan	GIE	2009	FICE	HD low (50x) and high (100x) magnification<5mm	107	93%	70%	87%
Teixiera (79)	Brazil	GIE	2009	FICE	HD with zoom polyps up to 50mm	309	99.2%	94.9%	98.3%
Parra-Blanco (78)	Spain	World Journal Gastro	2009	FICE (picture)	HD with and without zoom<5mm (picture)	19	NR	NR	58.9% 70.5%
Longcroft-Wheaton (48)	UK	Eur J. Gastro	2011	FICE	Polyps <10mm resolution not stated	232	88%	82%	86%
Longcroft-Wheaton (80)	UK	Endoscopy	2012	FICE	HD and SD assessments	293	SD 83% HD 93%	SD 82% HD81%	SD 83% HD 89%
Hoffman (81)	Germany	endoscopy	2010	i-scan	HD<10mm	145	98%	100%	98.6%
Hoffman (84)	Germany	Dig Liver Dis	2010	i-scan	HD<5mm rectosigmoid	335	100%	100%	100%
Basford P (85)	UK	GIE	2013	I scan	HD<10mm	209	97%	90.7%	94.7%

Table 4: Summary of papers published using FICE and i-scan for in-vivo diagnosis. NR=not reported

	Hyperplastic	Adenomas	Cancers
White light vascularity	Pale	Dark	Dark
FICE vascularity	Pale	Dark	Very dark
FICE vascular pattern	Absent vascular pattern or faint vessels not following crypts	Regular pericryptal pattern	Dense irregular pattern
FICE surface pattern	No surface pattern or large non compact crypt pattern	Small compact regular pattern	Disorganised irregular pattern

Table 5: N.A.C. classification system