

Gaining a complete picture of the GI tract through new image enhancement technology

i-scan and i-scan OE – a unique combination of digital and optical enhancements that supports powerful detection and characterization

Abstract

i-scan real-time image processing technology has proven to be a clinically-effective digital image enhanced endoscopy (IEE) technique, using virtual chromoendoscopy to provide superior visualization of vascular and tissue architecture on the mucosal surface. Now a new optical enhancement option using band-limited light has been added to the i-scan menu. This unique new combination of digital and optical chromoendoscopy in a single system offers the endoscopist the flexibility to select the best possible picture to further improve their detection and characterization needs at the push of a button.

This paper focuses on how i-scan virtual and optical enhancement options are already proving to be a powerful synergy, supporting and enhancing endoscopic practice throughout the entire luminal gastrointestinal tract.

Introduction

As highlighted by Professor Ralph Kiesslich (HSK Wiesbaden, Germany): "Detection and characterization are the most important steps during routine endoscopy. Firstly, all suspicious areas have to be identified. Subsequently, the endoscopist has to decide if an endoscopic intervention, such as a biopsy or endoscopic resection, is needed." Consequently, it is essential that the imaging technology used is the most effective possible to best support both of these key steps in everyday luminal gastrointestinal (GI) endoscopic practice. This will in turn ensure the earlier diagnosis and treatment of GI diseases with subsequent improved patient outcomes.

White-light endoscopy and dye-based chromoendoscopy limitations

White-light endoscopy (WLE) has been seen as the gold standard for use in routine endoscopic imaging of the GI tract. However, it has been found that by using conventional WLE a significant number of lesions may be missed, particularly flat ones, and it may also be unable to detect subtle, but important, signs of inflammation. This can result in delayed or suboptimal therapies.^{1,2} A further consideration is that conventional WLE is unable to characterize vascular patterns in detail, again potentially leading to a misinterpretation of findings.

In order to overcome such issues of using white light and to improve detection and characterization in endoscopy, dye-based chromoendoscopy was developed. However, this strategy does have its own limitations. According to Helmut Neumann, MD, PhD, professor of medicine and head of the Endoscopic Research Group at the University of Erlangen-Nuremberg in Erlangen, Germany, "Dye-based and spray chromoendoscopy, which involve the application of stains to the mucosal surfaces during endoscopy to highlight mucosal differences, as well as to detect dysplastic and malignant changes that are not apparent in white light, are useful, but also have important drawbacks

that limit their overall utility. These limitations include: the use of expensive, consumable dyes; added procedural time required to apply the dyes; a learning curve to learn how to interpret results using the dyes; and the potential for allergic reactions to the dye. Also, the dye does not always coat the area evenly; we have areas that are understained and areas that are overstained, and this is a major limitation of this approach, which has been used for more than 20 years."

Consequently, in recent years virtual chromoendoscopy, or digital image enhanced endoscopy, has been introduced to maintain the improved imaging capabilities provided by dye-based chromoendoscopy, but without the need to apply dyes. Virtual chromoendoscopy provides digital contrast in real time during an endoscopic procedure by making per-pixel modifications of sharpness, hue and contrast to enhance mucosal imaging. Notably, this digital enhancement of blood vessels and mucosal surfaces enables the identification of pathologic lesions that may not be visible with conventional white light imaging (Figure 1).³ Prof. Neumann observed that, "Contrast enhancement is extremely important to predict the invasiveness of a disease. High-definition WLE is extremely good at identifying big lesions in the colon, rectum, or even in the stomach, but again we are missing contrast and subtle lesions by only using WLE."

Figure 1
Diagnosis of an esophageal squamous cell cancer

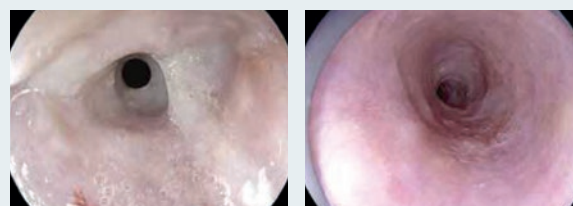


Image 1
White-light picture showing ring-like structures, initially interpreted to be compatible with eosinophilic esophagitis

Image 2
i-scan 1 (SE) clearly shows a flat lesion in the mid esophagus

(Images courtesy of Dr. Michael Häfner)

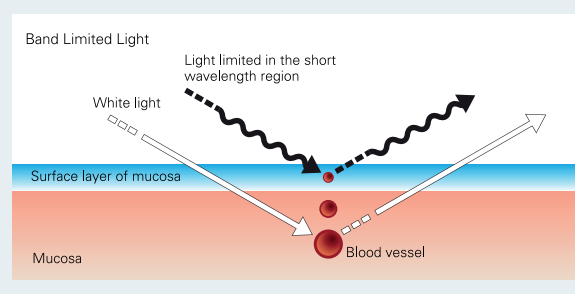
One such digital image enhancing technology is i-scan, which when used in combination with High-Definition (HD) endoscopy, offers superior visible details of the mucosal surface. This in turn enables clinicians to better visualize alterations in tissues and structures, allowing for improved detection of esophageal lesions, gastric cancer and colorectal pathologies, including colorectal polyps and inflammatory bowel diseases. Furthermore, i-scan facilitates more precise characterization of lesions throughout the entire luminal GI tract potentially enabling more accurate endoscopic therapies.

Virtual and optical chromoendoscopy (or image-enhanced endoscopy) explained

Recent advances in technology mean that i-scan image enhancing technology now uniquely incorporates both virtual chromoendoscopy and optical chromoendoscopy-based modes, all of which can be switched on and off by simply pushing a button on the endoscope. These image enhancements can be readily selected depending on the view required and without any need to spray any substances inside the colon. Since the video processor, which features i-scan, such as the PENTAX EPK-i series, performs the detail enhancement, this, as Prof. Neumann observes, means that: *“The gastroenterologist or endoscopist can concentrate fully on the endoscopic image, which is most important for adequate diagnosis.”*

The virtual chromoendoscopy modes – Surface Enhancement (i-scan SE) and Tone Enhancement (i-scan TE) – are based on the digital post processing of reflected light. Complementing these two digital enhancement modes, i-scan’s new optical chromoendoscopy mode – Optical Enhancement (i-scan OE) – uses band-limited light and pre-image processing (Figure 2). This is achieved through the use of optical filters limiting certain spectral characteristics of its emitted light while maintaining the processing and enhancement of the digital image (Figure 3).³ Unlike i-scan 1 (SE) and 2 (TE), which use white light alone to illuminate tissues and structures, i-scan OE aims to achieve higher overall transmittance by connecting the peaks of the hemoglobin absorption spectrum (415, 540, and 570 nm), thus creating a continuous wavelength spectrum.³

Figure 3
Optical enhancement employs band-limited light to differentiate surface layer of mucosa from tissues and structures

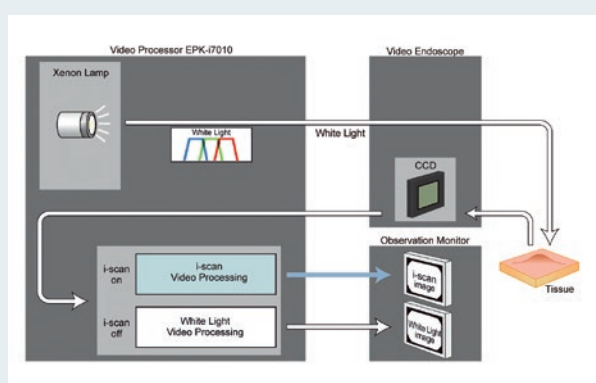


Fully supporting endoscopic clinical pathways

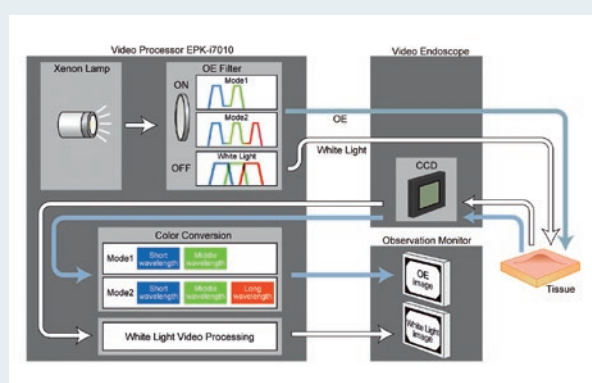
The different modes of i-scan fully complement one another to offer highly detailed visualization of the GI tract for detection and characterization of mucosal lesions. Clinicians are able to examine variations of image enhancement as the endoscopic examination progresses. i-scan SE (Surface Enhancement) highlights surface tissue architecture which may be used for the initial detection of circumscribed lesions or to highlight diffuse alteration (e.g. inflammation, atrophy). i-scan TE (Tone Enhancement) supports detailed pattern characterization such as pit patterns. i-scan OE particularly highlights mucosal vascular pattern morphology to support vessel characterization. This is achieved by the fact that it relies on the depth of penetration into the mucosa of all seven wavelengths that comprise white light, to differentiate blood vessels containing hemoglobin, which absorb certain wavelengths (peak absorption, 415 nm), from other areas of mucosa, which reflect them.

This new combination of virtual and optical chromoendoscopy offers a clear clinical pathway for endoscopic evaluation of GI tract pathologies, as noted by Professor Pradeep Bhandari, Queen Alexandra Hospital, Portsmouth, UK. *“The PENTAX HDWL image is a major advance, but when I switch i-scan 1 (SE) on, then the*

Figure 2



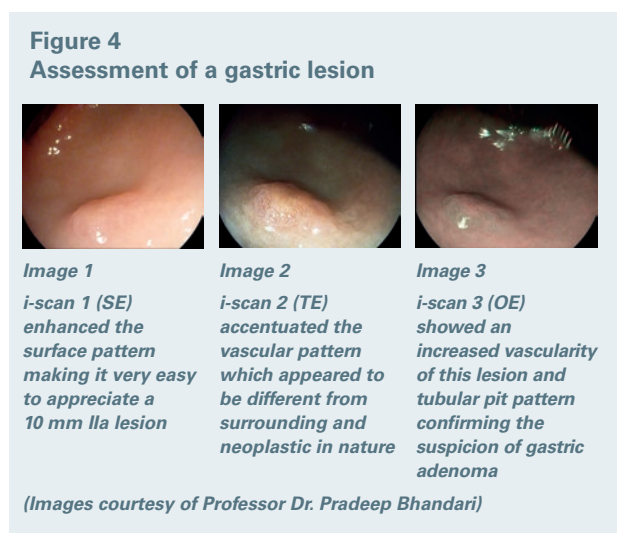
i-scan Digital Enhancement



i-scan OE Optical Enhancement

image becomes sharper and crisper without losing any other attribute of the image - so I don't see any reason why i-scan 1 (SE) should not be left on at all times. Once I find a subtle abnormality or any obvious lesion then I switch on i-scan 2 (TE) and that really highlights the lesion from the surrounding normal mucosa. Once the presence of neoplasia is confirmed, then I switch to i-scan 3 (OE) to fine evaluate the surface and vessel patterns of the lesion (to differentiate neoplastic from non-neoplastic lesion) and identify the exact margins of the lesion."

This clinical pathway is illustrated in Figure 4 in which Prof. Bhandari used i-scan 1 (SE), i-scan 2 (TE) and i-scan 3 (OE) to accentuate a subtle gastric antral lesion. He concluded that: "The recent addition of i-scan OE to the PENTAX family has been a major step forward in evaluation and characterization of gastrointestinal neoplasia."



Enhanced illumination for brighter images

Prof. Neumann also noted how the new i-scan technology is similar to narrow-band imaging (NBI) but with better illumination: "Both are narrowing the red light, leaving more blue and green light, providing a more intense look at the vascular pattern morphology. The main advantage of i-scan OE to me is that the image appears much brighter compared to narrow-band imaging, particularly in the stomach."

It has been reported that NBI images are dark, meaning that it is considered less useful in areas with a large lumen, such as the stomach and colon, due to insufficient light for a wide-range observation of the full extent of the tissue surface.^{3,4} i-scan OE's optical filters achieve high-illumination intensity by overcoming the limited spectral distribution of NBI with the continuous wavelength spectrum that connects the peaks of the hemoglobin absorption spectrum, as discussed above. This raises the baseline of the spectral transmission characteristics to achieve higher overall transmittance of the optical filter.⁴

Since, like NBI, i-scan OE is an optical chromoendoscopy technique, it can be used similarly to NBI, thus fitting

with existing optical filter classifications as explained by Dr. Federico Buffoli, Cremona Hospital, Italy: "i-scan OE should allow the use of existing classifications already accepted in the literature based on optical enhancement, making the data resulting from the use of PENTAX endoscopes more comparable."

Flexible choice of optical and digital modes

The flexibility that i-scan's combined virtual and optical chromoendoscopy technology now offers endoscopists is unique, as observed by Dr. Marietta Iacucci, clinical associate professor in the Division of Gastroenterology & Hepatology at the University of Calgary, Canada. "Currently this is the only equipment that can provide several multimodal platforms of electronic chromoendoscopy, with i-scan and NBI capabilities and i-scan OE with and without close magnification, within the same equipment. This provides flexible options to fully assess mucosal and vascular patterns."

Although it has been proposed that i-scan OE is best used for characterization of vessels, ultimately it is the choice of the endoscopist to select the image enhancement mode that suits their situation best and with which they are most comfortable. This was discussed by Dr. Buffoli based on his use of the new technology, "I think that i-scan OE represents a further step forward in the diagnostic capabilities of endoscopy. With the i-scan system we can see the mucosa and the lesions with different visualizations that allows us to collect different information, specific for each enhancement. We can choose the most suitable i-scan function depending on anatomical site, pathology or just according to the way the endoscopist feels more confident to be able to make the diagnosis."

In addition, since optical filter technology changes the appearance of blood and stool, this gives the endoscopist the flexibility to change the mode to best suit the clinical scenario. Dr Buffoli added: "The other important aspect that I want to underline is that i-scan 1 (SE) and 2 (TE), in addition to the diagnostic capability demonstrated in the literature, allow me also to perform an enhanced observation in difficult conditions like bleeding, bile or fecal residue, when it's not possible to use optical system."

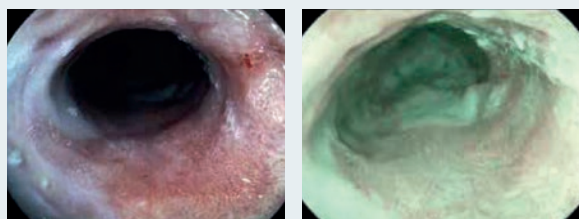
Dr. Michael Häfner, Elisabethinen Krankenhaus Wien, Austria, also commented on the flexible options that i-scan now offers endoscopists. "i-scan OE combines the versatility and flexibility of i-scan with ever sharper and crisper pictures. While i-scan 1 (SE) is my standard setting during every procedure because it gives you the extra bit of contrast and detail to detect even very subtle changes of the mucosa, i-scan OE offers an extremely sharp view of the surface pattern, for example in Barrett's esophagus. Combine it with the capabilities of the optical zoom endoscopes and you get the ultimate diagnostic tool in both lower and upper GI tract."

Optical zoom

As highlighted above, new endoscopes have recently been introduced by PENTAX that combine high-definition images with optical magnification called MagniView. These scopes magnify the image up to 136 times at a superior quality than standard scopes without optical zoom. Consequently, when i-scan technology is coupled with the optical zoom capabilities of the new MagniView scopes, this allows for detailed surface structure observation, that would not be possible with standard white light and scopes, to support enhanced characterization.

Use of MagniView with i-scan virtual chromoendoscopy modes has already been found to be useful in daily clinical routine, as observed by Dr Rehan Haidry, UCL, London, UK. *"In my own practice I rely on i-scan 1 (SE) (as my default initial mode for interrogating the upper GI tract. This has superseded the WLE mode for me and helps me to assess and detect early cancers. The depth and image resolution is excellent at defining mucosal patterns, that when disordered or irregular, lead one to suspect neoplasia. My own preference is then to switch to i-scan 2 (TE) to better characterize the lesion in terms of borders, but also it allows one to interpret vascularity in great detail. Coupled with the magnification range of endoscopes, I have used this mode with much success, for example in patients with early squamous cell cancer of the esophagus. With the combination of conventional chromoendoscopy and agents such as acetic acid it can provide very accurate delineation of flat lesions."* This is shown in Figure 5.

Figure 5
Diagnosis of early squamous cell carcinoma



Images 1 and 2

Non magnification images of an area of ESCN with i-scan 2 (TE) followed by i-scan 3 (OE)



Images 3, 4 and 5

Magnification endoscopy showing areas of ESCN and abnormal IPCL configuration

(Images courtesy of Dr. Rehan Haidry)

Dr. Carlos Robles-Medranda, Head of the Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas of OMNI Hospital, Guayas, Ecuador has also confirmed the power of i-scan OE in combination with MagniView. *"With the i-scan OE and magnification, I can see very small details that I can't see when using standard*

WLE. I can recognize the microscopic aspects of the pit patterns of the mucosa, I can recognize vascular lesions, and I can predict the histologic feature of the mucosa that is under inspection."

Clinical utility of digital and optical i-scan modes

Since i-scan's introduction over 8 years ago, accumulating evidence has shown the quality and usefulness of the technology's virtual chromoendoscopy modes in the clinical setting for the visualization of the entire luminal GI tract. The new i-scan Optical Enhancement mode has also been reviewed in a number of centers worldwide, including nine observational studies within Europe. Here we move on to discuss the proven effectiveness of i-scan virtual chromoendoscopy modes and the growing evidence supporting the efficacy of the newly introduced i-scan OE.

Clinical utility in the upper GI tract – virtual chromoendoscopy

The clinical relevance of i-scan virtual chromoendoscopy digital image enhancement has been demonstrated for endoscopic evaluation in a number of disease areas of the upper GI tract, including gastroesophageal reflux disease (GERD) and Barrett's esophagus, as well as duodenal pathologies.

Dr. Rehan Haidry noted: *"In the detection and treatment of esophageal cancers i-scan has transformed the way we can look at our patients. It has helped us to detect early cancers that might not have been possible to see with some of the older generation scopes. In the context of esophageal cancers which carry a poor prognosis, early detection offers these patients a very realistic chance of curative therapy with either minimally invasive endotherapy or early surgery."*

One such application of i-scan within the esophagus involves patients with gastroesophageal reflux disease (GERD). Such patients are divided into those with non-erosive reflux disease (NERD), erosive reflux disease (ERD) and Barrett's esophagus. However, it is possible that patients with NERD may have minute mucosal changes that are underestimated by conventional endoscopy due to visual limitations.

Consequently, a study by Hoffman *et al.*, investigated the efficacy of high-definition (HD+) endoscopy with i-scan and Lugol's solution (dye-based chromoendoscopy) for the differentiation of reflux patients.⁵ The study concluded that Lugol's solution used in conjunction with HD+ endoscopy significantly improved the identification of patients with esophagitis and reduced misclassification. i-scan and dye-based chromoendoscopy helped to identify reflux-associated lesions. The data from this study has subsequently been confirmed by two Korean studies.^{6,7} Kim and co-workers, for example, found that i-scan endoscopy significantly improved the identification

of minimal change in GERD and helped to identify more precisely the type of minimal change and so ideally define conditions for further management and therapy.⁷

i-scan virtual chromoendoscopy has also been found to improve dysplasia detection in Barrett's esophagus. Furthermore, in a randomized, comparative trial of 95 patients in Germany, i-scan was found to be as good as acetic acid-guided biopsies for the detection of specialized columnar epithelium (SCE) in Barrett's esophagus. i-scan also showed a significantly higher diagnostics yield for identifying SCE, with significantly fewer biopsies, as compared to a protocol of random biopsies.⁸

A further example of the clinical application of i-scan SE and TE in the Upper GI is provided by Dr. Giovanni Cammarota and colleagues, from the "A. Gemelli" University Hospital, Rome, Italy. They performed a prospective, single-center study of 115 patients undergoing upper endoscopy for histologic evaluation of duodenal mucosa.⁵ All patients underwent upper endoscopy using high-resolution view in association with i-scan technology. During endoscopy, duodenal villous patterns were evaluated and classified as normal, partial villous atrophy, or marked villous atrophy. Results were then compared with histology.

The investigators reported that the i-scan system had 100% accuracy for the detection of marked villous atrophy patterns and 90% accuracy for the detection of partial villous atrophy or normal villous patterns. The conclusion of the study was that i-scan IEE technology allows the clear visualization of villous patterns in the duodenum. By switching from standard to i-scan view, it is possible to optimize the accuracy of the endoscopy in recognizing villous alteration in subjects undergoing endoscopic evaluation.⁹

Clinical utility in the upper GI tract - combined effectiveness of i-scan digital and optical chromoendoscopy

As previously discussed, internationally-renowned experts have already had the opportunity to test the new video processor (OPTIVISTA, EPK-i7010) which combines i-scan 1 (SE), i-scan 2 (TE) and i-scan 3 (OE). Initial findings confirm the clinical value of this unique system, when moving through the clinical pathway for endoscopic evaluation.

Dr. Marc Giovannini, Institut Paoli-Calmettes, Marseille, France, commented on his use of the combined system in the upper GI: "I usually use as default i-scan 1 (SE) as a detection mode and I usually turn on i-scan OE when I want to better visualize the mucosal and vascular pattern; I find it particularly useful in Barrett's esophagus to diagnose areas of high grade dysplasia."

Dr José Miguel Esteban, Hospital Clínico San Carlos, Madrid, Spain, also confirmed the value of the endoscopic evaluation pathway offered by i-scan SE, i-scan TE and i-scan OE. "I usually use i-scan 1 (SE) at the beginning of all my endoscopic studies. It brings the characteristics of

the WL endoscopy with more resolution of the surface which is better to identify lesions. Once I identify a lesion, I turn to i-scan 2 (TE) to characterize the vascularity. The new Optical Enhancement provided by i-scan OE gives the best features of mucosal pattern and vascularity with the same tool." He also observed the ability of the new system to refine tissue diagnosis. "In Barrett's esophagus the new EPK-i7010 gives the chance to discriminate in the best way the suspicious areas for dysplasia. This means that you can take less biopsies in the protocol with better likelihood of getting the dysplastic Barrett's and of identifying the intramucosal neoplasia."

A number of case reports in Europe have been published which observed the clinical value of the combined system. For example, Dr Esteban used i-scan SE, i-scan TE and i-scan OE to determine the lateral extension of an ampullary lesion, which ultimately assisted in determining the appropriate method of treatment (Figure 6).

Figure 6
Determining the lateral extension and characterizing of an ampullary lesion



Image 1

i-scan 1 (SE)
revealed a lesion with abnormal irregular mucosal architecture greater than 4 cm

Image 2

i-scan 2 (TE)
demonstrated a central area of increased vascularity and abnormal microvascular pattern

Image 3

i-scan 3 (OE)
confirmed the lateral margins of the lesion to extend beyond those determined by white light endoscopy

(Images courtesy of Dr. José Miguel Esteban)

Dr Rehan Haidry has used the i-scan OE in combination with optical zoom endoscopy to help in the diagnosis of early squamous cell carcinoma (Figure 5), as well as to visualize an early neoplastic lesion arising from the Barrett's mucosa (Figure 7). He also observed; "Over the past six months I have been using newer optical enhancements that PENTAX have developed above and beyond the conventional i-scan. I have particularly liked i-scan OE, as the filtering technology here provides a very distinct and lighter image of the vascularity and mucosal pit patterns that become disordered in early cancer. This, coupled with i-scan SE, have in my practice become the two most common enhanced imaging modalities that I use."

Dr. Robles-Medranda also commented on the greater utility of i-scan OE in characterizing diseases of the upper GI tract and its superior visualization when used in conjunction with optical zoom scopes. "This technology is very helpful for the detection of various lesions that are not always well visualized when using standard WLE," he said. "For example, in my experience, it is much more helpful in detecting lesions associated with esophagitis or gastroesophageal reflux disease, as well

Figure 7
Detection and resection of an early neoplastic lesion in a Barrett's esophagus

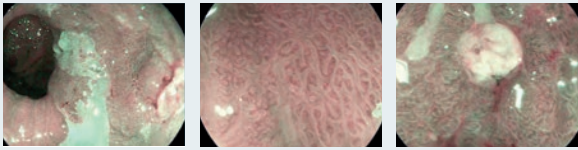


Image 1

Assessment for Barrett's esophagus with an early neoplastic lesion as seen with i-scan 3 (OE)

Image 2 and 3

Abnormal mucosal architecture and vasculature with magnification endoscopy and i-scan 3 (OE) in a patient with Barrett's neoplasia. These images were obtained using the MagniView endoscope (EG-2990Zi)

(Images courtesy of Dr. Rehan Haidry)

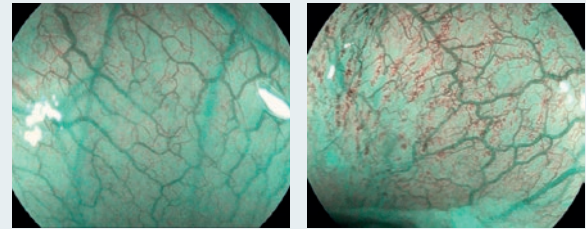
as with gastric lesions, including dysplastic lesions. With the OE technology and MagniView, we can even observe lesions that were not previously defined and that may be pathognomonic of non-erosive reflux disease, such as minimal esophageal lesions and intrapapillary capillary loops." Figure 8 shows some examples of endoscopic evaluations of upper GI structures using i-scan OE.

Indeed, Dr. Robles-Medrandá's team has very recently conducted a multiple patient study to evaluate the diagnostic ability of the i-scan OE and MagniView scopes to detect minimal esophageal lesions (MEL) and intrapapillary capillary loops (IPCLs), and to predict reflux in NERD patients.¹⁰ Endoscopic findings were compared with reference data from pH-impedancimetry and histopathologic assessment of biopsies to assess relative diagnostic utility. In the study, 57 patients were analyzed, including 36 patients with NERD and 21 control patients with non-reflux disease. IPCLs were observed in 94.4% of patients with NERD and in 38% of control patients ($p < 0.05$), and IPCLs was more commonly detected in patients whose biopsies showed signs of inflammation.

The ability of the OE system plus MagniView scope to predict GERD was compared with pH-impedancimetry, the gold standard. The sensitivity, specificity, positive-predictive value, negative-predictive value, and accuracy of the system for this purpose were 94.4%, 61.9%, 91.4%, 81.8%, and 86.67%, respectively. Based on these data, Dr. Robles-Medrandá's team concluded that the OE system plus MagniView scope can detect MEL and predict GERD with high sensitivity and accuracy. Furthermore, the presence of MEL was strongly correlated with histologic indicators of inflammation.¹⁰

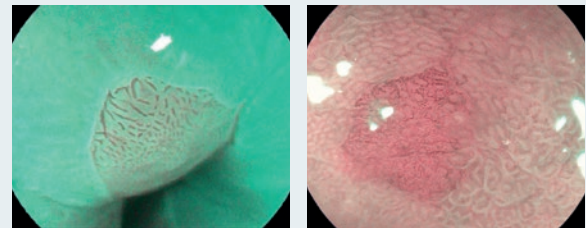
Prof. Neumann has also evaluated the effectiveness of i-scan OE for the diagnosis of GERD in a further multi-patient study. From his study of 100 areas, he found that i-scan OE significantly improved diagnosis of GERD compared to high-definition white light endoscopy. Furthermore, features seen only by i-scan OE were compared between controls and patients with GERD and multivariate analysis found that increased number and dilation of IPCL were the best predictors of GERD.¹¹

Figure 8
PENTAX i-scan OE images showing endoscopic evaluations of upper GI structures



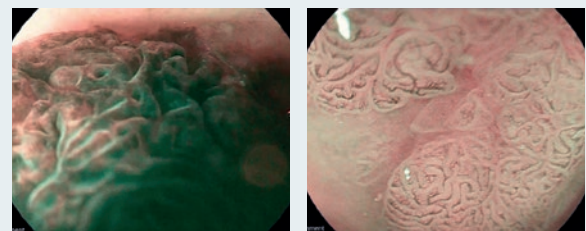
A: normal esophagus

B: intrapapillary capillary loops in a patient with non-erosive reflux disease



C: Barrett's esophagus

D: early gastric cancer



E and F: adenomatous polyps

(Images courtesy of Dr. Carlos Robles-Medrandá)

Clinical utility in the lower GI tract – virtual chromoendoscopy

As in the upper GI tract, a number of large studies have already shown the benefit of i-scan virtual endoscopy modes for highly effective patient management during ongoing endoscopy. Indications for image-enhanced endoscopy with i-scan digital modes in the lower GI tract include diagnosis of colorectal adenomas and cancer.³ As noted by Dr. Mikos Kassai, Monklands Hospital, Airdre, UK: "The i-scan has the potential to facilitate the decision of the nature of the polyp on the spot. i-scan Surface Enhancement is VERY useful."

As the second most common cause of cancer-related deaths in Europe and North America, it has been accepted that early detection and endoscopic treatment of colorectal cancer by colonoscopy screening has reduced colorectal cancer mortality. In recent colorectal studies, it has been found that i-scan can detect more polyps,^{12, 13, 14} particularly those that are small and flat,^{15, 16} including adenomas,^{17, 18} than high definition white light. Notably, this has also been demonstrated on the right hand side of the colon where polyps tend to be flatter.¹⁸

For example, one large study that demonstrates the superiority of high definition colonoscopy in combination

with i-scan for the detection of colorectal neoplasias, when compared to standard video colonoscopy, was undertaken by Hoffman *et al.*¹⁸ In the study, 220 patients were randomized in a 1:1 ratio, and it was found that i-scan detected significantly more patients with colorectal neoplasia (38%) when compared to standard resolution endoscopy (13%). In addition, significantly more neoplastic lesions and more flat adenomas could be detected using high definition endoscopy with i-scan surface enhancement. Furthermore, of particular note, final histology results were shown to be predicted by high definition endoscopy and i-scan with nearly 99% accuracy.

Such results have been confirmed by many others, including Testoni *et al.*, who in a study of 1101 consecutive colonoscopies showed that, during the withdrawal phase of colonoscopy, i-scan significantly increased the detection of colonic mucosal lesions, particularly small, flat polyps of <10 mm. Testoni has also demonstrated that i-scan can increase the detection rate of mucosal lesions by non-expert endoscopists.¹⁴ In this paper, 542 colonoscopies were evaluated and it was found that when using standard white light procedures, expert endoscopists detected mucosal lesions in more colonoscopies than non-experts. When using high definition endoscopy with i-scan, this enabled the less skilled endoscopists to achieve results comparable to those of experienced ones in detecting mucosal lesions.

In addition to improving *in vivo* polyp and adenoma detection rates in the colorectum, i-scan has also been shown to enhance *in vivo* characterization in colonic pathology. For example, Rath and co-workers found that HD endoscopy in combination with i-scan digital chromoendoscopy allowed real-time *in vivo* prediction of distal colorectal polyp histology.¹⁹ They noted that it is in fact accurate enough to leave distal colorectal polyps in place without resection, or to resect and discard them without pathologic assessment. Since this approach has the potential to reduce costs and risks associated with the redundant removal of diminutive colorectal polyps, this means that i-scan meets the American Society for Endoscopy (ASGE) PIVI guidelines.²⁰ The Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative includes two paradigms for the cost-effective management of diminutive polyps. One paradigm describes endoscopic resection of colorectal polyps without submitting them for pathological assessment ('resect and discard'). The other proposes leaving diminutive hyperplastic rectosigmoid polyps in place without resection. For both of these, PIVI advocates the use of real-time endoscopic technologies that can help predict the histology of colorectal polyps.

Clinical utility in the lower GI tract – combined effectiveness of i-scan virtual and optical chromoendoscopy

As discussed previously, international experts have also positively assessed the clinical utility of the new combined i-scan system in the lower GI. For example Dr. Federico Buffoli, Cremona Hospital, Italy, observed: "After my first

experience with i-scan OE, I feel that it allows me to better study the pit pattern of healthy mucosa and of lesions."

Dr. Cristina Trovato, European Institute of Oncology, Milan, Italy, also commented on how i-scan OE helps in the characterization of colorectal lesions. "Several studies have shown that digital-based chromoendoscopy is accurate in predicting the histology of polyps of the colon and rectum. The i-scan 1 (SE) is my favorite mode for obtaining the sharpest image. In 2013, we observed good inter-observer agreement among endoscopists in the evaluation of neoplastic and non-neoplastic lesions visualized with the PENTAX Medical i-scan technique, but a poor agreement in the evaluation of pit-pattern and margins. The recent addition of i-scan 3 (OE) is useful as it really helps me to better assess the vascular and pit patterns of the lesion and accurately identify its margins."

The value of i-scan OE for the *in vivo* characterization of colonic polyps has also been noted in a forthcoming publication by Dr. Iacucci and co-workers.²¹ This study utilized i-scan OE to evaluate the accuracy and inter-observer agreement in polyp characterization. The study concluded that gastroenterologists and physicians without prior experience in i-scan OE magnification colonoscopy could achieve significant improvements in predicting polyp histology after a brief training session using videos. Both NICE and ICE polyp classification performed equivalently.

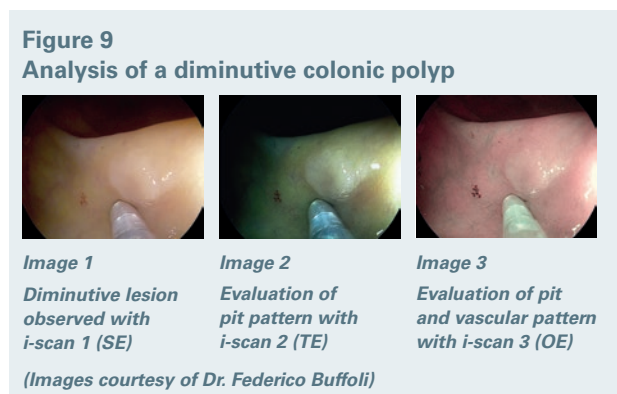
Dr. Iacucci has also noted that the capabilities of the i-scan technology with OE and magnification provide an excellent fit with the ASGE PIVI initiative. "This endoscopic technology has the capabilities, in real time, to decide if we need to remove the polyp and whether we can discard it or whether it should be submitted to pathology," she said. "It will help clinicians embrace the new policy of the ASGE of 'resect and discard,' and will be a great way to save money for the community."

Prof. Neumann also noted that i-scan technology with i-scan OE could help facilitate endoscopic mucosal resection and help patients avoid surgery. "In endoscopy, we are always deciding if a lesion is only superficially invasive or deeply invasive based on this so-called mucosal pit pattern. Superficially invasive would mean that we can perform an endoscopic resection, and deep invasion would mean that we have to perform a surgical intervention with resection of the lymph nodes. The advantage of i-scan, and now recently introduced i-scan OE, is that both technologies are adding much more contrast to the endoscopic image. It's not white-light anymore, but now it's a colored image, and therefore it is now much easier for us to detect subtle lesions and also to perform this prediction of mucosal invasion; is it, in essence, one tumor, or is it going deeper? So, can we perform endoscopic resection or would it be better to send the patient to the surgeon for resection of the lymph nodes, as well? This is the main advantage of these new technologies."

Prof. Neumann has, in fact, already developed and validated a simple and effective classification system for differentiating hyperplastic and adenomatous colorectal lesions by using i-scan OE technology during real-time

colonoscopy. These findings are to be evaluated in future prospective, controlled, and blind clinical trials.²²

A number of patient reports have also been drafted following the initial assessment of the new i-scan OE when used in conjunction with i-scan SE and i-scan TE. For example, Dr. Buffoli has found that HD endoscopy when coupled with both digital and optical i-scan is a helpful tool for the study of diminutive polyp features, enhancing polyp vascular pattern and pit pattern. Figure 9 highlights this endoscopic clinical pathway.



Clinical utility in IBD – virtual chromoendoscopy

Another area where i-scan can contribute to the accurate assessment of disease activity and extent to ensure optimized medical therapy, is within inflammatory bowel disease (IBD). For example, Neumann *et al.*, compared the use of i-scan with HD white-light endoscopy for the assessment of IBD patients.²³ They found that i-scan could significantly improve the diagnosis of severity and extent of mucosal inflammation in patients with IBD, which could, in turn, open new possibilities for therapeutic interventions in patients suffering from IBD.

Clinical utility in IBD - combined effectiveness of i-scan virtual and optical chromoendoscopy

The value of i-scan OE for the study of other disease areas such as IBD has also been noted by Dr. Iacucci: *“This technology has uses beyond those of characterizing polyps in the lower GI tract. It can also be used to assess for conditions such as microscopic colitis, and to characterize lesions of the lower GI tract in patients with inflammatory bowel disease.”*

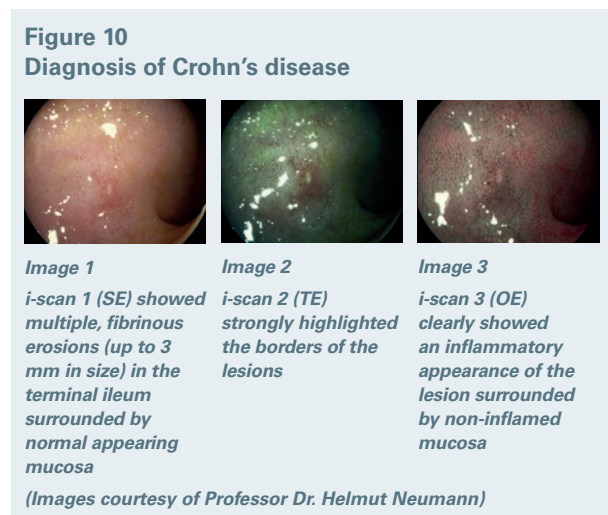
i-scan OE with magnification can assess details in mucosal and vascular pattern, and margins and mucosa surrounding these lesions in IBD patients. This ability will aid endoscopists in planning early endoscopic therapeutic management with organ-sparing endoscopic resection, rather than colectomy.

Iacucci *et al.*, have noted that i-scan OE technology enhances details of the surface structures of blood vessels, glandular

structure and the mucosa in much higher resolution than white light. Therefore, they investigated the potential of i-scan technology and an optical zoom endoscope to improve characterization of mucosal and vascular patterns to increase the accuracy of assessing and predicting the grade of inflammation in ulcerative colitis patients. They concluded that i-scan OE with magnification may accurately reflect histologic abnormalities demonstrated by the newly defined histological ECAP score – which incorporates the full spectrum of acute and histologic abnormalities. This demonstrates that by using advanced chromoendoscopy technology, such as i-scan OE, endoscopic assessment of ulcerative colitis is starting to approximate histology.²⁴

Dr Iacucci also noted that: *“In the past, every time we found a lesion in a patient with inflammatory bowel disease, we were concerned about the malignant potential and were more likely to refer for colectomy. This may no longer be the case. With this new technology, we can assess the margins and make a determination of its suitability for endoscopic resection, thereby avoiding the need for colectomy in many cases.”*

Prof. Neumann also affirms the clinical utility of the digital and optical modes of i-scan in IBD. In a recent case report discussing the diagnosis of Crohn’s disease, he highlights the importance of advanced endoscopic imaging techniques for detection of subtle mucosal lesions in the luminal GI tract and the potential of i-scan OE for characterization of inflammatory lesions in patients with IBD (Figure 10).



Prof. Neumann also added: *“In IBD, one can expect also to use the i-scan 3 (OE), especially to predict microscopic inflammation. This concept and assessment is very important for our patients because mucosal healing is associated with less steroid use, less hospitalization and less surgery for patients. I suspect that the i-scan 3 (OE) technology will be very helpful for the assessment of mucosal healing in patients with inflammatory bowel diseases. In this way, it will help to guide whether medical therapy should be advanced for patients with active mucosal disease or whether medical therapy can be decreased for those who demonstrate good mucosal healing.”*

Future outlook

As already suggested, using combined i-scan digital and optical chromoendoscopy could facilitate *in vivo* diagnosis. For example, Dr. Robles-Medranda commented: *"Because this technology enables me to see signs of underlying inflammation and provides endoscopic correlates of pathology in patients that were not previously considered to have organic disease, such as those with non-erosive reflux disease, I suspect that we will be able to avoid the need for further testing, such as manometry and pH testing."*

Prof. Neumann added: *"The future for OE, in my opinion, is not only guidance of endoscopic therapy, but also its ability to be used for in vivo characterization of the tissue. I think we will be using it to diagnose Barrett's esophagus, celiac disease, and normal colorectal polyps. In fact, we also know that it's extremely helpful for in vivo diagnosis of colorectal polyp histology to differentiate hyperplastic lesions from adenomas or cancers."*

As the use of i-scan OE increases, further study of its capabilities, settings and design will provide more data on the benefits of discovering and diagnosing GI adenomas and cancers, as well as subtle histological abnormalities relating to IBD. Future studies are already planned or ongoing in a number of disease areas including Barrett's esophagus, squamous cell carcinoma, colorectal polyps and flat lesions, as well as IBD.

Conclusion

The unique combination of optical with virtual chromoendoscopy is already proving to be a powerful new tool, aiding the endoscopic imaging and evaluation within

the luminal GI tract by delivering sharp and crisp images, as further highlighted by Professor Dr. Raf Bisschops (UZ Leuven, Belgium): *"I use systematically advanced imaging techniques such as i-scan and i-scan OE in the work-up of patients with suspicion of Barrett's associated neoplasia to help in the detection of small subtle lesions."*

In addition to the observations and references noted in this paper, the internationally-renowned experts, through their testing of the new system, have contributed to a new comprehensive i-scan Atlas.²⁵ All technological features are described within this and image examples are given with settings and clinical algorithms recommended for i-scan SE, i-scan TE and i-scan OE.

Future studies will also continue to clarify and highlight the scientific and clinical value of the unique combination of virtual and optical chromoendoscopy results for different diseases.

Dr. Silvia Sanduleanu, Maastricht UMC+, The Netherlands, confirms this. *"In order to implement optical enhancement (OE) in routine clinical practice, the endoscopist must firstly understand the rationale of this new technology. What is the additional value?"*

She notes that i-scan OE does show detailed views of the mucosal architecture, particularly blood vessels, and should work alongside standard HD and conventional i-scan technology to deliver a complete endoscopic clinical pathway of detection, characterization, verification and therapy. *"HD imaging remains key. Besides this, contrast enhancement using i-scan OE, which is an image pre-processing technology, highlights the epithelial mucosal surface pattern and especially the vascular pattern in detail. i-scan OE facilitates detection and in vivo diagnosis of lower gastrointestinal tract pathology enabling targeted endotherapy."*

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