REVIEW

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Narrow band imaging with near-focus mode for colorectal polyps' characterization

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Abstract

Conventional white light endoscopy is far from being an ideal tool to detect, characterize, and confirm the nature of colorectal lesions in order to indicate targeted biopsies or polyp resections only when necessary. Minimally invasive imaging techniques have gradually emerged to reveal previously unseen abnormalities to the operator during endoscopic examination. In this respect, technology and applications of narrow band imaging (NBI) are rapidly evolving. Magnification using NBI with near-focus mode has been introduced recently to enable closer examination under the control of a single button. The aim of this article is to offer an in-depth overview of this topic with emphasis on colorectal polyps through a literature review by using *PubMed* search tools including full-text articles, up-to-date guidelines and recent abstracts with obvious conclusions.

Keywords: optical biopsy, virtual chromoendoscopy, narrow band imaging (NBI), near-focus mode, colorectal polyps.

Introduction

White light endoscopy (WLE) has been the first endoscopic technique used to image the mucosa of the gastrointestinal tract. Conventional WLE is far from being an ideal tool to detect, characterize, and confirm the nature of intestinal lesions in order to indicate targeted biopsies or polyp resections only when necessary. Minimally invasive imaging techniques have gradually emerged, as a complement to WLE, to reveal previously unseen abnormalities to the operator during endoscopic examination of the gastrointestinal (GI) tract.

The development of endoscopic equipment over time has included increasing optical resolutions together with the miniaturization of components, which facilitate greater ease of access to the gastrointestinal tract for tissue sampling and treatment [1]. A shift from diagnostic and therapeutic interventions for symptomatic disease toward cancer prevention in asymptomatic patients has been accompanied by two competing but complementary approaches: one based on broad-view targeting of "areas of interest" or "red flags" such as WLE, high-definition (HD) endoscopy, and "electronic" chromoendoscopy (narrow band-type imaging) and another one based on multiple small area measurements, which can be either machine (spectroscopy) or human-interpreted (endomicroscopy, magnification endoscopy) [2].

Technology and applications of narrow band imaging (NBI) are rapidly evolving. Magnifying endoscopy using the conventional magnification method is widely used as a diagnostic method in hollow organs, including the colon. Magnification using near-focus mode (NFM) has been introduced recently to enable close examination under the control of a single button [3, 4].

The aim of this article is to offer an in-depth overview of this topic with emphasis on colorectal polyps through a literature review by using *PubMed* search tools including full-text articles, up-to-date guidelines and recent abstracts with obvious conclusions. The keywords *optical biopsy*, *early diagnosis*, *advanced endoscopic imaging techniques*, *electronic chromoendoscopy*, *virtual chromoendoscopy*, *narrow band imaging (NBI)*, *dual focus/near focus/close focus mode*, *colorectal polyps* were used alone or in various combinations. Additional relevant publications were also searched using the reference lists of the identified articles as a starting point.

"Red flag" techniques in colorectal endoscopy

Most colorectal lesions are polyps. A significant number, estimated between 5% and 30%, are flat or depressed lesions difficult to see by traditional endoscopy. Conventional colonoscopy misses 25% of small polyps (<5 mm) and 10% of large polyps (>1 cm) [5]. The ability to determine colorectal polyp pathology by endoscopy could potentially reduce the risks of unnecessary polypectomy (*e.g.*, diagnosing distal hyperplastic polyps *in vivo*) and improve the diagnosis of early colonic neoplasia.

The American Society for Gastrointestinal Endoscopy (ASGE) recently set threshold levels for optical diagnostic accuracy to be acceptable for clinical use [6]. *The European Society for Gastrointestinal Endoscopy* (ESGE) also published guidelines suggesting that virtual chromoendoscopy can be used under strictly controlled conditions for real time optical diagnosis of diminutive colorectal polyps to replace histopathological diagnosis [7]. Thus, there is promise for the development of a "resect and discard" policy for diminutive adenomas by using electronic chromoendoscopy.

Electronic chromoendoscopy (virtual chromoendoscopy) offers an alternative to dye-based chromoendoscopy and it refers to endoscopic imaging technologies that provide detailed contrast enhancement of the mucosal surface and blood vessels, including NBI (Olympus Medical Systems Tokyo, Japan), which is the most studied.

Dye-spray chromoendoscopy alone improves detection rates of hyperplastic, small polyps (<5 mm) and small adenomas [8]. Preliminary results on a new technique using methylene blue-based oral tablets to incorporate the dye within bowel preparation during ongoing colonoscopy were of 63.5% polyp detection rates [9].

In a large multicenter trial, the number of adenomas detected was almost 40% higher when using chromoendoscopy combined with magnification endoscopy as compared with standard colonoscopy [10]. On the other hand, in another multicenter study including 203 patients, no difference was found in the overall adenoma detection rate between standard colonoscopy and high-resolution colonoscopy associated with indigo carmine-based chromoendoscopy (49.5% *vs.* 59.4%, respectively). Nevertheless, high-resolution chromoendoscopy yields a higher number of small hyperplastic polyps as well as flat adenomas than pan-colonic chromoendoscopy with indigo carmine alone [11].

Despite the effectiveness of chromoendoscopy, a major disadvantage could be that it is a time-consuming procedure for staining of the entire colon [12] and that it does not allow detailed analysis of sub-epithelial capillary network [13]. These disadvantages can be diminished by NBI, which enhances the pattern of microvascular network microsurface structure between the epithelial surface and subjacent vascular pattern by using narrow band filter without using contrast substances or absorptive dyes. Currently, chromoendoscopy should be performed additionally if deep submucosal invasive cancer is suspected (only 5% of cases) [14].

Conventional NBI technology. Optical characteristics of NBI devices

Briefly, NBI represents an optical image enhancement technology that improves the visibility of vessels and other tissues on the mucosal surface by employing the light absorption characteristics of hemoglobin at a specific wavelength. While WLE uses the visible spectrum of light to form an image, NBI utilizes specific blue and green bands that are strongly absorbed by hemoglobin in the blood vessels. This enhances the visualization of the capillary network and mucosal morphology in a similar way to chromoendoscopy [15]. Imaged in blue light, the superficial mucosal vasculature of polyps, particularly adenomas, generates a sharp color contrast with the surrounding normal mucosa, which can enhance detection of lesions [16].

While short wavelengths penetrate only superficially into the mucosa, longer wavelengths are capable of penetrating more deeply into the tissue [6]. The placement of a NBI filter directly in front of the xenon arc lamp produces two narrow bands of light centered at the specific wavelengths of 415±15 nm (blue) and 540±15 nm (green), that are correspondent to the primary and secondary light absorption peaks of hemoglobin, respectively [17]. Thus, capillaries in the superficial mucosa are highlighted by the 415 nm wavelength and appear brown, whereas the longer 540 nm wavelength penetrates slightly more deeply into the mucosa and submucosa and makes the deeper veins appear blue-green (cyan) [18]. Vascular density and pattern differ between neoplastic (adenoma) and non-neoplastic (hyperplastic) polyps, allowing an endoscopist to use NBI to differentiate between the two [19].

The first commercially available NBI systems (Evis Exera II 180 system – color CCD system, and the Evis Lucera 260 spectrum series – RGB sequential system) were able to switch between WLE and NBI by the touch of a scope button or on the front panel of the light source, which resulted in movement of a narrow band filter in front of the xenon arc lamp after a 1- to 2-second delay. Although the concept and basic design was the same for both the NBI sequential and non-sequential systems, a difference in color images existed due to differences in the color spectral characteristics of the RGB rotary filters used in the Lucera Spectrum and the color CCD used in the Exera II [20]. The disadvantage was that they both used only a narrow band of light (comprising two wavelengths only) while filtering out the other wavelengths of white light, resulting in less bright images.

Starting from 2012, for the new-generation NBI systems (Evis Exera III – United States and Europe, Evis Lucera Elite – Japan and Korea), the brightness of the lamp in the light source increases accordingly with the switch from white light to NBI [6]. These NBI systems use an upgraded xenon lamp as a light source in combination with two filters transmitting blue light and one filter transmitting green light, compared to one filter each for blue and green light in basic NBI systems. With the combination of upgraded light source and an additional blue light filter, these new NBI scopes can achieve near-focus and a high-resolution macrofunction, producing brighter and clearer images [21].

Current standard NBI limitations

Pilot studies have demonstrated the safety and feasibility of polyp detection using NBI [22, 23]. Evaluating NBI studies, however, has been difficult because of the lack of standardization between NBI systems.

Several randomized controlled trials failed to show an increased adenoma detection rate when comparing NBI with WLE [24–26]. Similarly, other studies found limited benefit of NBI in improving adenoma detection rates compared with HD colonoscopy, although on pooled analysis, HD colonoscopy and NBI had higher diagnosis accuracy than standard white light colonoscopy alone [27] (Figure 1, A and B).

However, it is not proven whether NBI improves patient outcomes. Studies that compared NBI to WLE reported similar neoplasm detection rates and because of the lack of standardization between NBI systems, it is difficult to interpret the studies. In a prospective

randomized study, Adler *et al.* evaluated NBI *versus* conventional colonoscopy for adenoma detection. A total of 401 patients presenting for diagnostic colonoscopy were randomly assigned to undergo wide-angle colonoscopy using either conventional high-resolution imaging or NBI during instrument withdrawal. Although adenomas were detected more frequently in the NBI group than in the control group (23% *vs.* 17%), the difference was not statistically significant (p=0.129). Then, the two techniques were compared in subgroups of 100 eligible patients, with stable adenoma rates in the NBI group and rates steadily increased rates in the control group (8%, 15%, 17%, and 26.5%, respectively). Moreover, the significant differences in the first 100 cases (26.5% *vs.* 8%, p=0.02) could not be maintained in the last 100 cases (25.5% *vs.* 26.5%, p=0.91). Thus, the authors concluded that the increased adenoma detection rate of NBI colonoscopy were not statistically significant and whether the increasing adenoma rate in the conventional group was caused by a training effect of better polyp recognition on NBI remains speculative [26].

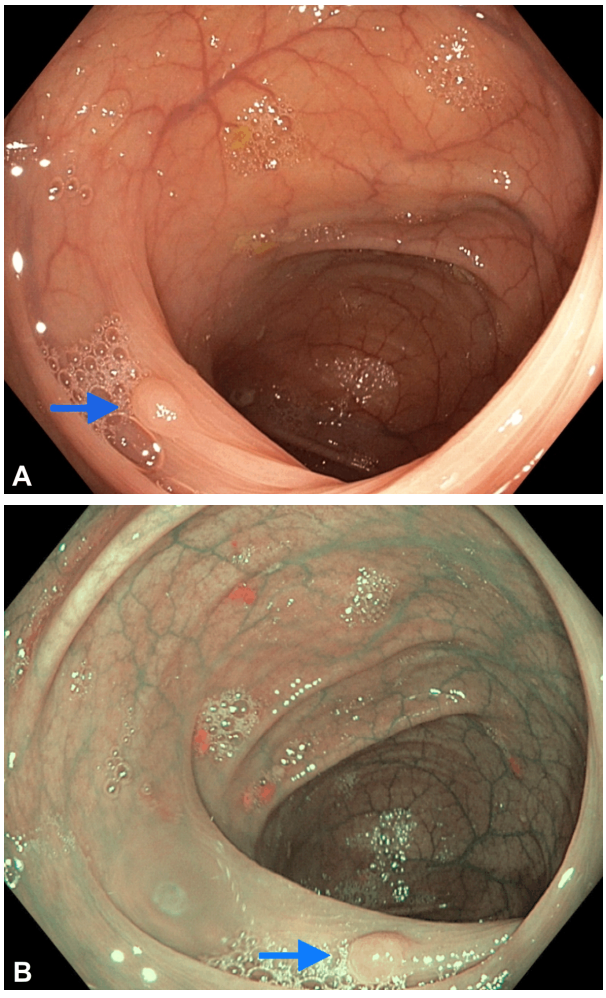

Figure 1 – ***Rectal small polyp <5 mm in white light view (A) and NBI mode (B).***

Similarly, in a randomized controlled trial comparing NBI *versus* WLE on 276 patients randomly assigned to undergo a colonoscopic examination using NBI or WLE, the patients who underwent tandem colonoscopy experienced no significant difference of miss or detection rates between the two techniques. Missed lesions with NBI showed similar characteristics to those missed with WLE – tubular adenomas, the majority (78%) less than or equal to 5.0 mm and none were larger than 1 cm (one-sided 95% confidence interval – CI: up to 1%). Non-polypoid lesions represented 35% (13/37) of missed neoplasms [28].

Accurate visualization of the colonic mucosa with virtual chromoendoscopy can be limited by insufficient brightness of the virtual image in a large lumen or inadequate bowel preparation [29]. A meta-analysis that indicated NBI superiority to standard definition white light endoscopy (SD-WLE) in the detection of flat adenomas, also indicated that the use of NBI was associated with increased colonoscope withdrawal times [30].

Recently, ASGE developed a *Preservation and Incorporation of Valuable Endoscopic Innovations* (PIVI) statement for *in vivo* endoscopic assessment of diminutive polyps [31]. ASGE meta-analyses indicate that optical biopsy with NBI, exceeds the negative predictive value (NPV) threshold for adenomatous polyp histology, supporting a "diagnose-and-leave" strategy for diminutive predicted non-neoplastic polyps in the rectosigmoid colon. Subgroup analysis indicated that the pooled NPV was greater than 90% for academic medical centers (91.8%; 95% CI, 89–94%), for experts (93%; 95% CI, 91–96%), and when the optical biopsy assessment was made with high confidence (93%; 95% CI, 90–96%). A recent update on "implementation of optical diagnosis of colorectal polyps" also suggests that *in vivo* training with feedback and assessment is needed before non-academic gastroenterologists are certified to perform optical diagnosis in routine clinical practice [32].

However, statistical heterogeneity may be explained by difference in the prevalence of polyps and adenomas in the population, the indication for colonoscopy (screening, surveillance and/or diagnostic), the age of the included population, bowel preparation, and the examiner's experience among others [24].

The gradual emergence of NBI

Sano *et al.* [33] first reported the clinical utility of NBI in the gastrointestinal tract in 2001 and since then has spread and changed the conventional approach to diagnosis. Originally developed for chromoendoscopy, the Kudo classification for diagnosis of small colorectal polyps was recently modified for NBI [34]. The vascular pattern intensity, as a measure of microvascular density, was proposed by East *et al.* as a new classification [35].

The NBI *International Colorectal Endoscopic* (NICE) *Classification*, applicable for non-magnified NBI imaging, have been validated by a group of international experts in order to characterize small colonic polyps and uses mucosal color, vessel and surface pattern to differentiate between hyperplastic polyps and adenoma [34]. Hewett *et al.* [34] have reported that NBI-experienced colonoscopists were able to differentiate hyperplastic (Figure 2) and adenomatous polyps (Figure 3) with high confidence for 75% of small colorectal polyps by using the NICE classification. The NICE classification is a valid tool for

differentiating not only non-neoplastic from neoplastic polyps, but also submucosal (SM)-invasive carcinomas from early colorectal carcinomas, but multicenter research involving endoscopists with different abilities will be necessary to validate these results in order to ensure that the classification can be used widely with satisfactory availability and reliability [14].

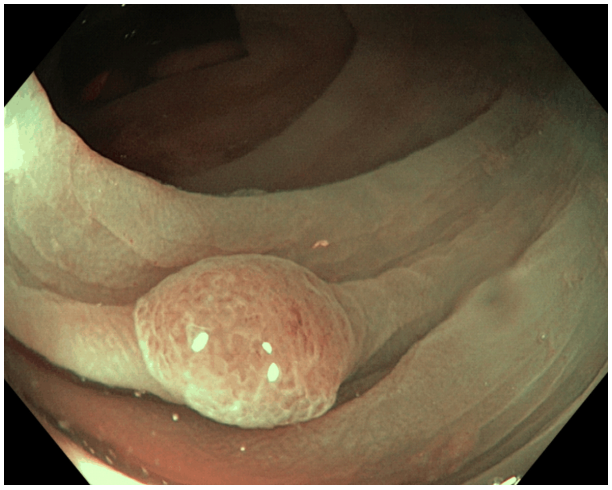

Figure 2 – ***Hyperplastic polyp located in the sigmoid colon in NBI mode view (isolated lacy vessels coursing across the lesion, white spots of uniform size and homogeneous absence of pattern).***

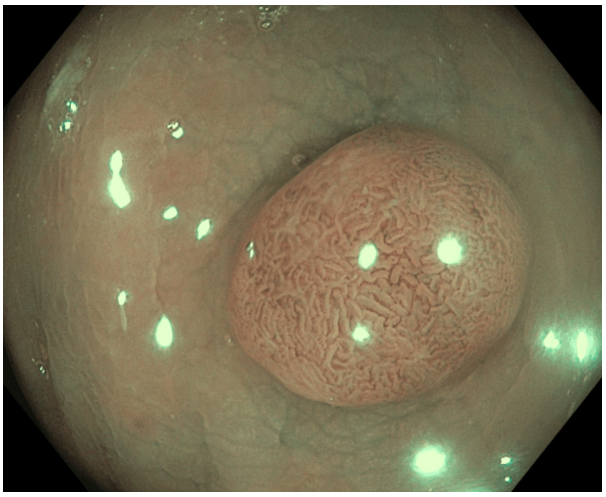

Figure 3 – ***Adenomatous polyp located in the colon in NBI mode view (brown vessels surrounding oval, tubular or branched white structures).***

At present, screening colonoscopy is performed using HD-WLE, and the NBI technique is employed mainly for diagnosis of any colorectal polyps that are detected [14]. NBI becomes more powerful when adapted to a magnifying endoscope providing a range of low to high optical magnification (×80 maximum) by means of a simple, one-touch operation [36].

Prospective comparative studies have demonstrated that *high magnification NBI* was more accurate than conventional colonoscopy and it was equivalent to magnification chromoendoscopy in distinguishing neoplastic from non-neoplastic polyps based on vascular and pit pattern characteristics [37]. The magnifying NBI endoscopy turned out to be useful not only for the differential diagnosis of colorectal adenoma from carcinoma, but also for the assessment of invasion depth of early colorectal carcinoma. Whereas in intramucosal or superficial SM-invasive carcinoma, an irregular meshed microvascular pattern is observed, a decreased or loose microvascular pattern is mostly observed in deep SM-invasive carcinoma (Figure 4).

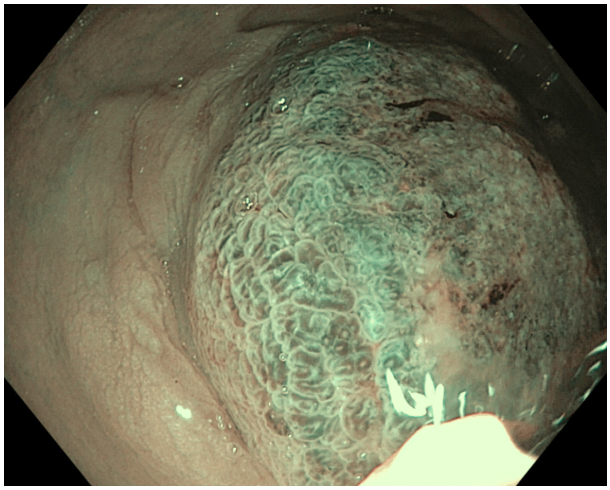

Figure 4 – ***Malignant degeneration of a large colon polyp in NBI mode view (absent surface pattern with disrupted vessels).***

Several magnifying NBI classifications currently proposed for the diagnosis of early colorectal neoplasia include type IIIA characterized by high microvessel density with lack of uniformity, and type IIIB characterized by the presence of the area showing nearly avascular or loose microvascular [38], while in Sano classification, type IIIB is observed in deep SM-invasive carcinomas [39, 40]. Unfortunately, there are no current comparative data among all of these classifications concerning the diagnostic accuracy for the malignancy of colorectal tumor and invasion depth of early colorectal carcinoma.

Most studies evaluating colon adenoma detection compared single technology improvements (*e.g.*, HD-NBI *vs.* HD-WLE) [30, 41, 42]. Conflicting data regarding the improvement of polyp detection have been reported, so a more accurate prediction of histology during colonoscopy could be useful in promoting real-time decisions regarding therapy and surveillance.

Beyond multiple improvements in definition and contrast incorporated in current commercially available colonoscopes, new two-stage optical lens technology allows the operator to switch from normal focus mode to *near-focus mode* (NFM) with a single button, so he can conduct close examination of mucosal tissue and capillary networks, select the desired depth of field and obtain high-quality images at the same time (Figure 5, A–C).

Compared to conventional magnification, where the scope needs to be moved close to the lesion to acquire a clear magnified image (depth of field of 1.5 to 3.0 mm), an enlarged, close-up image by moving the scope tip as close as 2 mm from the mucosa can be observed easily with NFM by the simple push of a button and with the depth of field relatively wide (3.0 to 7.0 mm) [15].

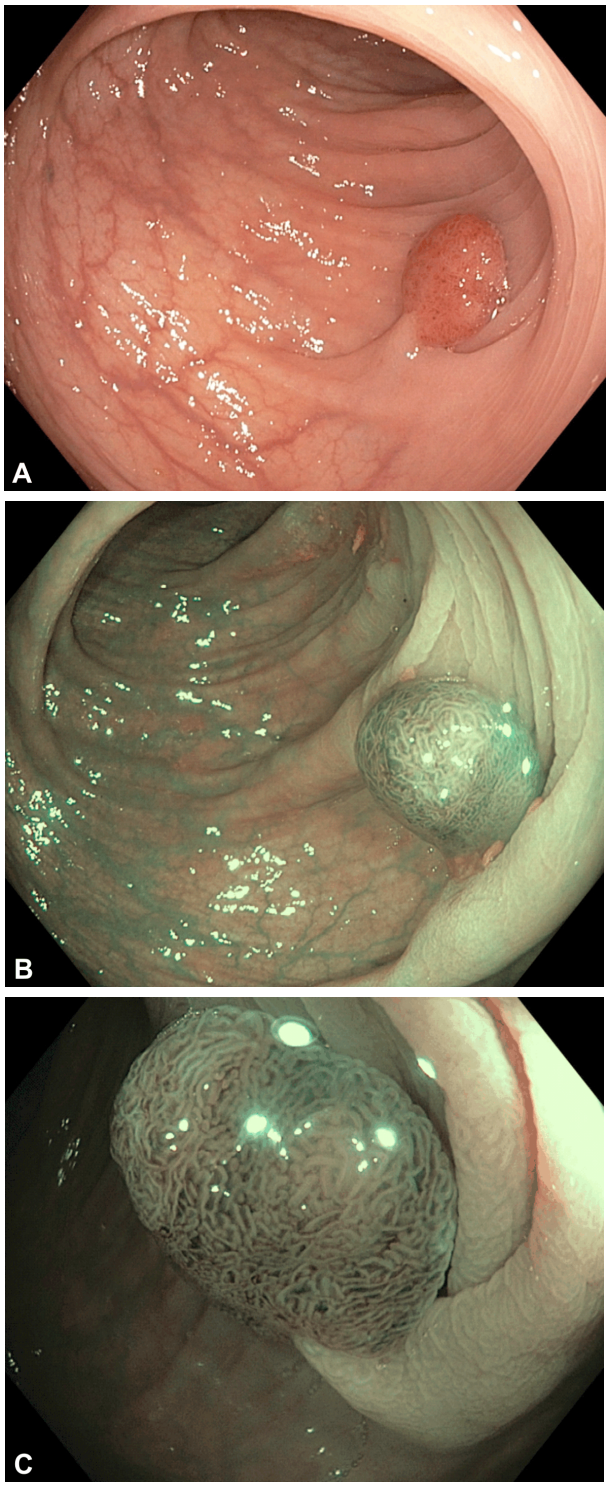

Figure 5 – ***Pediculated polyp in white light endoscopy view (A), NBI mode view (B) and NBI near-focus mode (C).***

Lower gastrointestinal applications of near-focus mode

NBI with NFM has the advantage over traditional chromoendoscopy as the image enhancement mode can be activated by push-button technology, it magnifies images using natural optical methods, without losing image resolution, and it is supposed to be cost-efficient, time-efficient and more user-friendly. This improvement could lead to a better adenoma detection rate and clearly there is potential for the reduction of overall procedure costs, patient distress, and risks as a consequence of biopsying and processing only diseased tissue [2].

Through integration with the colonoscopes, this approach ameliorates various parameters such as time spent for instrumentation set up, avoids fluorescein injections (*e.g.*, for confocal laser endomicroscopy) or insertion of probes through biopsy channel, need for careful inspection/image interpretation that could increase procedure time [43]. Apparently, dual-focus NBI (DF) is a more reasonable method, considering the high cost of other systems such as confocal laser endomicroscopy.

Considering adenoma detection rate (ADR) one of the key quality indicators of colonoscopy and as it has been shown to inversely correlate with post-colonoscopy interval cancers [44], recently ADR was significantly better in the NBI group when compared to WLE (48.3% and 34.4%, p=0.01) as well as polyp detection rate (61.1% and 48.3%, p=0.02) in a study comparing the new-generation NBI (Olympus Exera HQ190) and HD-WLE in a randomized trial with tandem colonoscopy [45]. Even if the superiority of conventional NBI over WLE for adenoma detection is not universal, one meta-analysis showed that NBI performed better in detecting flat adenomas (relative risk – RR 1.96, 95% CI 1.09–3.52, p=0.02) [30]. Similarly, detection of flat adenomas was significantly better with NBI in a randomized, controlled trial of NBI *versus* HD-WLE (RR 1.92, 95% CI 1.07–3.44, p=0.003) [46].

To date, most of the studies demonstrate that optical biopsy for lesion histological determination have sensitivity/specificity in the ~80–90% range [43]. Using colonoscopy with near-focus view is supposed to increase the confidence level of the optical diagnosis. The VALID randomized clinical trial on 558 subjects [47] was significantly more likely to make a high-confidence optical diagnosis with near focus (85.1%) than standard view (72.6%), with 96.4% *vs.* 92.0% NPV and a median diagnosis time of 14 seconds. Optical *versus* histopathological diagnosis showed excellent agreement between the surveillance intervals (93.5% in NFM and 92.2% in standard view, respectively).

Singh *et al.* (2013) assessed 149 polyps using Olympus 190 series Exera III NBI system with DF capabilities with the overall accuracy of NBI-DF when compared to final histopathology of 97%. In addition, post-polypectomy surveillance interval when based on optical diagnosis was accurate in 97% of cases with high NPV (100%) for diminutive recto-sigmoid polyps [48]. Their endpoints exceeded the ASGE PIVI thresholds for the management of diminutive polyps.

On the other hand, in a recent publication, Wallace *et al.* concluded that both traditional and new DF colonoscopes provide highly accurate optical polyp discrimination, consistent with ASGE guidelines for optical diagnosis of selected colorectal polyps without histological confirmation (77% *vs.* 79% optical diagnostic accuracy from analyzing a total of 927 polyps and compared with histology) [4].

As angiogenesis is essential for the transition of a premalignant lesion in a hyperproliferative state to a malignant lesion [49–51], diagnosis based on the vascular

pattern by combining NBI with NFM might also be useful for early detection and diagnosis of colorectal neoplastic lesions. Unfortunately, relevant published data regarding the accuracy of NBI with NFM endoscopy in early detection of neoplasia are limited. In their study on 270 patients, performed in conformance with the Kudo classification, Szura *et al.* [52] showed increased diagnostic accuracy of DF-NBI (as compared with conventional pit pattern diagnosis using NBI without magnification) for differentiating colorectal polyps with neoplastic potential, while no difference was observed in the recognition of polyps regarding non-neoplastic lesions (Kudo I and II). A prospective study on only 37 patients found an overall diagnostic accuracy, sensitivity, and specificity for differentiating adenomatous from hyperplastic polyps of 87.0, 89.5, and 79.2% for white light imaging, 93.0, 94.7, and 87.5% for NBI without magnification, and 94.0, 96.1, and 87.5% for DF-NBI, respectively, with a level of confidence significantly different between DF-NBI and WLE as well as NBI without magnification for diminutive (≤5 mm) lesions ($p<0.001$ and $p<0.01$). Thus, Ikematsu *et al.* considered that DF-NBI is especially useful for differential diagnosis of diminutive colorectal lesions [3].

There is a lack of data regarding the NBI with integrated NFM benefit to assess completeness of piecemeal polypectomy [43] or to determine the invasion depth of early colorectal cancers and evaluating free margins after endoscopic resection.

Although further studies are required to confirm the usefulness of NBI in screening colonoscopy for detection of colorectal polyps, the available evidence suggests that screening endoscopy using NBI with the newly developed endoscopy systems may become a standard tool, not only for the head and neck region or esophagus, but also for the colon and rectum [14].

More research is needed to determine the efficacy of different NBI system settings for surveillance colonoscopies, particularly to enhance the detection rate for flat adenomatous lesions [53], as well as to establish reliable criteria for the distinction between sessile serrated adenomas and hyperplastic polyps, which is difficult during conventional colonoscopy. Further research and development is also warranted for the clinical benefit of NFM under usually less prepped areas (such as the right colon).

Conclusions

Currently, NBI represents a technique with increasing clinical relevance for polyp detection as well as diagnosis and staging of patients with early gastrointestinal neoplasia. Magnification using NFM under NBI provides high-quality images of the microsurface structures of colorectal tumors by simply pushing a button on the scope, which could enhance the application of real-time optical diagnosis in routine clinical practice. Similar to conventional magnification, individual variation in subjective evaluation of the image quality NFM under NBI can interfere with its technical accuracy. Provided technological developments techniques able to enhance the optical imaging will be validated in the near future, they could serve as an important adjunct to conventional endoscopy for a more efficient management of colorectal challenging lesions, with a tendency to replace the gold standard of histology.

Conflict of interests

The authors declare that they have no conflict of interests.

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