



Polyp characterization at colonoscopy: Clinical implications



James E. Allen, Prateek Sharma*

Veterans Affairs Medical Center and University of Kansas School of Medicine, Kansas City, USA

ARTICLE INFO

Article history:

Received 1 July 2017

Accepted 5 July 2017

Keywords:

Electronic chromoendoscopy

Colonoscopy

Polypectomy

Narrow band imaging

Resect and discard

ABSTRACT

Although advancements in endoscopic imaging of colorectal mucosa have outstripped the pace of research in the field, the potential clinical applications of these novel technologies are promising. Chief among these is the ability to diagnose colorectal polyps *in vivo*. This feature appears most applicable to diminutive polyps, which have very little malignant potential yet represent over 70% of resected polyps. In an ideal application, the capability to predict diminutive hyperplastic polyp histology *in vivo* precludes the need for excision whereas diminutive adenomas do require excision, but not necessarily histopathologic analysis if the diagnosis is made *in vivo* with adequate confidence. However, the vast array of new advanced imaging modalities and polyp classification tools have been difficult to reconcile. We aim to highlight the current status of real-time colorectal polyp diagnosis and identify the barriers that remain to its widespread implementation.

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1. Introduction

Colonoscopy remains the standard approach in colorectal cancer (CRC) prevention. However, unlike many other screening mechanisms, it is simultaneously diagnostic, risk stratifying, and often therapeutic. Until recently, the paradigm for colonoscopy was universal polypectomy since both polyp size and histology are predictive of disease natural history and inform appropriate surveillance intervals. In addition to the number and size of adenomatous polyps, presence of high-grade dysplasia (HGD), serrated, or villous features dictate the interval [1]. However, experience shows that between 70% and 80% of all resected polyps are diminutive (<5 mm) and only about 50% of these are neoplastic [2]. Moreover, they are very unlikely to possess high grade dysplasia. Traditionally, these features were only identified microscopically and even diminutive lesions were resected to determine if they were neoplastic. Fortunately, advanced endoscopic imaging modalities can now reliably differentiate between hyperplastic and adenomatous polyps as well as predict more difficult characteristics such as serrated morphology. (see Table 1, Fig. 1)

The capability to predict diminutive hyperplastic polyp histology *in vivo* precludes the need for excision. Diminutive adenomas do require excision, but not necessarily histopathologic analysis if

the diagnosis is made *in vivo* with adequate confidence. These new models are commonly referred to as the *diagnosis and leave* and *resect and discard* strategies, respectively. While conceptually very feasible, there are numerous barriers their widespread adoption.

2. Cancer in diminutive polyps

Presence of villous histology, high-grade dysplasia or cancer are features that can occur irrespective of polyp size. However, diminutive and small polyps are at significantly less risk for such features. Adenocarcinoma is extremely rare in lesions <1 cm, 0.07% in one study [3]. Another large retrospective analysis found invasive cancer in 2/4381 diminutive polyps < 6 mm and 1/666 of small polyps 6–10 mm [7].

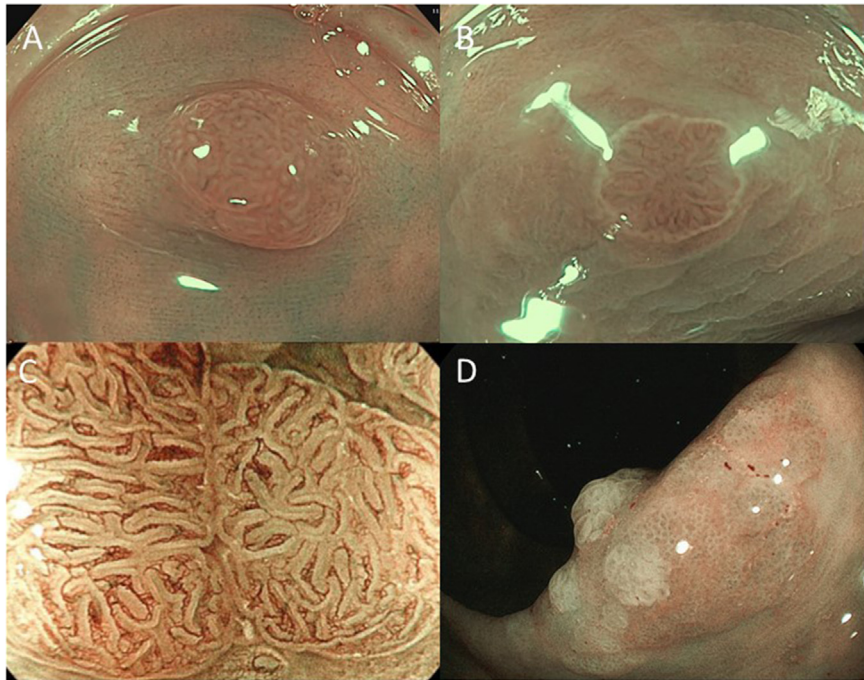
A study evaluating the resect and discard approach in minority groups found that polyps greater than 10 mm were far more likely to have at least one advanced feature than diminutive or small lesions (OR = 19.5; 95% CI, 4.4–85.6; OR = 6.1; 95% CI, 2.2–16.9) [4]. However, if a small polyp is adenomatous, it had a 10.1% chance of harboring advanced features or 0.9% change of malignancy [5]. In contrast, the rate of advanced histological features in diminutive polyps has been quoted at between 0.5% and 1.7% [5,6]. The largest and most recent study of neoplasia and advanced histology in diminutive polyps found that only 2.1% contained villous features or high-grade dysplasia. Remarkably, of the over 36,000 diminutive polyps characterized and over 6500 small polyps (6–9 mm), there was not a single incidence of malignancy [7]. The study also showed

* Corresponding author. Department of Veterans Affairs Medical Center, 4801 E. Linwood Blvd, Kansas City, MO 64128-2295, USA.

E-mail address: psharma@kumc.edu (P. Sharma).

Table 1Summary of perceived strengths and weaknesses of *diagnose and leave* or *resect and discard* protocols.

Pros	Cons
<ul style="list-style-type: none"> • Despite the current practice of universal polypectomy and histopathologic diagnosis, the incidence of interval (post-colonoscopy) cancer is already very high. This phenomenon is likely a product of missed neoplasia, aggressive lesions, missed diagnosis and incompletely resected lesions. • In current practice, a considerable number of polyps never make it to pathology (ie- incomplete specimen, lost). • Surveillance interval may be known at time of procedure for many patients. • Potential to save vast resources and mitigate complications from polypectomy. 	<ul style="list-style-type: none"> • PIVI threshold of 90% is arbitrary. • Initial cost to implement new technology. • Challenges in training endoscopists, especially in community practice. • No united classification system. • No mechanism to ensure competency/auditing • Difficulty in characterizing important lesions such as SSAs or presence of high-grade dysplasia.

**Fig. 1.** Examples of polyps under NBI (A,B) and BLI (C,D).

that of the 14,316 serrated polyps, 13,589 were hyperplastic [7]. Though largely retrospective, these data highlight the importance of polyp size in assigning risk. Therefore, errors made in real-time diagnosis of diminutive colorectal polyps should not be as significant.

3. Advanced imaging modalities

3.1. High-definition white light

Older-generation endoscopes used plain white light and a charge-coupled device to produce a digital video feed with around 300,000 pixels. High definition variants have been able to increase this number to over 1 million pixels, which increases the adenoma detection rate (ADR) [8]. However, they do not possess adequate contrast to make histological predictions.

3.2. Chromoendoscopy

Traditional chromoendoscopy involves spray/lavage with physical dye (indigo carmine, methylene blue, or crystal violet) on withdrawal of the colonoscope to enhance mucosal features that are difficult to appreciate under plain white light. Historically, this method has been widely employed in the ulcerative colitis

population to detect flat areas of dysplasia [9]. It also has been associated with higher adenoma detection rates, OR 1.53 (95%CI 1.31 to 1.79) in one study [10]. It is not widely used in the United States due to increased procedure time and convenience issues. Nevertheless, it is the basis for more modern approaches which use light filtration and modulation to achieve the same effect.

4. Electronic chromoendoscopy modalities

4.1. NBI

NBI is the most well-studied advanced imaging modality. The term “narrow band” refers to the use of two wavelengths of visible light: a 415 nm blue light and a 540 nm green light. The shorter wavelength blue light is absorbed by surface capillaries (appearing brown) while the green light penetrates deeper into the mucosa to highlight blood vessels (appearing cyan). This serves to highlight the surface pattern and deeper vasculature in contrast to the relatively avascular areas of surrounding mucosa.

Repici et al. conducted a multicenter trial (academic centers) for optical diagnosis of diminutive polyps using NBI. The NPV for adenomatous histology was 92% and the correct surveillance interval was assigned to 92% of patients [11]. The Detect Inspect Characterize Resect and Discard trial (DISCARD) was a prospective,

cohort study that used HD-WLE and NBI to predict histology and assign surveillance intervals. Sensitivity for neoplasia (adenomas) was (94%; 95% CI 0.90–0.97) and specificity (hyperplastic polyps) (89%; CI 0.78–0.95) [12]. Notably, small (<10 mm) polyps were included in addition to diminutives. Surveillance interval projections were 95% accurate using US multi-society guidelines against the gold standard.

Adenoma detection is one area that experts feel NBI may fall short as evidence is mixed regarding benefit to ADR compared with WLE [13–16]. Some users report that NBI darkens the field of view and thereby impair adenoma detection rate. They feel NBI sacrifices brightness for contrast thereby enhancing the ability to predict the histological diagnosis at the expense of initial observation. One meta-analysis of 7 RCTs found no significant difference in adenoma detection rate between NBI and WLE (36% vs 34%; $P = 0.413$) [17].

4.2. FICE, BLI, BLI-bright, and LCI

Developed in 2005 by Fujifilm (Fujinon Inc, Saitama, Japan), flexible spectral imaging color enhancement (FICE) uses a virtual filter modulator to select narrow spectra of white light images, providing a bright and contrasted picture of gastrointestinal lesions, even at a distance. It has been applied throughout the GI tract especially to esophageal and gastric lesions; however, now has been replaced by the LASEREO system that uses a tandem laser array: white light laser (450 ± 10 nm) as a vivid light source for observation and narrow band blue laser imaging (BLI) (410 ± 10 nm) for high contrast of capillary and mucosal surface pattern. A hybrid mode between these two is called BLI-bright. When this mode undergoes additional pre-processing to further separate red spectra, it is called linked-color imaging (LCI).

One study applied a visibility score to WLE, BLI-bright, and LCI for flat colorectal lesions and found that $LCI > BLI\text{-}bright > WLE$ in a qualitative measure of overall visibility [18]. BLI is also felt to help resolve some shortcomings of FICE (poor at distinguishing mucosal vasculature) and NBI (poor brightness at a distance) [19]. BLI-bright has already been shown to detect a significantly higher number of adenomas per procedure when compared with WLE in a real-time, multi-center randomized controlled trial (Mean \pm standard deviation; WLI 1.01 ± 1.36 , BLI 1.27 ± 1.73 ; $P = 0.008$) [20]. BLI was also directly compared to NBI in diagnostic accuracy in colorectal neoplasia. The two modalities demonstrated no statistical difference in accuracy (74.0% for BLI versus 77.8% for NBI) [21].

4.3. i-SCAN

i-SCAN is a post-processing video enhancement modality produced by PENTAX Endoscopy (Pentax Medical Company: Montvale, NJ). In a single center, open head-to-head trial with NBI and i-SCAN there was no significant difference for adenoma prediction (sensitivity, 88.8% vs 94.6%; specificity, 86.8% vs 86.4%; accuracy, 87.8% vs 90.7%, respectively; $P > .05$).

5. Subcellular imaging techniques

5.1. Confocal laser endomicroscopy (CLE)

CLE renders high magnification of the mucosa using an emitting laser light source and receiving polarizer lens. Light is focused to a desired mucosal depth and the same lens (hence confocal) selects reflected light from the surface mucosa that passes through a pinhole. This reduces scattering which allows for high resolution. CLE is either endoscope-based (Pentax) or probe-based (pCLE) via the accessory channel (Mauna Kea). The advantage of the endoscope-based array is freedom to use the channel. However, the

probe-based approach is compatible with a variety of endoscopes and could be used in combination with other imaging techniques simultaneously. A classification system for pCLE was developed by expert users in Miami 2011 [22].

Fugazza et al. performed a meta-analysis of 7 studies that applied CLE to colorectal polyps and found a pooled sensitivity of 83% (CI95%: 79%–87%), specificity of 90% (CI95%: 87%–92%). The area under the curve was 0.94 [23]. One study comparing pCLE to NBI found it had superior sensitivity (86% versus 64%, $p = 0.008$), similar accuracy (82% versus 79%, $p = 0.027$), but inferior specificity (78% versus 92%, $p = 0.59$) [24].

5.2. Microendoscopy

Chang et al. were the first to evaluate high resolution microendoscopy (HRME) in the diagnosis of colorectal neoplasia. This is novel modality that highlights a lesion's subcellular features. Thus, a diagnosis is made based off nuclear appearance, its relation to cell size, density etc. instead of macroscopic features such as vascular or surface patterning used in electronic chromoendoscopy [25]. Their study internally validated a classification system for HRME and then applied it to characterization of colonic neoplasia by expert and non-expert users [26]. Neoplasia were detected with 70% sensitivity (95% CI; 65%–76%) and specificity 94% (95% CI; 87%–100%) without much differences between experts and non-experts. Inter-observer variability was impressive ($\kappa = 0.78$ overall, 0.86 for experts). However, the study was not performed in real-time and was not exclusive for diminutive polyps. The low overall sensitivity despite excellent inter-observer agreement argues for a secondary role of HRME behind electronic chromoendoscopy. However, its capability to visualize subcellular characteristics means it potentially could be used in concert with NBI and others to strengthen detection of advanced histology.

6. Guidelines and societal recommendations

Throughout the early 2000s, new endoscopic tools for polyp diagnosis were employed on a largely investigational basis. The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee, in 2011, established the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) document specific to real-time histological assessment for diminutive colorectal polyps to establish benchmark quality thresholds [27]. Specifically, two performance standards were developed to guide the use of advanced imaging.

1. A "high confidence" decision to *diagnose and leave* a ≤ 5 mm hyperplastic polyp in the rectosigmoid must achieve a $\geq 90\%$ negative predictive value (NPV) for adenomatous histology.
2. A "high confidence" decision to *resect and discard* an adenomatous polyp ≤ 5 mm must agree with the gold standard $\geq 90\%$ in assigning the post-procedure surveillance interval (after the histology of all polyps > 5 mm is considered).

In 2015, the Committee conducted a systematic review and meta-analysis of all major studies applicable to the above thresholds performed in real-time endoscopy. There were about three times as many cited studies employing NBI than either FICE or i-SCAN, which better powered the analysis to draw conclusions about NBI. In aggregate, the PIVI threshold of 90% NPV for adenomatous polyps was met by expert endoscopists [93% (95% CI, 91–96)] but not novices [87% (95% CI, 83–91)]. For high confidence diagnoses, the NPV improved to 95% (95% CI, 92–98) and 90% (95% CI, 86–94) respectively. Regarding the second PIVI threshold, post-polypectomy surveillance, the NBI-directed interval coincided with

the histopathological gold standard interval 89% (95% CI, 85–93). Subgroup analysis found that expert operators again outperformed novices when diagnosis was made with high confidence 93% (95% CI, 90–96) versus 87% (95% CI, 82–93).

7. Classification systems

It is widely accepted that any *in vivo* diagnosis of colorectal lesions must be based on a validated and practical classification system. Kudo et al. first described that mucosal pit architecture in colorectal polyps is appreciable *in vivo* and predictive of histology [28]. However, since the advent of electronic chromoendoscopy and other modalities, there has been an explosion of disparate criteria to distinguish between colorectal lesions. Sano et al. used the presence of meshed capillary vessels by NBI to distinguish between neoplastic and nonneoplastic polyps. Those polyps with clearly visible meshed capillary vessels by this system were 96.4% sensitive for neoplasia; overall accuracy was 95.3%.

Hewett et al. developed the NBI International Colorectal Endoscopic (NICE) classification system with the added step of validating each individual criterion: color, vascular pattern, and surface pattern. It distinguishes hyperplastic polyps (called type 1) from adenomas (type 2) and proved very intuitive, even for inexperienced endoscopists [29]. Unfortunately, NICE has difficulty distinguishing between hyperplastic and SSA polyps as both appear as type I lesions. The Workgroup serrated polypS and Polyposis (WASP) classification system attempted to address this by combining known features of SSA polyps with the NICE criteria in a unified algorithm. The combined NPV for adenomas and SSAs (neoplasia) was 0.91 (95% CI 0.83 to 0.96) for high confidence decisions and these results sustained after six months [30]. Another study applied this expanded NICE classification system and found it may have some utility in detecting diminutive invasive cancers at risk to be discarded as an ordinary adenoma [31].

Many Eastern experts have attempted to improve or modify NICE to better suit differences in clinical practice regarding endoscopic submucosal dissection (ESD). Given the Japanese Gastroenterological Endoscopy Society's recommendation that any lesion not amenable to easy en bloc resection or superficial submucosal invasive cancer undergo ESD, Japanese experts sought to further risk-stratify adenomas (type 2 lesions by NICE). One modification of the NICE classification system was expansion for detection of deep submucosal invasive (SM-d) carcinoma using NBI. Sensitivity and negative predictive values for high confidence predictions were each 92%. Interobserver agreement was consistent ($\kappa = 0.70$). While this was an offline study, single center, and by experienced endoscopists, it illustrated how NBI could be expanded to diagnose more advanced features, leading to the creation of a type 3 polyp (SM-D) [32]. The Japanese Gastroenterological Endoscopy Society (JNET) developed their own classification system to separately categorize any adenoma that may have high grade dysplasia or superficially invasive cancer as it impacts the decision to proceed with piecemeal EMR versus ESD [33]. Unlike NICE, the JNET classification exclusively requires magnification, which is more widespread in Japan.

In addition, classification systems have been applied to other imaging modalities. The Hiroshima classification was used in one study with BLI with high diagnostic accuracy in distinguishing between neoplastic and nonneoplastic polyps <10 mm [34]. In fact, polyp features emphasized by electronic chromoendoscopy tend to be so consistent that one group was successful in developing a real-time, image recognition software to predict histology. It was concordant with NBI predictions for 97.5% of lesions in a trial of 41 patients [35].

8. Sessile serrated adenomas and other pitfalls

Sessile serrated adenomas are now considered distinct from hyperplastic polyps and implicated as cancer precursor lesions. Furthermore, cancer risk is equal to or greater than that of regular adenomas [36]. LCI was shown in one offline study to greatly enhance the visibility of SSA polyps when compared to WLE or NBI [18]. However, in a large Australian study, the use of near focus techniques with NBI increased confidence from 68.1% to 99.3% for diagnosis of SSAs with sensitivity of 85%, NPV of 98% [37]. Expert endoscopists applied the Kudo pit patterns and modified Sano capillary patterns as a classification method. Only 13 diminutive SSAs were characterized, which was greater than any previous *in vivo* study, illustrating the difficulty in developing criteria for a relatively uncommon lesion.

One prominent concern regarding resect and discard is that diminutive adenomas harboring advanced pathology may be excised but the optical diagnosis would not be sufficient to detect such changes. The prevalence of advanced histology in one study was 1.3% for diminutive polyps [38]. The US and ESGE guidelines consider the presence of villous components, high-grade dysplasia and adenocarcinoma in surveillance intervals. While established that incidences of advanced pathology are very low in diminutive polyps, concern remains. Magnifying NBI has some reported superiority in detecting small advanced lesions when compared with unmagnified NBI but similar investigations are still fairly sparse [39].

9. Cost savings

The most cited publication on potential cost savings in implementing a resect and discard strategy for diminutive polyps was work by Hassan et al., in 2010. Employing Markov modeling to simulate clinical application, polyps ≤ 5 mm with a high confidence NBI diagnosis were not sent for pathology after removal. Conversely, it was assumed any low confidence diagnosis would be sent to avoid mis-assignment of the colonoscopy surveillance interval. Overall cost for screening colonoscopy was estimated at \$3222 per patient, with \$46 related to pathology costs. The model revealed that a resect and discard protocol would result in a savings of \$25 per patient case without affecting the efficacy of screening [40]. When applied to the US population, this resulted in a savings of \$33 million annually. These calculations assumed a very achievable rate of high confidence diagnoses (84%) and sensitivity and specificity of 94% and 89% respectively for adenomas [13].

10. Application in community practice and dissemination

Development of new imaging modalities has quickly outpaced research in the field. As optical characterization of colorectal polyps becomes more pervasive, the final hurdle to its adoption will be education and standardization. NBI and other modalities have been met with limited success at the hands of community endoscopists. One study attempted to train 28 colonoscopists to use the NICE criteria with NBI to diagnosis small polyps <10 mm *in vivo*. The sensitivity for adenomatous histology was only 83.4% (95% CI 79.6%–86.9%), far short of the 90% PIVI threshold [41]. Similarly, a real-time study by Ladabaum et al. using a computer module to train community endoscopists in NBI saw only 25% of users characterized polyps with >90% accuracy with a 80% concordance in screening interval [42]. However, several studies demonstrate user improvement with formal training in electronic chromoendoscopy [43–46].

Finally, guaranteeing endoscopist competency in meeting PIVI thresholds has not yet been addressed. One option is including a

standardized assessment as part of the training tool, which would rely on videos and other non-real time content. However, it has not been established that adequate performance using electronic chromoendoscopy on video-based modules translates to realtime performance. Furthermore, no study has demonstrated the durability of an endoscopist's performance with optical diagnosis over more than several months. Therefore it has been proposed that ongoing auditing may be required to ensure standards are being met [46].

11. Current debate

Many operators will initially feel less comfortable abandoning conservative screening/surveillance intervals as doing so makes greater demands on the expertise of the endoscopist to make the correct optical diagnosis. This very issue was addressed in a survey of over 100 gastroenterologists at a national symposium. Only 72% were aware of the PIVI statement and 61% were willing to apply it to practice [47]. The two greatest concerns cited by those surveyed were medicolegal liability (85%) and reimbursement (32%). However, supposing a new financial incentive of \$75 for optical diagnosis of colorectal polyps, about half of those initially dissenting stated that they would be willing [47]. The study was likely over-representative of academic gastroenterologists due to the setting of a large national research meeting.

Patient acceptance is another important facet to consider. A new paradigm shift in polypectomy practice could be undermined if patients are not made comfortable, especially with the *diagnose and leave* approach. Only 49.6% of 981 Australian patients polled were supportive of intentionally leaving polyps behind. 21.2% stated they would ask for financial compensation if a polyp was incorrectly left behind and they developed stage III cancer with a patient-proposed median sum of \$1.3 million USD [48]. Another survey of patients were asked how willing they would be to pay out-of-pocket for polyp pathologic analysis if this practice was not routinely covered by their insurer. It found 360 out of 500 (71.9%) would do so and those unwilling tended to cite prohibitive cost rather than accepting that cancer risk would be low in these lesions [49, 50].

12. Summary

Real time diagnosis at time of colonoscopy remains a contentious issue. Research on emerging technologies is incomplete and there are relatively few head-to-head trials. Those that exist have seldomly been repeated in the same context (esophagus, colon etc.). Efforts are frustrated by operator bias/familiarity and limited accessibility to various technologies. Even so, new technology (much of which now comes standard on endoscope platforms) is allowing the endoscopist to visualize colorectal lesions with such detail that live diagnosis almost seems an inevitability. Before it becomes widespread, questions of reimbursement, patient trust, medicolegal vulnerability and training/competency will need to be answered.

13. Practice points

- Implementation of this practice will need to include endoscopist training and competency, support staff and patient education.
- Experts agree that, for now, the *resect and discard* and *diagnose and leave* approaches should be restricted to experienced endoscopists [51].

14. Research agenda

- A validated classification system for each modality and its context of use must be put in practice.
- Questions on limitations in diagnosing SSAs and HGD need to be answered.
- A validated teaching method should be developed for novel imaging technologies.

Conflict of interest

Dr. Prateek Sharma: Research support: Cosmo pharmaceuticals. All other authors disclosed no financial relationships relevant to this publication.

Acknowledgements

None.

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