Colonoscopy and Optical Biopsy: Bridging Technological Advances to Clinical Practice

See "Endoscopic trimodal imaging detects colonic neoplasia as well as standard video endoscopy," Kuiper T, van den Broek FJC, Naber AH, et al, on page 1887.

One of the major frontiers of translational gastroenterological research remains the development of adjunct approaches to improve the performance of colonoscopy. There have been a myriad of technologies currently being evaluated including chromoendoscopy, light scattering spectroscopy, optical coherence tomography, elastic light scattering spectroscopy (ESS), autofluorescence (AFI), narrow band imaging (NBI), and confocal endomicroscopy (CLE).[1] These approaches span the gamut with regard to expense, ease of use, skill requirement, and accuracy. From a clinical application perspective, one can broadly divide them into 4 categories—improved polyp detection, optical biopsy (for this editorial, we will define this as the determination of the histologic characteristics of a visualized lesion), identification of flat dysplasia, and the emerging area of risk stratification through field carcinogenesis detection (Figure 1).[2]

In this issue of GASTROENTEROLOGY, Kuiper et al[3] investigate the ability of endoscopic tri-modal imaging (high definition white light in combination with AFI and NBI) for 2 of these potential indications—improved adenoma detection and optical biopsy. This randomized study was designed rigorously (each colonic segment examined with either white light twice or white light followed by AFI) and adds to the literature by being conducted in a "non-academic" setting. The authors reported that trimodal imaging was unable to improve the adenoma detection rate, although there were some limitations, including a surprisingly high miss rate for advanced adenomas. Furthermore, the somewhat atypical study cohort (eg, enriched Lynch syndrome) may impact on the generalizability to the classic "non-academic" average risk colonoscopic practice.

A potentially important observation was that both AFI and NBI seemed to be useful in discriminating adenomas from nondysplastic tissue. The sensitivities were reasonable, but at the cost of specificity. This adds to substantial literature on the "optical biopsy" that has utilized a number of techniques (CLE, NBI, chromoendoscopy, etc).[1,2] Although there have been few "head-to-head" studies that have been sufficiently powered, the majority of the data suggest that the techniques all have good performance and are roughly equivalent. For instance, Buchner et al[4] noted that CLE and NBI had similar sensitivities (88% vs 84%, respectively) and specificity (63% vs 75%, respectively). Similarly, Chiu et al[5] noted that NBI and chromoendoscopy had comparable accuracy (83% and 85%, respectively for single observer without magnification). As noted, the Kuiper data with AFI/NBI were consistent with a large body of literature on other techniques with optical biopsy.

Taken together, optical biopsy seems to have reasonable diagnostics; undoubtedly, this can be further improved with technological refinements. However, the concept has been discussed for more than a decade and some technologies (chromoendoscopy, NBI, CLE) are available widely and yet optical biopsy is not commonly employed during gastrointestinal endoscopy. Thus, the real questions are whether these approaches are translatable into general clinical practice and what are the impediments. In this regard, it is paramount to understand the hurdles for endoscopists to adopt optical technologies into their lesion management armamentarium.

First, it needs to be determined what level of certainty would be necessary for optical biopsy to be used in clinical practice. Most studies to date demonstrate that optical determination of lesion histology can attain sensitivity/specificity in the ~80%–90% range. One would wonder if this performance would be acceptable to both patients and physicians, because the consequence of an error (especially false negatives) might result in cancer development. This is particularly concerning in the current medical-legal climate (eg, would any future cancer in that area of the colon leave the endoscopist vulnerable to litigation?). Finally, what is the incremental benefit of these technologies over an endoscopist's "gestalt" impression of a lesion? For instance, using conventional colonoscopy, endoscopists are ~75% accurate with predicting histology in small polyps.[6] However, few would consider this adequate for clinical practice. Although the improvement in diagnostics is significant with NBI, chromoendoscopy, CLE, and so on, one wonders whether this would rise above the high threshold for the level of certainty that would allow the endoscopist to have sufficient confidence to avoid polypectomy.

Second, what are the potential benefits to patients of these in situ diagnostics? The vast majority of endoscopic

Figure 1. (*A*) Improved polyp detection through techniques such as autoflourescence (AFI), narrow band imaging (NBI), Chromo-endoscopy, molecular imaging, etc. (*B*) Identification of flat dysplasia and targeting biopsies in conditions such as ulcerative colitis (UC). (*C*) Enhanced intrusive risk stratification. Techniques such as low coherence enhanced backscattering spectroscopy (LEBS), partial wave spectroscopic microscopy (PWS), and elastic light scattering spectroscopy (ESS) are being investigated for their ability to identify the microarchitectural consequences of the genetic/epigenetic alterations in field carcinogenesis. (*D*) Optical biopsy to characterize polyps. This can be performed with AFI, NBI, confocal endomicroscopy (CLE), chromoendoscopy, and so forth.

polypectomies are performed in a rapid and safe fashion. One argument is that optical biopsy may reduce the number of polypectomy-related hemorrhages/perforations, and, therefore, provide value to patient care. By and large, the risk of complications parallels the size of the lesion removed. However, while advanced histologic features are occasionally noted in smaller polyps, the probability of premalignant/dysplastic features is also roughly proportional to lesion size.[2,7] Thus, for larger lesions, the risk of polypectomy is higher, but the majority of these

lesions will be premalignant, meaning that optical information will not frequently alter polypectomy decision. Optical biopsy may provide more useful insights in smaller lesions, but the risk of removal is relatively low (eg, cold snare or cold biopsy). Alternatively, one could posit that these approaches may be useful for detection of malignant degeneration of an adenoma and this could impact on clinical decisions.[8] This is probably true, although this may apply to only a subset of lesions that are amenable to polypectomy (from both size and ability to lift with saline), because others would require surgical intervention regardless of optical data. Because many malignant pedunculated polyps can still be managed by endoscopic polypectomy, optical biopsy of these types of lesions may be even less likely to impact patient care.[8] Another potential beneficial scenario would be to forego retrieval of lesions (especially right-sided) and rely on optical data as a histologic surrogate for colonoscopic surveillance recommendations. However, the value is somewhat limited for smaller lesions, because these can be typically retrieved by suctioning, which is relatively easy to accomplish. If optical biopsy could ever completely replace histopathology (which is presently not feasible), then this may be appropriate for the management of larger lesions, which currently require pathologic evaluation for determination of more subtle features such as high-grade dysplasia.

Third, it is critical to consider the cost of these optical biopsy techniques. Indeed, pathology fees may be significant, potentially eclipsing the endoscopist charge in some cases. For instance, multiple small, left-sided polyps seem reasonable for optical biopsy. However, some of the cost differential can be mitigated by the common practice of placing all in a single pathology jar. This can be done because it is generally not essential to know the histology of a particular lesion (because lesions this size are so rarely malignant), but rather the total number of adenomas (0, 0–3, 3–10, and >10).[7] Therefore, for routine use, optical biopsy would need to be very inexpensive. Even with strategies such as reusable fiberoptic probes/spray catheters, and instrumentation costs (for techniques such as CLE) may make these technologies difficult to justify in the cost-conscious health care environment. Furthermore, because a large number of the lesions subjected to optical biopsy will eventually require polypectomy, many patients will also undergo both optical and standard pathology charges.

Fourth, given the pressure on endoscopists to improve efficiency (do more cases in same time while still maintaining high quality), will the optical biopsy technologies facilitate this imperative? Time for instrumentation set up, fluorescein injections (for CLE), insertion of probes through the biopsy channel, and the need for careful inspection/image interpretation will likely increase procedure time (although some approaches such as NBI ameliorate this through integration with the colonoscope). Furthermore, the positive results will require polypectomy as a second distinct procedure (although there are some innovative solutions being developed, such as combining ESS fiberoptic probe with a snare).[9] Additionally, there is the issue of some training required/learning curve and performing a sufficient number of procedures to maintain the skills for image-based techniques. Fundamentally, most endoscopists do not have the time or want the responsibility of becoming pathologists. Techniques that rely on automated signal analysis (eg, ESS) may mitigate some of these issues. These work flow implications should not be underestimated and may represent a significant impediment to the widespread adoption of these technologies by endoscopists.

Finally, and in many ways most importantly, the question of what is a lesion that one could safely be left in situ. In the past, the dogma suggested that all hyperplastic polyps were innocuous. Thus, optical biopsy would potentially be useful given the not infrequent finding of large, flat, hyperplastic lesions, which can be difficult to remove and have a propensity toward complications (because these lesions have a predilection for the thin-walled right colon). However, it is becoming increasingly recognized that these lesions, especially when located in the proximal colon, may be the precursors to microsatellite unstable colorectal cancer. Indeed, this is the hallmark of the serrated neoplasia pathway.[10,11] Thus, optical biopsy may be of less value because one could argue that, although these are clinically the most appealing lesions (large, flat lesions in the right colon), most should probably be removed regardless of the information gleaned through these in situ techniques.

Thus, although a technological breakthrough, it seems unlikely that the optical biopsy information will be employed for the lesions that are most commonly encountered during colonoscopy (ie, polyps or masses). However, there are several scenarios where this might be valuable. For instance, in the anti-coagulated patients or those experiencing acute GI bleeding, this may be useful in deciding upon repeat procedures. Additionally, an in situ approach may be helpful in patients with numerous non-premalignant polyps (eg, pseudopolyps from inflammatory bowel disease or hyperplastic polyposis) to target the most appropriate lesions to biopsy and/or remove. Finally, optical biopsy may be useful to assess completeness of piecemeal polypectomy (if not obscured by coagulation artifact). There are undoubtedly others, but it seems that the utility of optical biopsy may be confined to a somewhat smaller subset of cases.

What are the other potential uses for these exciting optical technologies? Clearly one of the most relevant is improving adenoma detection rate via technologies that

allow evaluation of the "far field."[2] This represents a powerful approach, especially given the emerging literature of high miss rate and relatively poorer protection against development of right-sided colon.[12] Proximal lesions are particularly challenging because they have a higher propensity for microsatellite instability and thus not only grow more rapidly but are also more difficult to visualize (flat, behind folds, etc).[13,14] In addition, the right colon is frequently less well prepped. Therefore, adjunctive technologies (NBI, chromoendoscopy, AFI, etc) would be particularly appealing to aid visualization. Although the data to date have been inconclusive on the efficacy[15] (including the report by Kuipers on tri-modal imaging), we believe that given the potential clinical benefit, further research and development in this area is warranted.

Another emerging application is to enhance endoscopic detection of flat (visually-inapparent neoplasia) in Barrett's esophagus or chronic ulcerative colitis (sometimes also referred to as "optical biopsy").[2] This "near-field" approach has the potential of being an important adjunct for endoscopists with promising clinical results in Barrett's esophagus for emerging techniques such as angular-resolved low-coherence interferometry, multispectral scanning, and ESS.[16–18] Indeed, several centers routinely use standard techniques such as NBI, CLE, and chromoendoscopy in high-risk patients.[19] The potential of this approach to improve the yield of dysplasia and reduce the number of biopsies has significant attraction in managing the subset of patients with conditions that manifest as flat dysplasia. Although it remains to be determined whether the natural history of flat dysplasia identified by enhanced versus conventional techniques is similar (because of the markedly higher incidence), this approach has real promise to impact a clinically vexing problem.

Finally, there is the issue of risk stratification through field carcinogenesis detection. Although still at a very early stage in development, it aims to address the inefficiency inherent in the conventional use of colonoscopy for population screening (screen relevant neoplasia rate of only ~5%–6% in the average risk population). Risk stratification could conceivably be performed through interrogation of the rectal mucosa for changes of field carcinogenesis (the notion that the genetic and environmental risk factors that give rise to a focal neoplastic lesion should impact upon the entire colon mucosa—the "field of injury" concept).[20] This could serve as a minimally intrusive prescreening to identify subjects more likely to receive a cancer prevention benefit (ie, removal of a significant polyp). Previous markers of field carcinogenesis have predominantly focused on cellular (apoptosis/proliferation) and molecular (genetic/epigenetic/proteomic) approaches.[21] Importantly, despite the fact that the distal colonic mucosa seems microscopically normal (sensitive to objects >~500 nm), there can be profound architectural abnormalities in smaller structures that are critical for neoplastic transformation (ribosomes, chromatin organization, etc).[20] These alterations may be detectable using a variety of platforms including ESS, low coherence-enhanced backscattering spectroscopy, and partial wave spectroscopic microscopy.[9,20,22] These nascent technologies/approaches have been reviewed recently in GASTROENTEROLOGY.[20]

In conclusion, we are entering an era when optical technologies are poised for potential transition into colorectal cancer screening. These in situ approaches seem to be sufficiently accurate and technologically feasible. However, the crux of the matter is whether these approaches will actually bridge the "bench to bedside" chasm. Although optical biopsy for management of endoscopically visualized lesions may not be practical for widespread clinical implementation owing to issues related to clinical rubrics (management of right-sided serrated lesions), risk management, expense, and so on, this may find application in certain very specific scenarios. Other more clinically transformative applications of optics in gastroenterology include improved endoscopic polyp visualization, flat dysplasia detection, and potentially risk stratification. To translate these revolutionary technologies into clinical practice, it is paramount that future developments be integrally linked with the clinical/biological paradigms and endoscopic practice considerations.

HEMANT K. ROY
MICHAEL J. GOLDBERG
SHAILESH BAJAJ
Department of Medicine
NorthShore University Health Systems
University of Chicago Pritzker School of Medicine
Evanston, Illinois

VADIM BACKMAN
Biomedical Engineering Department
Northwestern University
Evanston, Illinois

References

1. Wang TD, Van Dam J. Optical biopsy: a new frontier in endoscopic detection and diagnosis. Clin Gastroenterol Hepatol 2004;2:744–753.
2. Wallace MB, Kiesslich R. Advances in endoscopic imaging of colorectal neoplasia. Gastroenterology 2010;138:2140–2150.
3. Kuiper T, van den Broek FJC, Naber AH, et al. Endoscopic trimodal imaging detects colonic neoplasia as well as standard video endoscopy. Gastroenterology 2011;140:1887–1894.
4. Buchner AM, Shahid MW, Heckman MG, et al. Comparison of probe-based confocal laser endomicroscopy with virtual chro-

moendoscopy for classification of colon polyps. Gastroenterology 2010;138:834–842.
5. Chiu HM, Chang CY, Chen CC, et al. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373–379.
6. Chang CC, Hsieh CR, Lou HY, et al. Comparative study of conventional colonoscopy, magnifying chromoendoscopy, and magnifying narrow-band imaging systems in the differential diagnosis of small colonic polyps between trainee and experienced endoscopist. Int J Colorectal Dis 2009;24:1413–1419.
7. Levine JS, Ahnen DJ. Clinical practice. Adenomatous polyps of the colon. N Engl J Med 2006;355:2551–2557.
8. Robert ME. The malignant colon polyp: diagnosis and therapeutic recommendations. Clin Gastroenterol Hepatol 2007;5:662–667.
9. Rodriguez-Diaz E, Bigio IJ, Singh SK. integrated optical tools for minimally invasive diagnosis and treatment at gastrointestinal endoscopy. Robot Comput Integr Manuf 2011;27:249–256.
10. Sugumar A, Sinicrope FA. Serrated polyps of the colon. F1000 Med Rep 2010;2:89.
11. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology 2010;138:2088–2100.
12. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22–30.
13. Sawhney MS, Farrar WD, Gudiseva S, et al. Microsatellite instability in interval colon cancers. Gastroenterology 2006;131:1700–1705.
14. Butterly LF, Chase MP, Pohl H, et al. Prevalence of clinically important histology in small adenomas. Clin Gastroenterol Hepatol 2006;4:343–348.
15. Amateau SK, Canto MI. Enhanced mucosal imaging. Curr Opin Gastroenterol 2010;26:445–452.
16. Terry NG, Zhu Y, Rinehart MT, et al. Detection of dysplasia in Barrett's esophagus with in vivo depth-resolved nuclear morphology measurements. Gastroenterology 2011;140:42–50.
17. Qiu L, Pleskow DK, Chuttani R, et al. Multispectral scanning during endoscopy guides biopsy of dysplasia in Barrett's esophagus. Nat Med 2010;16:603–606.
18. Lovat LB, Johnson K, Mackenzie GD, et al. Elastic scattering spectroscopy accurately detects high grade dysplasia and cancer in Barrett's oesophagus. Gut 2006;55:1078–1083.
19. Neumann H, Kiesslich R, Wallace MB, et al. Confocal laser endomicroscopy: technical advances and clinical applications. Gastroenterology 2010;139:388–392.
20. Backman V, Roy HK. Light-scattering technologies for field carcinogenesis detection: a modality for endoscopic prescreening. Gastroenterology 2011;140:35–41.
21. Roy HK, Turzhitsky V, Kim Y, et al. Association between rectal optical signatures and colonic neoplasia: potential applications for screening. Cancer Res 2009;69:4476–4483.
22. Bista RK, Brentnall TA, Bronner MP, et al. Using optical markers of nondysplastic rectal epithelial cells to identify patients with ulcerative colitis-associated neoplasia. Inflamm Bowel Dis 2011 Feb 23 [Epub ahead of print].

Reprint requests

Address requests for reprints to: Hemant K. Roy, MD, Duckworth Professor of Cancer Research, Section of Gastroenterology, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, 1001 University Place Suite 326, Evanston Illinois 60201. e-mail: h-roy@northwestern.edu.

Conflicts of interest

The authors disclose the following: Drs Roy, Goldberg, and Backman are co-founders/share holders of American BioOptics, LLC.

Funding

Supported in part by grants from the National Institutes of Health (R01CA156186, R01CA128641, U01CA111257).

0016-5085/$36.00
doi:10.1053/j.gastro.2011.04.027

Endoscopic Management of Large Sessile Colonic Polyps: Getting the Low Down From Down Under

See "Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia," by Moss A, Bourke MJ, Williams SJ, et al, on page 1909.

Colorectal cancer is the second leading cause of cancer and cancer death in the United States. Yet, most colon cancers can be prevented through the detection and removal of premalignant lesions.[1] Colorectal cancer screening and polypectomy have been credited with progressive trends in decreased rate of colorectal incidence.[2] The majority of benign neoplasms detected at screening colonoscopy are small and removed easily with widely employed biopsy-and-snare polypectomy techniques. However, larger flat and sessile lesions are increasingly recognized, predominantly in the proximal colon.[3] Failure to identify these lesions in the past may account for disappointing rates of "missed cancers" in patients who have undergone prior colonoscopy.[4] Enhancements in endoscopic image acquisition and display along with increased vigilance and improved recognition on the part of the colonoscopist have resulted in higher detection rates of