Colonoscopy and Optical Biopsy: Bridging Technological Advances to Clinical Practice

One of the major frontiers of translational gastrointestinal 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). 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).

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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. Thus, for larger lesions, the risk of polypectomy is higher, but the majority of these lesions...
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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.” This represents a powerful approach, especially given the emerging literature of high miss rate and relatively poorer protection against development of right-sided colon. 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.). 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 (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”). 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. Indeed, several centers routinely use standard techniques such as NBI, CLE, and chromoendoscopy in high-risk patients. 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). 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. 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.). These alterations may be detectable using a variety of platforms including ESS, low coherence-enhanced backscattering spectroscopy, and partial wave spectroscopic microscopy. These nascent technologies/approaches have been reviewed recently in GASTROENTEROLOGY.

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

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. Colorectal cancer screening and polypectomy have been credited with progressive trends in decreased rate of colorectal incidence. 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. Failure to identify these lesions in the past may account for disappointing rates of “missed cancers” in patients who have undergone prior colonoscopy. 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 colorectal polyps for classification of colon polyps. Gastroenterology 2010;138:834–842.


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
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