Published in final edited form as:

Gastroenterology. 2011 June ; 140(7): 1863–1867. doi:10.1053/j.gastro.2011.04.027.

Colonoscopic Optical Biopsy: Bridging Technological Advances to Clinical Practice

Hemant K. Roy, MD¹, Michael J. Goldberg, MD¹, Shailesh Bajaj, MD¹, and Vadim Backman, Ph.D.²

¹Department of Medicine, NorthShore University Health Systems, Evanston IL 60201

²Biomedical Engineering Department, Northwestern University, Evanston IL 60208

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 chromo-endoscopy, light scattering spectroscopy (LSS), optical coherence tomography (OCT), elastic light scattering spectroscopy (ESS), autofluorescence (AFI), narrow band imaging (NBI) and confocal endomicroscopy (CLE)¹. These approaches span the gamut with regards to expense, ease of use, skill requirement and accuracy. From a clinical application perspective, one can broadly divide them into four categories—improved polyp detection, optical biopsy (for this editorial we will define as the determination of the histological characteristics of a visualized lesion), identification of flat dysplasia and the emerging area of risk stratification through field carcinogenesis detection (see figure)².

In this issue of *Gastroenterology*, Kuiper and colleagues investigate the ability of endoscopic tri-modal imaging (high definition white light in combination with AFI and NBI) for two of these potential indications—improved adenoma detection and optical biopsy. This randomized study was rigorously designed (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 tri-modal imaging was unable to improve adenoma detection rate although there were some limitations including a surprisingly high miss rate for advanced adenomas. Furthermore, the somewhat atypical study cohort (e.g. enriched Lynch syndrome etc) may impact upon 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 non-dysplastic tissue. The sensitivities were reasonable but at the cost of specificity. This adds to substantial literature on the “optical biopsy” which has utilized a number of techniques (CLE, NBI, chromo-endoscopy etc.)^{1, 2}. While there have been few head-to-head studies that have been sufficiently powered, the majority of the data suggests that the techniques all have good performance and are roughly equivalent. For instance, while Buchner and colleagues noted that CLE and NBI had similar sensitivities (88 vs 84% respectively) and specificity (63% versus 75%, respectively)³. Similarly, Chiu and colleagues noted that NBI and chromo-endoscopy had comparable accuracy (83% and 85% respectively for single observer without magnification)⁴. As noted, the Kuiper data with

Correspondence, Hemant K. Roy, Duckworth Professor of Cancer Research, Section of Gastroenterology, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, 1001 University Place Suite 313, Evanston IL 60201, Phone: 847-570-3115, Fax: 847-733-5041, h-roy@northwestern.edu.

Conflict of interest: Drs. Roy, Goldberg and Backman are co-founders/share holders of American BioOptics LLC.

AFI/NBI was similar and consistent with a large body of literature on other techniques with optical biopsy.

Thus, taken together, optical biopsy appears to have reasonable diagnostics and undoubtedly this can be further improved with technological refinements. The real question is whether these approaches will be translatable into general clinical practice. Indeed, the concept has been discussed for more than a decade and some technologies (chromo-endoscopy, NBI, CLE) are widely available and yet optical biopsy is not commonly employed during gastrointestinal endoscopy. Therefore, it is paramount to understand the hurdles for endoscopists to adopt optical technologies into their lesion management armamentarium.

First, for clinical practice, it needs to be determined what level of certainty would be necessary. Most of the studies to date demonstrate that optical biopsy for lesion histological determination have sensitivity/specificity in the ~80–90% range. One would wonder if this performance would be acceptable to both patients and physicians since the consequence of an error (especially false negatives) might result in cancer development. This is particularly concerning in the current medico-legal climate (e.g. 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 polyps⁵. However, few would consider this adequate for clinical practice. While the improvement in diagnostics is significant with NBI, chromo-endoscopy, CLE etc., 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 since endoscopic polyp removal is routinely performed in generally a rapid and safe fashion? One could argue that optical biopsy may reduce the number of polypectomy 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 histological features are occasionally noted in smaller polyps, the probability of premalignant/dysplastic features is also roughly proportional to lesion size^{2, 6}. Thus, for larger lesions, 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 (e.g. 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 upon clinical decisions⁷. 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) since others would require surgical intervention regardless of optical data. For pedunculated lesions, the number of lesions where management decisions that could be altered from optical biopsy is even less because many malignant polyps can be managed by endoscopic polypectomy⁷. Another potential beneficial scenario would be to forego retrieval of right-sided lesions (resect but not recover lesions thereby avoiding need for colonoscope removal/reintubation) and rely on optical data as a histological surrogate for colonoscopic surveillance recommendations. However, the value is somewhat limited since smaller lesions can typically be retrieved by suctioned (no need for colonoscope removal) and larger lesions may need pathological evaluation for determination of more subtle findings such as high-grade dysplasia or carcinoma *in situ*.

Third, it is critical to consider cost of these optical biopsy techniques. Indeed, pathology fees may be significant, potentially eclipsing the endoscopist charge in some cases. The argument that this may be useful for multiple small left sided polyps seems reasonable

although the common practice of placing all in a single pathology jar may mitigate some of the cost issues. This can be done because it is generally not essential to know the histology of a particular lesion (since lesions this size are so rarely malignant) but rather the total number of adenomas (none, 0–3, 3–10 and >10)⁶. Therefore, for routine use, optical biopsy would need to be very inexpensive. Even with strategies such as reusable fiberoptic probes/spray catheters, instrumentation costs (for techniques such as CLE) may make these technologies difficult to justify in the cost-conscious healthcare environment. Furthermore, since a large number of the lesions subjected to optical biopsy will eventually require polypectomy, many patients will also have 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 biopsy channel, need for careful inspection/image interpretation will likely increase procedure time (although some approaches NBI ameliorate this through integration with the colonoscopes). Furthermore, the positive results will require polypectomy as a second distinct procedure (albeit there are some innovative solutions being developed such as combining ESS fiberoptic probe with a snare). Additionally, there is the issue of some training required/learning curve and performing sufficient volume of procedures to maintain skill for image-based techniques. These work flow implications should not be underestimated and may represent a significant impediment to 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 towards complications (because these lesions have a predilection for the thin-walled right colon). However, it is becoming increasingly recognized that these lesions, especially located right side of the colon, may be the precursors to microsatellite unstable colorectal cancer. Indeed, this is the hallmark of the serrated neoplasia pathway^{8, 9}. Thus, optical biopsy may be less value since one could argue that while these clinically 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, while a technological breakthrough, it appears unlikely that the optical biopsy information will be employed in the general practice of colonoscopy for most visually apparent lesions encountered (i.e. polyps or masses). However, there are several scenarios where this might be valuable. For instance, in the anti-coagulated patients or those undergoing acute GI bleed this may be useful in deciding upon repeat procedures. Additionally, an *in situ* approach may be helpful in patients with numerous non-premalignant polyps (e.g. pseudopolyps from IBD or hyperplastic polyposis) to target the most appropriate lesions to biopsy and/or removal. Finally, optical biopsy may be useful to assess completeness of piecemeal polypectomy (if not obscured by coagulation artifact). There are undoubtedly others but it appears 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 colon¹⁰. Proximal lesions are particularly challenging because they have a higher propensity for microsatellite instability and thus not only grow more rapidly but also more difficult to

visualize (flat, behind folds etc.)^{11, 12}. In addition, the right colon is frequently less well prepped. Therefore, adjunctive technologies (NBI, chromo-endoscopy, AFI etc.) would be particularly appealing aiding to aid visualization. While the data to date has been inconclusive on the efficacy¹³ (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-unapparent 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 lowcoherence interferometry (aLCI), multispectral scanning and ESS)^{14–16}. Indeed, several centers are routinely using standard techniques such as NBI, CLE, chromo-endoscopy in high risk patients¹⁷. The potential of this approach to improve yield of dysplasia and reducing the number of biopsies has significant attraction in managing the subset of patients with conditions that manifest as flat dysplasia. While it still 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 upon 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)¹⁸. This could serve as a minimally intrusive pre-screen, identifying subjects more likely to receive a cancer prevention benefit (i.e. removal of a significant polyp). Previous markers of field carcinogenesis has predominantly focused on cellular (apoptosis/proliferation) and molecular (genetic/epigenetic/proteomic) approaches¹⁹. Importantly, despite the fact that the distal colonic mucosa appears microscopically normal (sensitive to objects (greater ~500 nm), there can be profound architecture in smaller structures that are critical for neoplastic transformation (ribosomes, chromatin organization)¹⁸. These alterations may be detectable using a variety of platforms including ESS, low coherence enhanced backscattering spectroscopy (LEBS) and partial wave spectroscopy (PWS) etc^{18, 20, 21}. These nascent technologies/approaches have been recently reviewed in *Gastroenterology* not be further discussed¹⁸.

In conclusion, we are entering an era when optical technologies are poised for transition into colorectal cancer screening. The techniques appear to be sufficiently accurate. However, the crux of the matter is whether these approaches will actually bridge the bench to bedside chasm. While optical biopsy for management of endoscopically-visualized lesions appears to be technologically feasible, we believe it may not be practical for widespread clinical implementation because of issues related to clinical rubrics (management of right-sided serrated lesions), risk management, expense etc. Therefore, it may be more prudent focusing research and development resources onto applications that are more likely to be clinically achievable such as improved endoscopic polyp visualization, flat dysplasia detection and potentially riskstratification. This is an exciting time with numerous important technological advances in optics that have potential for revolutionizing colonoscopy. However, to make a significant impact upon patient care, it is paramount that future developments be integrally linked to the clinical/biological paradigms and endoscopic practice considerations.

Acknowledgments

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

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