Improving the Vision of Colonoscopy: Does the Fine Print Really Matter?

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Colonoscopic surveillance with polypectomy is the standard of care for patients with prior colorectal neoplasia and a bedrock of management for persons with inherited predispositions to colorectal cancer (CRC). This is the case because colonoscopic polypectomy done at scheduled intervals reduces the risk of CRC (1, 2) and, in Lynch syndrome (LS), CRC mortality as well (3).

Although effective, colonoscopic surveillance with polypectomy is not perfect because interval cancers occur in LS patients (4) and in patients with prior sporadic CR neoplasia (5, 6). Indeed, studies of dual colonoscopy have revealed adenoma “miss rates” of 2% to 26% in the sporadic setting, depending strongly on adenoma size; for example, 1- to 5-mm lesions were missed up to one third of the time (7–9).

To address this problem, various endoscopic improvements have been developed and tested, including dye-spray chromoendoscopy (10–15), magnifying/high-resolution endoscopy (16), and narrow-band imaging (17). All of these methods enhanced the sensitivity of colonoscopy for CR neoplasms, but their real gain was in detecting small and/or “flat” lesions. The long-term implications of finding and removing these lesions are unknown because large, representative trials of this issue have not been done.

Small polyps (<10 mm in diameter) are typically assumed to have little or no immediate implications for CRC risk (18), but a couple important issues are implicit in this assumption. First, because large adenomas presumably arise from smaller adenomas over time, the timeline of surveillance relative to the biology of neoplastic progression is an issue. Second, small adenomas may assume greater importance in high-risk individuals, especially those with underlying genetic predispositions such as patients with LS, in whom carcinogenic progression may be accelerated. A recent study involving 1,933 small adenomas suggested that the prevalence of “advanced histologies” including cancer may be as high as 10.1% in 5- to 10-mm adenomas and at least 1.7% in 4-mm or smaller adenomas (19). Furthermore, the prevalence and implications of flat adenomas in the U.S. population are coming under greater scrutiny as a result of recent studies detecting them with greater frequency (20, 21). For example, flat and depressed colorectal adenomas were detected with dye-assisted colonoscopy in 22.7% of 211 U.S. patients, and these lesions were more likely to be smaller and to harbor invasive cancer compared with adenomas detected by conventional colonoscopy (20). Another study found nonpolypoid colorectal neoplasms in 15.44% of patients in a surveillance population, and these lesions were much more likely to harbor carcinoma than were polyps of any size (21).

Previous studies have shown that various approaches—from tandem/repeat exams to colonoscopy with enhanced technologies—can improve detection rates, but it remains controversial whether these improvements in sensitivity are due to the improved technologies, the additional time devoted to detection, or both. As reported in this and the previous issue of the journal, Stoffel and colleagues conducted two small randomized controlled trials that evaluated traditional optical colonoscopy with polypectomy followed by randomization to a second exam of either chromoendoscopy or standard colonoscopy with intensive inspection (≥20 min) in patients with prior significant sporadic CR neoplasia (22) or LS (23). Although the primary objective of these two studies was to compare the adenoma detection rates in chromoendoscopy and intensive inspection colonoscopy, the authors note that after controlling for procedure time, their data support that the increase in adenoma detection seen in the sporadic neoplasia group with chromoendoscopy is independent of inspection time. Although this observation is intriguing, it is premature to consider it definitive because of the small sample size in these studies and the fact that in the LS group, this was not observed. Clearly, larger studies specifically designed to definitively determine if improved sensitivities afforded by chromoendoscopy are indeed independent of inspection time are needed and anticipated.

Looking across both trials, LS patients were younger, had undergone more surveillance exams, and had a stronger personal history of CRC, as one would have predicted, and smoked less (versus sporadic CR neoplasia patients). Randomization distributed baseline risk variables evenly in the LS study, whereas baseline factors were substantially, although not statistically significantly, different between the randomized groups in the sporadic study. In the sporadic neoplasia study, patients randomized to chromoendoscopy were more often female (52% versus 30%), had more-recent prior surveillance exams (18.8 versus 26.3 months), had a lower percentage of participants with prior CRCs (7% versus 13%), but somewhat curiously had more than double the rate of prior partial colonic resections (30% versus 13%).

The first exams give us an opportunity to evaluate the performance of traditional standard colonoscopy following a similar standardized protocol in two different types of patients (Table 1). The trials involved roughly the same number of patients in each study. In patients with LS, 17 polyps were identified, 10 of which were adenomatous, and 15% of patients harbored an adenoma. In patients with sporadic neoplasia, 61 polyps were identified, including 40 adenomas,

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and 34% of patients harbored an adenoma. Therefore, patients with prior sporadic neoplasia had a much higher burden of polyps and adenomas (i.e., >3-fold) compared with patients with LS, affecting twice as many patients. These differences may be due in part to the slightly longer mean interval of sporadic patients since their last colonoscopy, or to the inherently faster progression of preinvasive neoplasia in those with LS, giving them fewer prevalent polyps at any given point in time. Whatever the case, these studies show that adenomas can be found by conventional colonoscopy even within a couple of years of prior exams in surveillance populations.

The studies of Stoffel and colleagues also allow us to estimate the “miss rate” for polyps and adenomas, recognizing differences from prior miss-rate studies because the second exams here did not only repeat standard colonoscopy but also involved either intensive inspection or chromoendoscopic enhancement. As noted above, simple tandem exams have previously suggested adenoma miss rates of 2% to 26%, with smaller lesions being missed more frequently (9). However, chromoendoscopy in the studies by Stoffel and colleagues found much-higher miss rates of 58% for polyps and 55% for adenomas in LS patients. Miss rates for polyps and adenomas were slightly lower at 42% and

| Table 1. Characteristics of the first and second colonoscopies in patients with prior significant sporadic neoplasia or LS |
|---------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| **First colonoscopy**                                        | **Second, randomized colonoscopy**                                  |
| **LS**                                                       | **Sporadic neoplasia**                                              | **LS**                                                       | **Sporadic neoplasia**                                              |
| Subjects                                                    | 54                                                                  | 50                                                                  | 26                                                                  | 28                                                                  | 23                                                                  | 27                                                                  |
| Procedure time (min)                                        | 18.2 ± 8.0                                                          | 20.8                                                               | 25.3 ± 5.8                                                          | 29.8 ± 9.5                                                          | +4.5 (+18%)                                                         | 27.3 ± 6.2                                                          | 36.9 ± 14.5                                                         | +9.6 (+35%)                                                         |
| Total polyps                                                | 17                                                                  | 61                                                                 | 8                                                                   | 15                                                                  | +88%                                                               | 10                                                                  | 35                                                                  | +250%                                                               |
| Subjects with polyps                                        | 13                                                                  | (24%)                                                              | 25 (50%)                                                            | 8                                                                   | (19%)                                                              | 10 (36%)                                                            | 8 (35%)                                                            | 17 (63%)                                                            | +80%                                                               |
| Polyps per subject                                          | 0.3 ± 0.6                                                           | 1.0-1.4                                                            | 0.3 ± 0.7                                                           | 0.5 ± 0.8                                                           | +67%                                                               | 0.4 ± 0.7                                                           | 1.3 ± 1.4                                                           | +225%                                                               |
| Polyps *missed* on first exam                               | 23                                                                  | 45                                                                 |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |
| Polyp missed rate                                           | 58%                                                                | 42%                                                                |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |
| Subjects with biopsies                                      | 15                                                                  | (28%)                                                              | 27 (54%)                                                            | 9 (35%)                                                            | 15 (54%)                                                            | +54%                                                               | 12 (52%)                                                            | 19 (70%)                                                            | +35%                                                               |
| Total adenomas                                              | 10                                                                  | 40                                                                 | 7                                                                   | 5                                                                   | −29%                                                               | 5                                                                   | 19                                                                  | +280%                                                               |
| Subjects with adenomas                                      | 8 (15%)                                                            | 17 (34%)                                                            | 5 (19%)                                                            | 3 (11%)                                                            | −42%                                                               | 4 (17%)                                                            | 12 (44%)                                                            | +159%                                                               |
| Adenomas per subject                                        | 0.2 ± 0.5                                                           | 0.7-0.9                                                            | 0.3 ± 0.6                                                           | 0.2 ± 0.5                                                           | −33%                                                               | 0.2 ± 0.5                                                           | 0.7 ± 1.0                                                           | +250%                                                               |
| Adenomas missed on first exam                               | 12                                                                  | 24                                                                 |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |
| Adenoma missed rate                                         | 55%                                                                | 38%                                                                |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |                                                                     |


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38%, respectively, in sporadic neoplasia patients. Therefore, the miss rates in both groups were much higher than in previous studies, albeit involving mostly very small lesions of uncertain long-term significance. Nevertheless, the authors point out that this finding might have changed management recommendations for as many as 26% of patients with sporadic neoplasia who otherwise would have been categorized as adenoma-free, depending on whether adenomas identified by more sensitive second exams should carry similar clinical implications as those identified by traditional colonoscopy.

Comparing the enhanced colonoscopic techniques applied in the second exam across both studies shows that intensive inspection yielded an additional 10 polyps, of which 5 were adenomas, and that chromoendoscopy revealed an additional 35 polyps, of which 19 were adenomas. Therefore, chromoendoscopy was more sensitive in both detecting adenomas and patients with adenomas. That said, the detected adenomas were small and more often right sided, and the enhanced sensitivity of chromoendoscopy came at the price of modestly longer procedure times (an additional 9.6 min, on average) and more frequent normal biopsies. Nevertheless, the authors made the important observation that more than half of the patients with detected adenomas in the chromoendoscopy group would not have been identified without the second exam.

In LS patients, the second exam using intensive inspection identified 8 additional polyps (7 adenomas) and chromoendoscopy revealed 15 additional polyps (5 adenomas). Therefore, in this cohort, a second exam more than doubled the rate of adenoma detection, but there was no significant difference between intensive inspection and chromoendoscopy. By contrast, chromoendoscopy improved the detection of polyps relative to intensive inspection, but it also led to more biopsies (54%) versus intensive inspection (35%), required slightly longer procedure times (on average, ~4.5 min longer), and had lower sensitivity for adenomas.

Our attention next turns to a brief consideration of the location, size, and histopathology of polyps and adenomas in the two studies. In the sporadic neoplasia cohort, polyps were generally small (2-4.5 mm in diameter) and slightly smaller on the second exam regardless of the technique used to identify them. Chromoendoscopy was especially effective (versus intensive inspection alone) in identifying right-sided and flat adenomas with good specificity, suggesting the possibility of reducing neoplastic recurrence or new second primary cancers without a significant increase in programmatic costs or morbidity. This is particularly important because 72% of all adenomas were right sided and 35% were flat in this population.

In LS patients, polyps were a bit larger on first exam (mean of 3.75-5.44 mm in diameter) but clearly smaller (mean of 1.88-2.67 mm in diameter) on the second exam, regardless of the technique. Subjects undergoing chromoendoscopy had more biopsies, which identified significantly more hyperplastic polyps, but not more adenomas compared with patients undergoing intensive inspection. Sixty-four percent of adenomas in LS patients were flat, and the majority of these (71%) were only identified on the second exam—most via intensive inspection. Last, chromoendoscopy identified larger adenomas than did intensive exams, but after controlled analyses, chromoendoscopy was not more sensitive for adenomas or polyps compared with intensive inspection in LS patients.

Of great importance, neither trial reported significant adverse events associated with tandem exams involving either intensive inspection or chromoendoscopy.

Of course, these trials have important limitations that should be considered. Both trials were designed as “pilot investigations” with convenience samples not determined by a priori power assessments so their power to detect many potential associations of interest was limited. In addition, both had a restricted ability to explore the effect of procedure times because minimal procedure durations of 20 min were suggested by the protocol. It is unclear what level of detection could be expected from either of these approaches applied in exams of shorter duration. In the sporadic trial, there were more biopsies than polyps, causing one to wonder what other endoscopic pathologies warranted endoscopists to pursue histopathologic assessments. It is also interesting to note that these studies identified a relatively high percentage of flat adenomas (35% and 64% of adenomas in the sporadic-risk and LS cohorts, respectively); thus, the generalizability of the results is currently unclear.

In sum, these trials are significant additions to the literature because they help to unravel the relative contributions of chromoendoscopy to the identification of polyps/adenomas in two different at-risk cohorts (prior significant sporadic colorectal neoplasia and LS) independent of intensive inspection. In LS patients, second exams of any form increased the identification of polyps and adenomas by as much as 55%, but chromoendoscopy was not necessarily better than an intensive exam alone. In prior sporadic neoplasia patients, second exams identified significantly more polyps and adenomas (indeed, 38-42% more) but chromoendoscopy was superior to intensive inspection especially for right-sided and flat adenomas. In both patient cohorts, the adenomas detected on the second exams were small and of uncertain long-term significance, but their presence suggests that routine surveillance recommendations for at least a fraction of patients could or should be amended in an effort to reduce the occurrence of interval cancers.

The prevalence of small adenomas in these cohorts, the substantial miss rates associated with traditional surveillance endoscopy in these trials, and the suggestion that chromoendoscopy (or in the case of LS, either intensive inspection or chromoendoscopy) can significantly improve adenoma detection rates lead to several important questions. Perhaps most important, what is the biological significance of these small adenomas in these or other patient subsets? Do small adenomas portend a significantly increased risk for CRC or not, and if so, in which subsets and in what settings? If there are associated cancer risks, can those risks be mitigated by polypectomy, lifestyle alterations, chemoprevention, combinations of these interventions, or other approaches? Assuming that future studies answer some of these questions and chromoendoscopy seems promising, can it be done more efficiently, with less disruption to clinical flow, and with greater specificity for adenomas through the use of more specialized dyes or endoscopic technologies? Finally, it is intriguing to speculate how molecular
assessments of these small adenomas might help to clarify their biology and provide insights into their potential for progression to cancer.

The answers to these questions will help to define the future role of chromoendoscopy in colorectal screening and surveillance. For now, Stoffel et al. have made a substantial contribution to our consideration of CRC risks by generating important preliminary data on the prevalence of small adenomas in these patients and the potential advantages offered by improving the “vision” of optical colonoscopy.

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No potential conflicts of interest were disclosed.
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