

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Evolving Protocols in Colorectal Cancer Surveillance

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G&H What is the historic reasoning for colorectal cancer screening that has led to the current colonoscopy protocols?

MR The current strategies for colorectal cancer (CRC) screening hinge on the premise of a dysplasia-cancer pathway. This idea posits that before a patient develops cancer, they have a dysplastic lesion in the colon. The aim of surveillance is to detect premalignant dysplastic lesions and remove them endoscopically, if feasible, or by having the patient referred for colectomy, to preempt the development of cancer.

In support of this effort, the initial strategy of random biopsy to maximize detection of premalignant dysplastic lesions was developed. These recommendations came from a study published in 1992 by Rubin and colleagues, who estimated that approximately 33 biopsies would be required from a single procedure to detect the premalignant dysplastic lesions with 90% confidence. From that study, a recommendation was made that patients undergo quadrantic biopsies from every 10 cms of colon and rectum, which equates to approximately 30–32 biopsies per patient. That random biopsy approach has been the main recommendation for surveillance for many years.

G&H Could you describe the currently accepted method of selecting patients for CRC surveillance?

MR There are several sets of guidelines available, and they currently differ slightly between the United States and the United Kingdom. The UK guidelines are in the process of revision and will differ more significantly after publication of the update.

The current general recommendation is that all patients who have ulcerative colitis (UC) or Crohn's colitis undergo an index colonoscopic assessment between 8 and 10 years after the initial onset of symptoms. It is important to assess the extent of colonic involvement because the extent of colitis is an important risk factor for CRC and the initial endoscopy allows the clinician to decide whether the particular patient requires ongoing surveillance. If the disease is limited to the rectum, then there is no significant increased risk of bowel cancer and these patients, in general, need not be included in surveillance programs. If patients have extensive disease, affecting at least 50% of the mucosa, they are at significantly increased risk and should be recommended for ongoing colonic surveillance.

When the disease is between those two extremes, (ie, left-sided or distal disease), current protocols recommend surveillance but at less frequent intervals. There are no clear data supporting the benefit of surveillance in these patients, who are at moderately increased risk. Nonetheless, with distal disease, the UK recommendation is that surveillance start 15 years after disease onset, rather than 10 years. Intervals for repeat colonoscopy depend on a number of variables.

G&H What are the factors driving the re-evaluation and revision of current guidelines?

MR It must first be noted that no randomized trials have been performed to assess whether current surveillance programs are effective in preventing cancer or reducing mortality. At this point, a study with a control arm offering no manner of surveillance would be deemed unethical. Retrospective studies have been published reporting surveillance program success, showing undoubtedly that some patients do benefit because early asymptomatic cancers and precancerous lesions are detected. However, in each study, there are patients who develop cancers from one colonoscopy to the next or present with a symptom-

atic cancer between procedures, showing that the current form of surveillance is not perfect.

Over the last 5 years, there have been a number of prospective controlled trials that have demonstrated that utilizing chromoendoscopy to dye spray the colon and take targeted biopsies from lesions unmasked by the dyes is a superior method of detecting dysplastic lesions. Chromoendoscopy increases the yield of lesions by 2.5–5 times that of random biopsy. In the United Kingdom, there has been a movement to encourage chromoendoscopy and move away from random biopsy methods.

The initial hope when surveillance was devised, nearly 30 years ago, was that it would have a greater impact than it currently is having on rates of cancer prevention. Therefore, these new imaging technologies, coupled with renewed interest in enhancing risk stratification algorithms, have motivated experts to consider revisions to protocols in the hope of improving detection rates.

G&H What novel factors are being incorporated into risk stratification algorithms?

MR Over the last 5 years, we have learned that, along with disease duration and disease extent, disease severity is an important independent risk factor for CRC. This was demonstrated first in a study that we performed at St. Mark's Hospital in the United Kingdom and has recently been confirmed by a US study that was published last year. The new UK guidelines will incorporate this fact into patient risk stratification. Data collected from the initial surveillance colonoscopy regarding severity of inflammation could be used to guide the clinician regarding the question of when the next procedure should be performed. In the St. Mark's Hospital study, we demonstrated that patients who have quiescent disease, with no additional risk factors, have no higher a cancer incidence than the general population over the next 5 years. Therefore, revised guidelines will recommend that this cohort have their next surveillance colonoscopy deferred for 5 years.

Patient age has proven a more contentious issue. There are a number of studies, particularly from Scandinavian centers, which suggest that early onset of disease is an independent risk factor for cancer. However, an equal number of studies suggest the contrary, that age is either not a risk factor or that patients who develop disease at a later age are at increased risk. Current UK guidelines do not consider age of onset an independent risk factor.

G&H Are biomarkers under consideration as another method to further stratify patient risk?

MR Biomarkers and serum markers are a very exciting avenue of continued research. Investigation is ongoing,

including examination of a stool model to detect DNA alterations that signal development of sporadic bowel cancer or premalignant lesions. At present, the use of this strategy for colitis surveillance is not yet feasible. However, one can envisage a day in the not-too-distant future when patients will provide their laboratory with a stool specimen, which will be analyzed to determine the need for subsequent colonoscopy. This scenario represents a hope rather than a current practice in research, but a great deal of progress is currently being made, and I would hope that first-line screening tests incorporating specific, independent markers for precancerous changes in the colon will be developed within 10–15 years.

G&H How do issues of patient compliance affect the success of colonic surveillance?

MR Compliance is an issue in any surveillance program. Unfortunately, the patients who are least compliant are generally those at the greatest risk of developing the disease. The more health-aware the patient is, the more likely they are to comply in order to lower that risk. There is a great deal that can be done to encourage and educate our patients regarding the potential benefits of participating in surveillance programs. It is also extremely important to ensure that the colonoscopies that are performed are of high quality, both in terms of maximizing dysplasia yield and minimizing discomfort caused to the patient. Patients who associate colonoscopy with a severely unpleasant experience are far less likely to comply in the future.

G&H Are there other new endoscopic technologies, beyond chromoendoscopy, that might potentially improve the quality of colonoscopic examination?

MR There are a number of novel endoscopic modalities, some of which may have application in CRC screening. Narrow-band imaging (NBI) is already available in many endoscopic units. However, in the field of colitis surveillance, it is not proving effective. NBI enhances the superficial vascular pattern, and it was initially hoped that because dysplastic lesions have a greater vascular supply, they could be differentiated through NBI. However, colitis patients, even when their disease is quiescent, have an altered vascular pattern throughout the mucosa, which creates noise that reduces the effect of NBI in this setting. Last year, a prospective randomized trial was performed to assess the use of narrow band versus standard endoscopy and found no significant difference between lesions detected with white light compared to narrow band.

Autofluorescence endoscopy is in a relatively early stage of development, but at last year's United European Gastroenterology Week in Paris, there was an abstract

presented examining the accuracy of autofluorescence in detecting lesions. Although not statistically significant, it did suggest a trend of benefit from autofluorescence compared to standard white-light endoscopy. This technology is at an early stage of development, and continued improvements may provide a useful method of flagging lesions for biopsy.

Finally, confocal endomicroscopy is an exciting technology that allows the endoscopist to produce real-time, nearly histologic-type images of specific areas of mucosa to assess whether an already detected lesion is neoplastic. Early studies by Ralph Kiesslich and Paul Hurlstone suggest that confocal microscopy is an accurate method for determining whether the lesion is neoplastic at the time of colonoscopy. Lesion detection still requires the use of chromoendoscopy, but once lesions are found, confocal endomicroscopy can be utilized to determine whether the lesion requires endoscopic resection or is nonneoplastic and can be left.

G&H Do these advances and revisions have parallels in other types of endoscopic surveillance, such as that for Barrett esophagus?

MR There are a number of similarities between CRC surveillance and endoscopic monitoring of Barrett esophagus (BE). Both colitis and BE are conditions that impart an increased risk of cancer in the affected organs. BE surveillance once required multiple random biopsies. However, as with CRC surveillance, there is a definite move toward targeted biopsy of specific lesions. The same new imaging modalities have been applied quite successfully in BE to enhance the detection of specific lesions.

The other development that applies to both conditions is that after discreet lesions are detected, they can be endoscopically resected. There have been a number of studies, in both BE and colitis, showing success of endoscopic resection of specific lesions and very good prognosis in carefully selected lesions. Whereas 10 years ago it was set in stone that patients with a premalignant lesion should have a panproctocolectomy, the present emphasis is on assessing the lesion and, where appropriate, resecting it. This obviously represents a huge advance for the patient in terms of quality of life and avoidance of surgery. These advances are possible because of the better visualization techniques discussed above and better resec-

tion techniques, such as endoscopic mucosal resection, that can ensure removal of all dysplastic tissue.

It should be noted that these similarities apply only in patients with established colitis and BE. In terms of screening for BE as opposed to surveillance, the population of patients with GERD, and thus potential BE, is much larger and more difficult to screen effectively than those with UC, all of whom have inflammation and are at increased risk of CRC.

G&H Could you describe the coming revisions to UK guidelines that will further differentiate them from current US practice?

MR Essentially, patients will be stratified according to previous history of primary sclerosing cholangitis, ongoing active inflammation, previous history of dysplasia or strictures, strong familial history of bowel cancer, and several other risk factors. If patients have any of these high-risk factors, the recommendation will be for annual surveillance. An intermediate cohort will include patients with postinflammatory polyps, as two studies now suggest that patients with postinflammatory polyps have an increased cancer risk. Patients with a weak family history for bowel cancer will also fall into the intermediate category. These patients will be recommended for surveillance every 3 years. Patients with quiescent disease and no other risk factors will be recommended for surveillance every 5 years. In addition, use of dye-spray chromoendoscopy will also be recommended.

Suggested Reading

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