The risk of colon cancer is increased in patients with both ulcerative colitis and Crohn’s colitis and therefore surveillance colonoscopy is recommended in patients with elevated risk factors for neoplasia. The guidelines developed during the era of standard white light endoscopy recommend targeted biopsies of visible neoplastic lesions as well as random biopsies to detect invisible dysplasia. The practical adoption of these guidelines has been thwarted by low yield and limited effectiveness in preventing colon cancer. Image-enhanced endoscopy and particularly chromoendoscopy have demonstrated an increased diagnostic yield for dysplasia while essentially eliminating the need for random biopsies. Although very promising, additional studies are needed to assess the utility of image-enhanced endoscopy and to demonstrate the superiority of these techniques in preventing colon cancer in IBD.

INTRODUCTION

It is well established that both ulcerative colitis (UC) and Crohn’s disease (CD) involving the colon increase the risk of colon cancer (CRC) although the magnitude of the incremental risk varies considerably with the epoch and the study population. Risk factors for colorectal neoplasia include duration and anatomic extent of disease, family history of colon cancer, persistence and degree of inflammation, coexistent primary sclerosing cholangitis and possibly male sex. In contrast to sporadic colorectal neoplasia, colitis-associated neoplasms are more frequently multifocal and flat, thus being more challenging to diagnose particularly in an inflamed colon. Furthermore, colon cancer in patients with colitis tends to occur at a younger age compared to non-IBD patients. As is the case with sporadic colon cancer, dysplasia is believed to be the precursor of the majority of cases of colitis-associated carcinomas and thus surveillance guidelines have been developed by several professional societies based on limited supportive evidence. In the era of standard-definition white light endoscopy, these guidelines called for surveillance colonoscopy every 1-2 years after 8-10 years of established disease, with removal of all visible “suspicious” lesions and adjacent biopsies around lesions removed from within the area of colitis. In addition, random 4-quadrant biopsies every 10 cm were recommended in order to increase the detection of “flat”
facilitate the performance of targeted biopsies and polypectomies. Chief among these has been dye-based chromoendoscopy (CE) which has been evaluated in multiple prospective and retrospective studies mostly from referral centers. CE consists in the application of dye onto the colonic mucosa via either a catheter or using the water-jet channel provided with most colonoscopes. The stained mucosa enables a superior visualization of both elevated and depressed polypoid and non-polypoid lesions. In addition, particularly with the use of high-definition endoscopy, the pit pattern of the glandular crypts becomes visible and may help differentiate between neoplastic and hyperplastic or inflammatory pathology. Indigo carmine at concentrations of 0.2-0.4% and methylene blue at a concentration of 0.1% are the most commonly utilized dyes. Indigo carmine is commercially available both as a solution and as a powder – which is less expensive – although recent FDA restrictions on the use of non-sterile compounds in medical practice have limited drastically the use of the latter. Methylene blue is available as a 1% solution in vials containing either 1 or 10 mL and, in contrast to indigo carmine, is an absorptive dye which can penetrate the epithelial cell cytoplasm.

Chromoendoscopy Technique

Since a substantial proportion of colon cancers in IBD can be attributed to missed or unrecognized neoplastic lesions using white light colonoscopy and the yield of random biopsies is extremely low, several image-enhancing techniques have been developed in order to maximize dysplasia detection and to facilitate the performance of targeted biopsies and polypectomies. Chief among these has been dye-based chromoendoscopy (CE) which has been evaluated in multiple prospective and retrospective studies mostly from referral centers. CE consists in the application of dye onto the colonic mucosa via either a catheter or using the water-jet channel provided with most colonoscopes. The stained mucosa enables a superior visualization of both elevated and depressed polypoid and non-polypoid lesions. In addition, particularly with the use of high-definition endoscopy, the pit pattern of the glandular crypts becomes visible and may help differentiate between neoplastic and hyperplastic or inflammatory pathology. Indigo carmine at concentrations of 0.2-0.4% and methylene blue at a concentration of 0.1% are the most commonly utilized dyes. Indigo carmine is commercially available both as a solution and as a powder – which is less expensive – although recent FDA restrictions on the use of non-sterile compounds in medical practice have limited drastically the use of the latter. Methylene blue is available as a 1% solution in vials containing either 1 or 10 mL and, in contrast to indigo carmine, is an absorptive dye which can penetrate the epithelial cell cytoplasm.

Chromoendoscopy for IBD Surveillance

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients (n)</th>
<th>Dye</th>
<th>Design</th>
<th>Chromoendoscopy</th>
<th>WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich ’03</td>
<td>165</td>
<td>MB</td>
<td>Randomized</td>
<td>11/80 (13.8%)</td>
<td>6/81 (7.4%)</td>
</tr>
<tr>
<td>Rutter ’04</td>
<td>100</td>
<td>IC</td>
<td>Tandem</td>
<td>7/100 (7%)</td>
<td>2/100 (2%)</td>
</tr>
<tr>
<td>Hurlstone ’05</td>
<td>700</td>
<td>IC</td>
<td>Cohort</td>
<td>69/350 (19.7%)</td>
<td>24/350 (6.9%)</td>
</tr>
<tr>
<td>Kiesslich ’07</td>
<td>153</td>
<td>MB</td>
<td>Randomized</td>
<td>13/84 (15.5%)</td>
<td>4/73 (5.5%)</td>
</tr>
<tr>
<td>Marion ’08</td>
<td>102</td>
<td>MB</td>
<td>Tandem</td>
<td>17/102 (16.7%)</td>
<td>9/102 (8.8%)</td>
</tr>
<tr>
<td>Gunther ’11</td>
<td>150</td>
<td>IC</td>
<td>Randomized</td>
<td>2/50 (4%)</td>
<td>0/50 (0)</td>
</tr>
<tr>
<td>Hlavarty ’11</td>
<td>30</td>
<td>IC</td>
<td>Tandem</td>
<td>4/30 (13.3%)</td>
<td>0/30 (0)</td>
</tr>
</tbody>
</table>

WLE = white light endoscopy; MB = methylene blue; IC = indigo carmine

or invisible dysplasia. Based on a mathematical model developed in the early ‘90s, a minimum of 32 random biopsies were required to achieve a sensitivity of 90% for detecting dysplasia or carcinoma. Aside from the tedious and time consuming approach, this strategy has never been clearly shown to be effective in preventing or increasing survival from colon cancer in patients with IBD. The yield of random biopsies for dysplasia obtained using both standard- and especially high-definition white light endoscopy (WLE) is extremely low (< 1:500 biopsies). In a large retrospective series from the St Mark’s hospital, more than 50% of the colon cancers detected in a cohort of patients enrolled in a surveillance program were interval cancers. Moreover, given the considerable costs associated with frequent colonoscopies and multiple biopsies, any marginal benefit of surveillance may not be cost-effective. Therefore, not surprisingly, many studies showed that the compliance with these guidelines was poor.

Chromoendoscopy for IBD Surveillance

Since a substantial proportion of colon cancers in IBD can be attributed to missed or unrecognized neoplastic lesions using white light colonoscopy and the yield of random biopsies is extremely low, several image-enhancing techniques have been developed in order to maximize dysplasia detection and to facilitate the performance of targeted biopsies and polypectomies. Chief among these has been dye-based chromoendoscopy (CE) which has been evaluated in multiple prospective and retrospective studies mostly from referral centers. CE consists in the application of dye onto the colonic mucosa via either a catheter or using the water-jet channel provided with most colonoscopes. The stained mucosa enables a superior visualization of both elevated and depressed polypoid and non-polypoid lesions. In addition, particularly with the use of high-definition endoscopy, the pit pattern of the glandular crypts becomes visible and may help differentiate between neoplastic and hyperplastic or inflammatory pathology. Indigo carmine at concentrations of 0.2-0.4% and methylene blue at a concentration of 0.1% are the most commonly utilized dyes. Indigo carmine is commercially available both as a solution and as a powder – which is less expensive – although recent FDA restrictions on the use of non-sterile compounds in medical practice have limited drastically the use of the latter. Methylene blue is available as a 1% solution in vials containing either 1 or 10 mL and, in contrast to indigo carmine, is an absorptive dye which can penetrate the epithelial cell cytoplasm.
the inspection of the colon mucosa on insertion using either standard or high-definition WLE. This allows a good evaluation of the level of disease activity, lavage and suction of excess fluid from the colon, and the identification of gross abnormalities that can be sampled or removed upon withdrawal. A solution of 5 or 10% N-acetyl cysteine may be sprayed during the introduction of the scope in order to wash off the mucus layer and allow a superior staining of glandular crypts and an improved visualization of subtle abnormalities. Once in the cecum, the stain is sprayed on withdrawal, either using the water-jet device provided with the scope or a dedicated spray (continued on page 21)
catheter introduced through the operative channel.\textsuperscript{24} The water-jet device is faster and less messy but uses a larger volume of dye compared to the spray catheters (average 250 mL). A disadvantage of spray-catheters is that they have to be removed and reintroduced each time a lesion that requires an intervention is discovered thus increasing the down-time during the procedure. In our center, we prefer sequential segmental staining of the colonic mucosa after the excess fluid was adequately removed. An excellent quality of the prep is paramount and the use of anti-motility agents is optional. Most experts recommend against the use of random biopsies in patients with adequate mucosal healing.\textsuperscript{27} When significant inflammation or distortion of the lumen (including strictures) is present, or in patients with PSC, random biopsies should still be considered.

**Diagnostic Yield of Chromoendoscopy**

Regardless of the agents utilized, CE increases the yield of dysplasia by 2-5 fold per procedure compared to standard or HD WLE (Table 1). The per patient incremental yield for dysplasia with CE and targeted biopsies vs. WLE with random biopsies is approximately 7% with a number needed to test of 14. Conversely, the odds ratio for missed lesions with CE compared with WLE is 0.07.\textsuperscript{26} Although no head to head studies are available, data suggests that indigo carmine and methylene blue produce equivalent results.\textsuperscript{28} Using decision-analytic models, CE was found to be both more effective and less costly compared with WLE regardless of the surveillance interval.\textsuperscript{29} Given the consistent superiority of CE for neoplasia detection, some professional societies such as the British Society of Gastroenterology and the European Crohn’s and Colitis Organization have endorsed CE with targeted biopsies as the preferred surveillance method in patients with UC and Crohn’s colitis.\textsuperscript{30}

Despite its obvious advantages, there has been a relatively slow uptake of chromoendoscopy in gastroenterology practices in the United States. Among the shortcomings, the most frequently cited are lack of basic knowledge and expertise, lack of opportunities for training during or after fellowship, a relatively slow and steep learning curve, variation in detection and resection skills, additional equipment requirements, the need for additional time for lengthy procedures and lack of specific procedure codes for reimbursement. The increased procedure time associated with CE – average 10 minutes - may be offset in part by obviating the need for random biopsies. In addition, some IBD thought leaders have questioned the significance of the incremental yield of CE for neoplasia as prospective outcomes studies evaluating the utility of CE for colon cancer prevention have not been performed. This seems somewhat counterintuitive as a very similar outcome, the adenoma detection rate, is widely considered a quality indicator of the adequacy of screening colonoscopy in the general population.\textsuperscript{31} Furthermore, there is ample indirect evidence of the benefit of CE from one of the largest and oldest UC surveillance programs in the world. A recent 40 year retrospective review of the data from the St Mark’s Hospital in the UK has shown that, although the rate of colectomy for dysplasia has decreased during the era of chromoendoscopy, the number of cases of interval cancer and advanced

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Design</th>
<th>Control</th>
<th>NBI yield</th>
<th>Control yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekker ‘07\textsuperscript{44}</td>
<td>42</td>
<td>Tandem</td>
<td>WLE</td>
<td>8/11 (73%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Van den Broek ‘11\textsuperscript{45}</td>
<td>48</td>
<td>Tandem</td>
<td>WLE</td>
<td>8/11 (73%)</td>
<td>9/11 (72%)</td>
</tr>
<tr>
<td>Pellise ‘11\textsuperscript{46}</td>
<td>60</td>
<td>Tandem</td>
<td>CE</td>
<td>7/13 (53.8%)</td>
<td>11/13 (84.6%)</td>
</tr>
<tr>
<td>Ignatovic ‘12\textsuperscript{47}</td>
<td>112</td>
<td>Randomized</td>
<td>WLE</td>
<td>5/56 (9%)</td>
<td>5/56 (9%)</td>
</tr>
<tr>
<td>Efthymiou ‘13\textsuperscript{48}</td>
<td>44</td>
<td>Tandem</td>
<td>CE</td>
<td>10/44 (22.7%)</td>
<td>11/44 (25%)</td>
</tr>
</tbody>
</table>

NBI = narrow-band imaging; WLE = white light endoscopy; CE = chromoendoscopy
Furthermore, the negative predictive value of CE seems to be substantially higher compared with WLE; patients diagnosed with high-grade dysplasia or cancer during surveillance were twice as likely to have had a previous normal white light colonoscopy than a normal chromoendoscopy.\textsuperscript{32} Taken together, this data suggests

\begin{figure}[h]
\centering
\includegraphics[width=0.45\textwidth]{figure5.jpg}
\caption{Non-polypoid, flat, hyperplastic lesion detected in the descending colon of a patient with long-standing UC after indigo carmine chromoendoscopy.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.45\textwidth]{figure6.jpg}
\caption{Close-up chromoendoscopic view of hyperplastic lesion in Figure 2 showing larger, longitudinal and stellate crypts (modified Kudo pit pattern 2). In IBD patients this pattern can be easily confused with the type 3L pattern seen in patients with dysplastic lesions.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.45\textwidth]{figure7.jpg}
\caption{Multiple hyperplastic flat polyps or plaques can be often seen at chromoendoscopy in patients with UC in deep remission usually in the left colon and have no clinical significance.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.45\textwidth]{figure8.jpg}
\caption{Resectable polypoid sessile serrated lesion detected in the proximal ascending colon of a patient with Crohn’s colitis after indigo carmine chromoendoscopy.}
\end{figure}

(Duke’s stage C and D) colon cancer diagnosed during surveillance has also decreased.\textsuperscript{32} This implies that more patients with ulcerative colitis who are diagnosed with dysplasia at surveillance colonoscopy are able to preserve their colon after the dysplastic lesions are removed, without the risk of dying from colon cancer.
that CE may be more effective at reducing the cancer risk compared with WLE. Obviously this is heavily dependent on the success of removing neoplastic lesions as they are identified.

**Narrow Band Imaging for IBD Surveillance**

Narrow-band imaging (NBI) available on the Olympus endoscopy system utilizes an electronically activated filter placed in front of the light source which allows only limited wavelengths of 415 nm and 540 nm (narrow band) of the white light spectrum to reach the mucosa. The blue-green light has a lower depth of penetration in the colon tissue and coincides with the optimal absorption wavelengths of hemoglobin. This makes blood vessels in the lamina propria appear darker against the white background of the mucosa and superficial submucosa. Angiogenesis and abnormal capillary patterns have long been associated with neoplasia and thus NBI is considered superior to WLE for differentiating between neoplastic and hyperplastic polyps. However, what may be an advantage in a healthy colon can become a limitation when evaluating mucosa in patients with colitis as the vascular pattern is diffusely distorted due to chronic inflammation. In addition, the pit pattern with NBI is not as neatly seen as with chromoendoscopy. NBI has been evaluated for IBD neoplasia surveillance in a few studies and was found not to be superior to high-definition WLE and was inferior to CE for detecting neoplasia in patients with chronic colitis (Table 2). The obvious advantage of all forms of “electronic chromoendoscopy” is that they are extremely accessible and easy to use; however their potential application in IBD surveillance is unclear.

**The SCENIC Consensus Statement**

As of 2010, the American Gastroenterology Table 3. Summary of recommendations for surveillance and management of dysplasia in patients with inflammatory bowel disease (from the SCENIC consensus panel).

**Detection of dysplasia on surveillance colonoscopy**

1. When performing surveillance with white light colonoscopy, high definition is recommended rather than standard definition (strong recommendation, low-quality evidence).
2. When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy (strong-recommendation, moderate-quality evidence).
3. When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy (conditional recommendation, low-quality evidence).
4. When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, low-quality evidence).
5. When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy (conditional recommendation, moderate-quality evidence).
6. When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy (conditional recommendation, moderate-quality evidence).

**Management of dysplasia discovered on surveillance colonoscopy**

1. After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy (strong recommendation, very-low quality evidence).
2. After complete removal of endoscopically resectable non-polypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy (conditional recommendation, very-low quality evidence).
3. For patients with endoscopically visible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy (conditional recommendation, very-low quality evidence).

*adapted from Laine et al. – Gastroenterology ’15.
Association has endorsed colonoscopy with multiple random biopsies as the standard method for dysplasia detection in IBD based on the available evidence at that time. However, major advances in this field in the last decade have resulted in a significant variation in guideline recommendations among different gastroenterological societies throughout the world. In 2015, an international multi-disciplinary panel of experts was convened with the goal of developing unifying consensus guidelines for the diagnosis and management of dysplasia in patients with IBD. This process was based on an extensive critical review of the literature, used Institute of Medicine standards of guideline development and incorporated the GRADE methodology. In order to standardize reporting for both clinical practice and research purposes, the panel recommended abandoning the confusing terms of DALM (dysplasia-associated lesion or mass) and ALM (adenoma-like mass) in favor of ‘endoscopically

(continued on page 26)
resectable’ or ‘non-resectable’ and ‘polypoid’ or ‘non-polypoid’ lesions. The defining elements of the appearance and resectability of a lesion are diameter, height, symmetry and appearance of the margins, along with endoscopic and histologic evidence of successful removal. Needless to say, these features are therefore, to some extent subjective and operator-dependent. The other recommendations of the SCENIC consensus panel regarding the detection and management of dysplasia in IBD are listed in Table 3. Overall, the SCENIC panel has endorsed chromoendoscopy and high-definition imaging as superior methods for neoplasia detection in IBD; however the panel stopped short of relinquishing the need for random biopsies. The SCENIC authors acknowledge the controversy surrounding this issue as well as the technological and logistic hurdles for adopting chromoendoscopy as the standard surveillance method. Nevertheless, these guidelines represent a big first step in the right direction which will undoubtedly create the foundation for further research in this field.

CONCLUSION

In conclusion, despite its rather modest contributions in routine screening colonoscopy, CE is an endoscopic technique with fairly obvious advantages for dysplasia detection in patients with inflammatory bowel disease at high risk for neoplasia. There is a mounting level of evidence supporting its superior performance for surveillance in patients with chronic colitis. Over time, additional studies will likely strengthen the evidence on improved outcomes for dysplasia diagnosis and management and ultimately, survival from colon cancer and improvement in the quality of life in patients with IBD. While easier to use and more accessible than dye-based chromoendoscopy, electronic chromoendoscopy such as narrow band imaging has an as yet undefined role in colorectal neoplasia surveillance in IBD.

References