Evolving endoscopic strategies for detection and treatment of neoplastic lesions in inflammatory bowel disease CME

Sanjay K. Murthy, MD, MSc, FRCP(C),[1] Ralf Kiesslich, MD, PhD[2]

Toronto, Ontario, Canada; Mainz, Germany

Colorectal cancer (CRC) is a serious potential complication of inflammatory bowel disease (IBD). Regular surveillance colonoscopy to diagnose early neoplasia is currently the main approach to CRC prevention in IBD. Traditional surveillance recommendations advocate obtaining interval random biopsy specimens throughout the colon because IBD patients have a propensity toward the development of flat and subtle neoplasms that may evade detection and rapidly progress to advanced CRC. Total proctocolectomy is further recommended for the treatment of advanced precancerous lesions in IBD, including a dysplasia-associated lesion or mass (DALM) and high-grade intraepithelial neoplasia (HG-IEN). However, newer endoscopic technologies, including high-definition endoscopy, chromoendoscopy, narrow-band imaging (NBI), and confocal laser endomicroscopy, have significantly improved the detection and characterization of neoplastic lesions and have the potential to alter the surveillance paradigm in IBD in favor of targeted neoplasia detection with endoscopic resection of even advanced precancerous lesions. In this article, we review the historical evidence base for current concepts in neoplasia surveillance among IBD patients and present newer evidence that may support the need for a change in the current paradigm of neoplasia detection and management in this patient population.

TRADITIONAL CONCEPTS FOR NEOPLASIA DEVELOPMENT AND STRATEGIES FOR SURVEILLANCE IN IBD

CRC is among the most dreaded complications of IBD, accounting for 15% of IBD-related deaths.[1] Ulcerative colitis (UC) patients have a 7% to 30% risk of the development of CRC over 30 to 40 years from the time of diagnosis and a 2- to 6-fold higher lifetime incidence of CRC compared with age-matched non-IBD patients.[2-5] Patients with colonic Crohn's disease also have a 4- to 18-fold higher risk of CRC compared with non-IBD patients.[6,7] CRC risk increases significantly after 8 to 10 years of disease in UC patients and is probably similar in Crohn's disease patients.[3,4] Established risk factors for CRC in IBD patients include longer disease duration,[3-5] pancolitis,[4] greater disease severity,[8,9] younger age at diagnosis,[4] family history of CRC,[10,11] primary sclerosing cholangitis (PSC),[12] and lower use of 5-aminosalicylates.[13,14] Notably, not all studies have demonstrated a higher risk of CRC among IBD patients, which may relate to differences in patient follow-up and study methodology.[15-17]

In an effort to promote early neoplasia detection, multiple societies have advocated that patients undergo annual or biennial colonoscopy after 8 years of colonic IBD.[18-20] Recommendations for optimizing neoplasia detection during these examinations include obtaining targeted biopsy samples of visible lesions as well as 33 or more random biopsy samples at regular intervals throughout the colon,[21] based on a study demonstrating that this approach has 90% sensitivity for detecting colorectal neoplasia in IBD patients.[22] Further underpinning these guidelines are studies demonstrating widespread clonal genetic changes within colitic epithelium in IBD patients (termed *field carcinogenesis*), which have caused many to speculate that these patients have a propensity toward the development of multifocal flat and subtle neoplastic lesions that may go undetected and rapidly progress to invasive CRC.[22-27] Recently, pancolonic chromoendoscopy with targeted biopsies of suspicious lesions has been accepted as an alternative surveillance strategy for endoscopists experienced in the use of chromoendoscopy, based on studies demonstrating improved neoplasia detection rates with this technique.[18,19,28-31]

A considerable amount of ambiguity exists in the nomenclature for neoplastic lesions in IBD. Neoplasia occurring within a field of colitic mucosa has traditionally been referred to as "colitis-associated dysplasia," based on characteristic histologic features that distinguish it from a sporadic adenoma.[32] Nevertheless, colitis-associated dysplasia

Abbreviations:: ALM, adenoma-like mass; CRC, colorectal cancer; DALM, dysplasia-associated lesion or mass; HG-IEN, high-grade intraepithelial neoplasia; IBD, inflammatory bowel disease; IEN, intraepithelial neoplasia; LG-IEN, low-grade intraepithelial neoplasia; NBI, narrow-band imaging; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

DISCLOSURE: *The following author disclosed a financial relationship relevant to this publication: Dr Kiesslich holds an unrestricted research grant from Pentax Europe. The other author disclosed no financial relationships relevant to this publication.*

See CME section; p. 491.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2012.11.030

progresses through a series of characteristic low-grade and high-grade neoplastic changes en route to developing into carcinomas, as is observed with sporadic adenomas. Moreover, bona fide adenomas do occur within colitic mucosa in IBD patients and some neoplastic lesions demonstrate mixed features of adenoma and colitis-assiociated dysplasia. Furthemore, it is unknown whether the natural history of these two types of lesions differ. In an effort to avoid this ambiguity in terminology, the term *intraepithelial neoplasia* (IEN) has been suggested as an alternate term to describe all neoplastic lesions arising in IBD patients. Histologic grading of neoplastic lesions in this system follows the Vienna classification of GI neoplasms, based on the following definitions: (1) negative for neoplasia, (2) indefinite for neoplasia, (3) noninvasive low-grade neoplasia, (4) noninvasive high-grade neoplasia, and (5) invasive neoplasia.[33]

Neoplasia also develops as a heterogeneous group of lesions in IBD patients that includes both flat and raised lesions. The term *flat dysplasia* has generally been ascribed to dysplastic foci arising within flat colitic mucosa in random biopsy specimens. Visibly raised neoplastic lesions also often display relatively flat morphology in IBD patients, frequently developing as irregular ill-defined neoplasms, ulcerated lesions, or laterally spreading tumors. The term *dysplasia-associated lesion or mass* (DALM) was originally coined to describe any raised neoplastic lesion in IBD patients.[34] More recently, a neoplastic lesion having the appearance of a sessile or pedunculated adenoma with well-defined borders has been termed an adenoma-like DALM or an adenoma-like mass (ALM), to distinguish it from a "non-adenoma-like DALM," which has come to reflect a highly irregular neoplastic lesion not bearing any resemblance to a typical sporadic adenoma, or else a visible neoplastic lesion with dysplasia in surrounding flat mucosa. Overall, this distinction is highly subjective and its significance is uncertain, because the most important characteristic of a neoplastic lesion that influences management is its endoscopic resectability. Adding to the confusion, this terminology, while inherently histologic in nature, is actually based on endoscopic characteristics of neoplastic lesions. This ambiguity in terminology may further contribute to the variability in physicians' understanding of the implications and appropriate management of raised lesions in IBD patients.[35,36] Future classification of such lesions based on endoscopic resectability may be a more useful strategy.

Current guidelines recommend total proctocolectomy (colectomy) for IBD patients with invasive carcinoma, high-grade IEN (HG-IEN) in flat mucosa or a nonadenoma-like DALM.[19,20] These recommendations are supported by studies that have reported a 40% to 70% rate of synchronous CRCs (in colectomy specimens) and a 25% to 30% risk of metachronous CRCs among UC patients with a diagnosis of HG-IEN in flat mucosa, as well as a 42% to 45% risk of synchronous CRC among UC patients who are have a diagnosis of a DALM.[5,37-40] Flat low-grade IEN (LG-IEN) has also been associated with a 20% to 25% rate of synchronous CRC,[5,37,41,42] although the reported rate of metachronous HG-IEN or invasive cancer has varied considerably.[37,41-46] A meta-analysis of 20 studies reported a pooled CRC risk of 14 per 1000 person-years among UC patients with LG-IEN, corresponding to a 9-fold increased risk relative to IBD patients without IEN.[42] Therefore, most guidelines recommend colectomy if LG-IEN is found in random biopsy specimens, particularly in the setting of multifocal or metachronous LG-IEN because future detection of such lesions before progression to advanced CRC cannot be ensured.[18-20] However, close endoscopic surveillance has been suggested as an alternative approach for the management of unifocal flat LG-IEN.[18-20]

It is also now generally accepted that patients who undergo complete resection of ALMs with low-grade neoplastic changes do not require colectomy,[18-20] based on the findings of several studies that such patients are not at increased risk of the development of CRC.[47-51] However, evolving areas of uncertainty include whether clearly delineated DALMs and lesions harboring HG-IEN that are potentially amenable to complete endoscopic resection should be treated endoscopically or surgically. One study evaluated 9 IBD patients with HG-IEN within resected lesions; 3 patients who underwent colectomy did not have synchronous CRCs and in 6 patients who continued under endoscopic surveillance metachronous CRCs did not develop over a 6-year median follow-up period.[45] Nevertheless, endoscopic management in such patients should be carefully considered on a case-by-case basis, and, at a minimum, these patients should have aggressive follow-up surveillance.

LIMITATIONS OF INTERVAL RANDOM BIOPSIES FOR NEOPLASIA DETECTION IN IBD

There are a number of shortcomings to using interval random biopsies as a surveillance strategy for diagnosing IEN in IBD. First, there is no compelling evidence that this approach decreases the risk of CRC or CRC-related mortality. In addition to the absence of randomized, controlled data, a Cochrane systematic review of 3 observational studies found no clear evidence that endoscopic surveillance improves survival among UC patients.[52] Notably, 2 studies reported increased survival associated with detection of CRC at an early stage in this setting; however, it is unclear to what extent lead-time bias influenced these results.[53,54]

In addition, in a significant proportion of IBD patients, CRC continues to develop despite traditional endoscopic surveillance. Among 600 UC patients enrolled in an endoscopic surveillance program over a 30-year period at St. Mark's Hospital, the cumulative risk of CRC was 10.8%, with more than half of the diagnosed cancers being inter-