Management of Low-Grade Dysplasia in Ulcerative Colitis

by Titus Thomas and Richard J. Robinson

The management of low-grade dysplasia (LGD) in chronic ulcerative colitis remains highly contentious. The treatment options have conventionally been either immediate colectomy or continued intensive surveillance. There are many factors that contribute to the uncertainty surrounding the management of these lesions. Conventional endoscopic surveillance and biopsy protocols are disappointing and the identification of LGD remains challenging. Additionally, it is very difficult to endoscopically distinguish dysplasia-associated lesions or masses (DALM) from the less important sporadic adenomas in patients with chronic colitis. The variable and uncertain natural history of low-grade dysplasia in colitis coupled with significant inter-observer variability in histological interpretation of the lesion even among expert pathologists adds to the confusion. Should patients with LGD be managed conservatively with intensive surveillance, endoscopic polypectomy or mucosal resection, or do all patients require early colectomy? This article will explore some of the arguments regarding the management of these highly controversial lesions in patients with chronic ulcerative colitis.

INTRODUCTION

It is widely accepted that chronic inflammatory bowel disease increases the risk of colorectal cancer, with the risk being proportional to the extent and the duration of colitis (1). The principle behind colonoscopic surveillance in chronic colitis is to detect and remove early malignant lesions thereby preventing the progression to colorectal cancer. Prior to developing cancer the disease usually but not always progresses through stages of inflammation with no dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD) and eventually adenocarcinoma. The natural history of such disease progression is highly variable. LGD has been shown to progress to colonic cancer without the intermediate stage of HGD and therefore can be considered as a stage in the disease where a curative intervention such as prophylactic colectomy could be considered (2). However the optimum management of this lesion has been marred by controversies with enthusiasts advocating colectomy while skeptics recommending continued intensive surveillance.

Although the term dysplasia by definition “is an area of unequivocal epithelial neoplasia” many surveys have shown that gastroenterologists still consider them to be pre-malignant lesions (3). The adoption of any particular approach to management may be influenced by this inaccurate perception and understanding of the disease. The management conundrum is multi-factorial:

1. Variable and uncertain natural history of the disease
2. Difficulty in histological interpretation during the active phase of colitis
3. Wide inter-observer variability in the histological diagnosis of low-grade dysplasia (LGD) even among expert pathologists

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Furthermore it is important to differentiate adenoma like mass (ALM) with less carcinogenic potential that can be safely treated by endoscopic polypectomy from dysplasia associated lesion or mass (DALM) which conventionally has been considered a sentinel lesion warranting colectomy because of its significantly increased cancer risk. A survey of British gastroenterologists has shown that we are uniformly poor at distinguishing these lesions endoscopically (4), although colonoscopic techniques of detecting dysplasia have recently improved. Targeted biopsies following dye spraying (chromendoscopy) and high magnification colonoscopy are superior to conventional colonoscopy in detecting dysplasia and neoplasia (5). A randomized controlled trial comparing immediate colectomy at LGD diagnosis versus continued surveillance to compare outcomes in terms of colorectal cancer related deaths and quality of life has overwhelming ethical and practical barriers (6). Such a study is not likely to be performed. Our recently published meta-analysis points out the high cancer incidence and the significantly increased risk of progression to cancer or an advanced lesion when LGD is diagnosed endoscopically. Published guidelines by both British and American Gastroenterological Societies have valiantly attempted to address these problems but failed to answer them due to a lack of agreed consensus (7,8).

Prior to considering the management of LGD it is vitally important to point out the difficulties in diagnosing these lesions histologically. Histological diagnosis of dysplasia is based on the 1983 IBD Morphological Study group diagnostic criteria (9). Failure to redefine LGD diagnosed prior to 1983 based on the new criteria has significant implications in terms of the perceived carcinogenic potential of these lesions. For example if 50 patients were diagnosed as having LGD prior to 1983 in a particular center of which 10 progressed to cancer in five years the five-year risk of developing cancer would be 20%. However, if these 50 patients were reclassified and only 20 of them were confirmed as having LGD based on the new criteria and 10 patients progressed to cancer over five years the five-year risk of progression would be 50% rather than 20%. As is evident from the above example reclassification of these lesions has a significant impact on their perceived carcinogenic potential of LGD. This in turn may have a significant influence on management decisions (surgical vs. conservative). The difference in risk has been elegantly demonstrated in the St’ Marks study. In this study when biopsies of LGD were retrospectively re-examined by two GI pathologists blinded to the initial diagnosis, the number of patients with LGD decreased from 51 to nine, thereby increasing the five-year rate of progression of LGD from 16% to 54% (10). In a prospective follow-up study of LGD by Lim, et al, histological slides showing low-grade dysplasia were sent to five gastrointestinal pathologists for re-coding. A consensus diagnosis (agreement of three out of five pathologists) of LGD was reached in only 38% of the cases demonstrating the poor agreement between pathologists in diagnosing these lesions (11). The difficulty is in differentiating LGD from regenerative epithelium. Therefore, prior to considering a treatment strategy it is first important to establish the diagnosis firmly with an agreement by at least two specialist gastrointestinal pathologists. Secondly, one needs to clearly differentiate between flat LGD, LGD in the presence of dysplasia-associated lesion or mass (DALM) and LGD in adenoma like mass because the malignant potential of each of these lesions differ from one another. This differentiation has a crucial bearing on the treatment options.

Flat LGD refers to an area of dysplasia in endoscopically normal looking colonic mucosa. DALM’s are visible at colonoscopy and can be macroscopically polypoidal, flat or depressed lesions with dysplasia on biopsies and areas of dysplasia in the mucosa surrounding it. In contrast, adenoma like mass (ALM) are macroscopically polypoidal lesions with dysplasia in the presence of histologically normal mucosa surrounding it. Differentiation of these lesions to a large extent depends on the operators’ technical ability. Flat LGD is usually an incidental finding on surveillance. It can be difficult to endoscopically differentiate DALM from ALM. However, this differentiation is vital as treatment strategies differ as mentioned above. A clear and agreed consensus and robust criteria, which can be uniformly applied for gastroenterologists to distinguish ALM’s from DALMs, is wanting.

**MANAGEMENT OF FLAT LOW-GRADE DYSPLASIA**

Endoscopically “flat” LGD, i.e., with no lesion or mass is the most contentious area of management. The main
area of disagreement results from the conflicting data regarding the risk of harbouring synchronous cancer when flat LGD is found on surveillance, and the subsequent risk of progression to high-grade dysplasia or cancer. The traditional concept that progression of LGD to cancer follows a defined sequence with the intermediate stage of high-grade dysplasia has been challenged by a recent retrospective study of 46 patients with LGD by Ullman, et al (2). In his study, seven of the 46 patients with LGD on surveillance had colorectal cancer or high-grade dysplasia when colectomized. Four of the seven patients progressed directly from low-grade dysplasia to cancer without the intervening stage of high-grade dysplasia. Based on these findings, Ullman and his team advocated early colectomy when flat LGD is found on surveillance. The failure to subject the biopsy specimens to a blinded retrospective re-evaluation by two pathologists has been pointed out as a drawback of the study. Several other studies have reported very different results. Befritis and his colleagues followed up 60 patients with flat LGD for a mean duration of 10 years (12). No patients in this cohort developed HGD or cancer, (2/60 developed DALM). Similarly Lim, et al showed no significant difference in the proportion of patients with LGD progressing to cancer or HGD compared to a control group of patients with ulcerative colitis and no dysplasia. In a recent study by Tine, et al, 75% (6/8) of patients with flat LGD did not progress to cancer or high-grade dysplasia at a median follow-up of 17.8 years (13). In our meta-analysis, the positive predictive value of flat LGD for concurrent cancer and progression to cancer was 22% and 15% respectively and we found a nine-fold increased risk of developing cancer once these lesions are detected (14). These figures are vitally important when discussing management options with patients.

Successful identification of flat LGD or depressed lesions during surveillance colonoscopy depends on a number of factors including the number of surveillance biopsies taken, the operators’ ability to detect dysplasia and the use of advanced endoscopic techniques such as chromoendoscopy and magnification. In order to minimize the risk of sampling error, thirty three surveillance biopsies are needed to detect dysplasia or cancer with 90% confidence using conventional colonoscopic techniques (15). However, only 2%–3% of gastroenterologists adhere to these recommendations (4). Studies have shown that surveillance with targeted biopsies using dye spraying and/or magnification colonoscopy is superior to conventional colonoscopy (5). Magnification colonoscopy with dye spraying enhances the structural details of the mucosa. Dysplasia can be identified by mucosal redness and characteristic pit patterns of the affected mucosa. Rutter and his colleagues highlight this in a landmark study where 29 lesions were detected from 1,200-targeted biopsies compared to no lesions from 2,900 non-targeted biopsies (5).

Keeping the above factors in mind the management options for flat LGD are limited to either early colectomy or continued intensive surveillance every three- to-six months. Since there is no reliable data on variables that can discriminate which patients with flat LGD will progress to cancer, treatment of these lesions vary between centers and largely rests on physician and patient choice. Factors to consider include: age of the patient, co-morbidity, duration of colitis, activity and severity of underlying inflammation and the quality of life. It is essential to include the patient in an open and frank discussion of the options. When flat LGD is found on routine surveillance (presuming the recommendation of 32 biopsies per surveillance colonoscopy has been followed to minimize the effect of sampling bias) the diagnosis should be first confirmed by a second gastrointestinal pathologist. Colonoscopy should then be repeated at three months after maximal doses of 5-aminosalicylates to suppress any underlying inflammation to aid the histological diagnosis of LGD and reduce inter-observer variation. Targeted biopsies following indigo-carmine dye spraying or a combination of dye spraying and high magnification colonoscopy should be carried at three months to increase the chances of identifying flat LGD. Patients with persistent LGD should be counseled about the frequency of synchronous cancer and the risk of progression to cancer. These synchronous cancers may be at an incurable stage on subsequent follow-up. The possibility of missing cancers with a conservative approach especially in patients with flat LGD cannot be over emphasized and needs to be explained to patients. This has been highlighted in the Ullman, et al study where 4/17 patients (23%) with flat LGD who had not progressed to an advanced lesion on surveillance had advanced neopla-
sia at colectomy. Therefore, these patients should be offered an early colectomy. In patients who decline colectomy intensive surveillance ideally using dye-spraying and targeted biopsies should be carried out every three-to-six months.

MANAGEMENT OF LGD IN RAISED LESIONS (ALM AND DALM)

Before discussing the management of LGD in raised lesions it is important to explain the type of endoscopic lesions and their definitions. Essentially raised lesions in colitis could either be DALM’s or ALM’s. Dysplasia associated lesion or mass could be polypoidal (adenoma like) or non-polypoidal (non-adenoma like). Polypoidal DALM endoscopically and histologically resembles sporadic adenomas. Non-polypoidal DALM’s are sessile, broad-based, flat, depressed or constricting lesions. ALM’s are well circumscribed sessile or polypoidal lesions found within or outside areas of established ulcerative colitis where there is no histological evidence of dysplasia in the surrounding flat mucosa. As mentioned previously, the absence of dysplasia in the surrounding mucosa differentiates ALM’s from DALM’s.

The ALM lesions can be successfully removed by colonoscopic polypectomy with studies suggesting no subsequent risk of developing cancer or dysplasia on long-term follow-up (15,16). Therefore, the treatment strategy is similar to that of sporadic adenomas found in patients without colitis. However, results of these long-term studies are influenced by the experience of endoscopists in defining and distinguishing ALM’s from DALM’s and care needs to be exercised when extrapolating results to general gastroenterological practice. In a retrospective study by Rubin, et al, 70 polyps were endoscopically resected in 48 patients with a mean colitis duration of 25.4 years. No cancers or dysplasia was found at a mean follow-up of 4.1 years although additional polyps were seen in 48% on subsequent colonoscopies (15). In addition, Hurstone, et al has shown that flat dysplastic ALM’s in chronic ulcerative colitis can also be safely removed with endoscopic mucosal resection (16). Therefore, both polypoidal and flat ALM’s can be successfully resected endoscopically without the long-term risk of progression to cancer or dysplasia.

DALMS were first described in a seminal paper in 1981 by Blackstone and his colleagues. Seven of the 12 DALM’s (58%) identified in a cohort of 112 patients with chronic ulcerative colitis harbored cancer at resection in contrast to one cancer in 27 patients with flat LGD (17). Based on these findings it has become standard practice to recommend colectomy when these lesions are found on surveillance. These lesions are not a common finding during surveillance. Only 31 DALM’s were found in more than 2,677 patients on surveillance in our meta-analysis (1 DALM in every 86 patients with chronic ulcerative colitis on surveillance) (14). As mentioned earlier, DALM’s can be adenoma like or non-adenoma like. Adenoma like DALM’s can be removed by endoscopic polypectomy similar to the

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approach adopted for ALM’s as they pursue a relatively benign course (18). Younger age, family history of colorectal cancer and presence of primary sclerosing cholangitis are additional risk factors for development of cancer and colectomy should be recommended for adenoma-like DALM’s if these factors are present. The presence of cancer in a resected DALM should be considered an indication for colectomy. Patients with colitis associated DALM’s had longer duration of disease and a higher proportion of polyps with tubulovillous or villous architecture compared to patients with sporadic adenomas (19). Despite these findings, there is no agreement that these features are specific to DALM’s. The use of molecular markers to distinguish these lesions is shown to be useful but still remains experimental (REF). Non-adenoma like DALM’s on the other hand are harbingers of cancer and pursues a more aggressive course. Our meta-analysis showed that 41% (7/17) of DALM’s have synchronous cancer and 64% (9/14) progress to high-grade dysplasia or cancer. A similar series by Bernstein, et al showed DALM’s were associated with cancer in 43% of cases (20). The aggressive nature of non-adenoma like DALM’s warrants a colectomy. The flowchart (Figure 1) summarizes the management approach when LGD is found on surveillance in patients with chronic ulcerative colitis.

To conclude, the management of LGD dysplasia is complex and controversial. One has to balance the cancer risk when these lesions are found on surveillance against the limitations of conventional surveillance and the fact that panproctocolectomy completely eliminates such risk when deciding management strategies in these patients. The complexity of management warrants a multidisciplinary approach. The treatment choice rests on several factors but is eventually made by patients based on the information we provide and this should be a well-informed one. Based on current evidence, a uniform treatment algorithm for flat LGD is arguable. An aggressive approach to these lesions may be guided by individual experiences in tertiary referral centers. Whether the results of such centers can be applied to a wider community is debatable. Adenoma-like DALM lesions seem to follow a benign course and endoscopic polypectomy may be an alternative to colectomy where as non-adenoma like DALM’s should be colectomized. Clinically applicable predictive variables that can distinguish patients with LGD who can be treated conservatively are eagerly awaited.

References