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Surveillance of Dysplasia in Inflammatory Bowel Disease: The Gastroenterologist-Pathologist Partnership

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Abstract

Cancer prevention in inflammatory bowel disease depends on the detection of precancerous dysplasia during scheduled screening and surveillance colonoscopy, but the detection and diagnosis of dysplasia remains challenging. In this article, we review the risks of cancer and dysplasia in ulcerative colitis, the current prevention recommendations and, through a sample case, demonstrate an approach that involves an active partnership between the gastroenterologist or surgeon and pathologist. We address the challenge of management of polypoid lesions and incorporate new information about degree of inflammation as an additional risk of neoplasia in these patients.

Keywords

ulcerative colitis; surveillance; dysplasia; colorectal cancer

Case Presentation

A 45 year-old man with left-sided ulcerative colitis diagnosed at age 21 is seen in your office as a new patient and inquires about colorectal cancer prevention. He has undergone periodic surveillance colonoscopy since he was in his early 30s and his last examination was performed 2 years ago and revealed no dysplasia. After discussing current guidelines, you recommend an endoscopic examination with surveillance biopsies. Colonoscopy reveals vascular blunting and minimal touch friability diffusely from the rectum to the hepatic flexure, and an endoscopically normal ascending colon and cecum. This also a 2 cm polypoid lesion with exudate on its surface (Figure 1), but no masses or strictures. You obtain numerous surveillance biopsies throughout the colon and perform snare polypectomy of the polyp, with additional biopsies of the flat mucosa surrounding it. You submit these to the Pathology Department along with a report of the patient's history and these endoscopic findings. Your pathologist calls to report that all of the biopsies show mild active inflammation and architectural distortion, typical of mildly-active chronic ulcerative colitis, and the polyp appears inflammatory in nature (Figure 2). However, there are also two separate biopsies from non-polypoid areas that include low grade dysplasia. A second gastrointestinal pathologist was consulted and concurs with the diagnosis of mulitfocal low grade dysplasia. You inform the patient and recommend proctocolectomy and ileo-pouch anal anastomosis, to which he agrees. The colectomy specimen reveals several

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additional areas of low and high grade dysplasia and a single focus of superficially invasive adenocarcinoma (Figure 2), without vascular or lymphatic invasion or lymph node metastases.

The Risk of Cancer in Inflammatory Bowel Disease

The preceding case illustrates an example of the application of current cancer prevention strategies in ulcerative colitis. The patient with long-standing disease undergoes periodic endoscopic examination with extensive mucosal sampling in which dysplasia is identified. This results in a therapeutic proctocolectomy. This approach has been developed in an attempt to prevent death from colorectal cancer in patients with chronic ulcerative colitis. A similar approach is also employed in Crohn's disease of the colon, where the risk of colorectal cancer is less well-described but appears to be similar to ulcerative colitis [1,2]. In ulcerative colitis, the risk of colorectal cancer is associated with longer duration of disease, greater extent of colonic involvement, presence of primary sclerosing cholangitis, and a family history of colorectal cancer [3]. Younger age at diagnosis has also been suggested as a potential risk factor. Although previous studies suggested that histologic inflammation was not related to dysplasia, several recent studies have suggested that the degree of mucosal inflammatory activity and presence of pseudopolyps may be associated with increased risk of dysplasia [4, 5] Greater understanding of these risk factors has resulted in recommendations for prevention of cancer. The cardinal feature of which is periodic surveillance colonoscopy and biopsies looking for pre-cancerous dysplasia.[6-8] Although pre-cancerous dysplasia has been associated with concurrent or subsequent colorectal cancer, its reliable diagnosis is limited by difficulties in sampling and inconsistencies in biopsy interpretation. We advocate an effective approach to prevention to involve a dynamic partnership and detailed communication between the endoscopist and pathologist. Our recommendations are summarized in Table 1.

Current Guidelines for Cancer Prevention in Ulcerative Colitis

The recommendations for cancer prevention in ulcerative colitis have been based primarily on expert-opinion and consensus rather than rigorous prospective trials. This approach relies on secondary prevention by screening and surveillance colonoscopy and random and targeted sampling of the involved colitic mucosa in search of pre-cancerous dysplasia. It is recommended that a screening examination begin 8 to 10 years after the diagnosis of colitis of any extent that is greater than proctitis. Follow-up examinations should be performed at one to three year intervals, subject to the impression of the managing physician in the context of the overall clinical situation including the combination of identified cancer risk factors for the individual patient and the findings on prior screening and surveillance examinations. Specific risk factors that should be considered are discussed below. One important exception to this approach is the patient with ulcerative colitis and co-existent primary sclerosing cholangitis, in whom screening is advised at the time of diagnosis of primary sclerosing cholangitis and subsequent surveillance recommended annually.[6-8]

Endoscopic Approaches to Surveillance

While regular screening and surveillance colonoscopies are well-accepted as the standard of care in ulcerative colitis and Crohn's colitis, a number of significant challenges remain. These include issues of detection, diagnosis, and interpretation of neoplasia in the setting of active inflammation or within polypoid lesions in the setting of colitis. Although the entire involved colorectum is thought to be at risk for neoplastic transformation in ulcerative colitis patients, the process may often be focal or multifocal. Thus, extensive sampling is necessary; it is estimated that a single biopsy of the colon only represents 0.05% of the total surface area of the colon.[6] Current guidelines for dysplasia surveillance recommend a minimum of 33 biopsies. This number was developed based on a retrospective analysis that showed a 90% positive predictive value after 33 biopsies and a 95% positive predictive value after 56 biopsies.

[9] In practice, there are important considerations to this recommendation. First, it should be recognized that this study made use of jumbo biopsies. Thus, the amount of mucosa sampled using standard biopsy forceps is less and may require additional biopsies for comparable sensitivity. More concerning are the results of a survey that found that U.S. clinicians did not routinely obtain 33 or more biopsies.[10] In addition, a little-discussed practical consideration is the difference between the number of biopsies obtained by the endoscopist and those that are reviewed by the pathologist. This potential discrepancy may be based on institutional practice and policies related to processing of samples, number of biopsies per submitted jar, and the approach by the pathologist. It is important that there be good communication between the endoscopist and pathologist in order to address these issues.

Optimally, multiple specimen jars are used with no more than six biopsies in each jar. In addition, when specimens are processed in pathology each paraffin block should include only as many biopsy fragments as can be accurately embedded. Overcrowding of many biopsies into a single paraffin block has the potential to cause inadequate representation of each tissue fragment on the slides produced. While these approaches have potential limitations based on cost as well as the practical reality that location of identified dysplasia may not change the decision to perform proctocolectomy, the practices of limiting the number of biopsies per jar and block may well improve the positive and negative predictive value of surveillance colonoscopy.

Recently, a retrospective review has suggested that in many cases, foci of colonic neoplasia in ulcerative colitis are visible to the endoscopist as irregular suspicious mucosa, strictures, polypoid lesions or masses in 79% to 89% of cases[11,12]. Therefore, it is important to recognize recognize such lesions, to biopsy these often subtle abnormalities, and to communicate the endoscopic impression of suspicious findings to the pathologist. Ideally, biopsies from these areas are placed in separate specially-designated jars.

Biopsy Diagnosis of Dysplasia in Ulcerative Colitis

Dysplasia has been defined as the morphological correlate of unequivocal neoplastic change. Because early steps of neoplastic progression in ulcerative colitis are thought to occur multi-focally, it is not surprising that dysplasia is associated with an increased risk of concurrent adenocarcinoma as well as the development of subsequent dysplasia or adenocarcinoma. Morphological examination by a skilled gastrointestinal pathologist remains the gold standard for diagnosis of dysplasia; at present there are no molecular assays that are superior to morphology. In such evaluations, inter-observer agreement among experienced gastrointestinal pathologists is generally excellent at the extremes, i.e. cases that are negative for dysplasia and those that include either high grade dysplasia or carcinoma. Unfortunately, inter-observer agreement is poorer in cases with inflammation-associated regenerative changes. These changes tend to confound interpretation with the result that there is relatively poor concordance, even among experienced gastrointesintal pathologists, in cases classified as indefinite for dysplasia and low grade dysplasia. This problem is similar to that which has been well-characterized in grading Barrett's esophagus-associated dysplasia.[13] As a result, diagnoses of dysplasia are routinely reviewed internally by a second gastrointestinal pathologist. In addition, dysplasia diagnoses that directly affect patient management, e.g. decisions regarding colectomy, are discussed in regularly-scheduled multidisciplinary patient management conferences in which endoscopy reports, photos, and pathology are presented.

Does Disease Activity Influence Diagnosis of Dysplasia?

As noted above, the diagnosis of dysplasia can be hindered if biopsies are obtained during periods of active inflammation. In this case, the pathologist may opt to categorize the biopsy as “indefinite for dysplasia”. It is generally recommended that this diagnosis be accompanied

by a qualifier of “favor negative for dysplasia” or “favor positive for dysplasia.” In this case, aggressive medical therapy to reduce active inflammation followed by short-term (3-6 months) repeat surveillance examination is advised. Moreover, the recent reports that degree of inflammatory activity may be independently associated with dysplasia and colorectal cancer in ulcerative colitis suggests that patients with a history of frequent histologically-evident active inflammation may warrant a more intense surveillance program with more frequent examinations. [4,14,15] These data suggest that, although there is no well-accepted standard for histological grading of active inflammation, it may be worthwhile for the gastroenterologist and pathologist to correlate endoscopic and histological impressions of disease activity. Increased understanding of the association of degree of inflammation and neoplasia and the potential chemoprotective effects of aminosalicylates may result in future management algorithms that stratify follow-up examinations.

How should dysplasia be managed?

High grade dysplasia has been associated with concurrent adenocarcinoma in up to 67% of cases, while low grade dysplasia has consistently been associated with concurrent adenocarcinoma in 19-20% of cases, and progression to higher grades of neoplasia in approximately 50% of cases followed over time.[16,17] The predictive value of dysplasia has therefore led to consensus and expert-opinion guidelines that advise proctocolectomy when high grade dysplasia is identified and suggest that it be carefully considered when low grade dysplasia is identified. Despite these recommendations, there remains no prospective study demonstrating a mortality benefit from proctocolectomy,[18] and it is believed that due to ethical and logistical challenges, such a study will not be performed. The natural history of cases diagnosed as “indefinite for dysplasia” is unknown, likely because this group of cases represents a heterogeneous mixture of regenerative and dysplastic lesions. Figure 3 is an adapted algorithm for approaching dysplasia which considers disease activity as a risk factor for dysplasia.

The Approach to Polyps in ulcerative colitis

An additional challenge in the management of ulcerative colitis-related neoplasia is the interpretation and management of polypoid lesions (see Figure 3). It is recognized that some patients develop inflammatory polypoid lesions which themselves do not have cancerous potential, but have been associated with subsequent neoplasia (it is possible that this is because these lesions represent previously foci of severely active inflammation).[5] When discrete polypoid lesions are identified that contain dysplasia, the dilemma is whether this represents a risk for multifocal dysplasia elsewhere in the colon or progression to subsequent higher grades of neoplasia. Such lesions should be resected and biopsies of the flat mucosa placed in a separate jar clearly labeled for the pathologist to review. This practice can help the pathologist and gastroenterologist determine whether the polyp is more likely to be a sporadic adenoma or a polypoid focus of colitis-associated dysplasia. A general guide to this determination is presented in Table 2. It is essential to consider both the natural history of sporadic or hereditary adenomas not associated with colitis as well as the biology of dysplasia in ulcerative colitis. For example, colitis-associated dysplasia is unlikely to be the diagnosis for a polyp with dysplasia located proximal to the field of colitis in a 60 year old patient. Conversely, a polyp with dysplasia in a 25 year old patient with a 12 year history of ulcerative colitis is almost certainly colitis-associated dysplasia; if not, the rare possibility of dysplasia associated with a genetic disease, e.g. hereditary nonpolyposis colorectal cancer, should be considered. Management of colitis-associated polypoid dysplasia remains an area in need of further study, but current data suggest that discrete polyps in a field of colitis without associated dysplasia in flat mucosa can be endoscopically resected and followed, probably with more frequent surveillance examinations.[19,20]

When extensive pseudopolyps are present and it is impossible to adequately resect them all to assess for dysplasia, a discussion about risks of unidentified neoplasia should occur with the patient and prophylactic proctocolectomy be considered both because of inability to adequately survey as well because of the reported risk of subsequent colorectal cancer.

Future Directions in Dysplasia Diagnosis

There are a number of technological developments that may improve the ability to detect and to diagnose dysplasia in ulcerative colitis. This includes chromoendoscopy, magnifying endoscopy,[21] optical coherence tomography ("optical biopsy"), and a variety of proposed tissue or serum biomarkers. Such improvements conceivably increase the accuracy of dysplasia surveillance. At this time, however, these promising tools are experimental and are not substitutes for standard surveillance.

Summary

The risk of colorectal cancer in chronic ulcerative colitis is well described, and prevention strategies have been defined to include periodic colonoscopy and biopsy in search of pre-cancerous dysplasia. There are limitations to the detection and interpretation of dysplasia especially within polypoid lesions. We advocate a dynamic communication between endoscopist and pathologist to more effectively characterize patient risks in our collaborative effort to prevent the development of advanced cancer. As we look into the future, it is also possible that further refinements of *in vivo* imaging may improve our ability to identify suspicious areas endoscopically and guide direct targeted biopsy approaches. The implementation of such approaches will further emphasize the need for effective endoscopist-pathologist communication.

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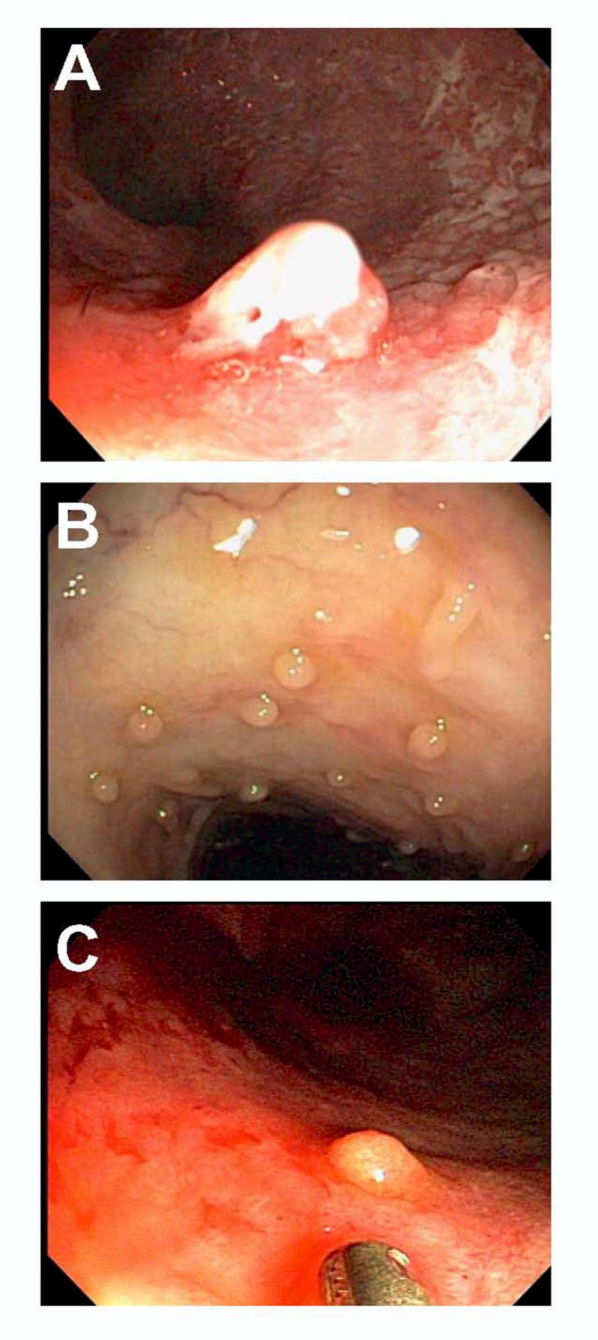

Figure 1.

Examples of polypoid lesions seen in the setting of colitis. A. 2 cm polypoid lesion in the sample case in our patient with endoscopically mildly to moderately active ulcerative colitis. This polypoid lesion demonstrates typical endoscopic features of an “exudative cap” seen in inflammatory polyps. Biopsies of this lesion and the surrounding mucosa placed in a separate, clearly-labeled jar do not show dysplasia and are seen in Figure 2D. B. Multiple smooth glistening polyps seen in the hepatic flexure of a 35 year old woman in symptomatic remission from ulcerative pancolitis. Although these appear diminutive in size and uniform in appearance, the large number of them makes endoscopic resection and sampling of all of them to exclude polypoid dysplasia impractical. In such a case, resection of several as well as careful sampling

of surrounding flat mucosa is advised. In this case, all had features of inflammatory or "pseudo" polyps, and there was no dysplasia in the surrounding flat mucosa. C. 3 mm polypoid lesion in the setting of endoscopically mildly active colitis in a 23 year old man with 12 years of ulcerative pancolitis. This lesion was in the proximal transverse colon. Snare resection revealed features consistent with a low grade dysplasia-associated polypoid lesion, without flat dysplasia identified anywhere else in his colon. Despite the fact that this lesion was endoscopically resectable and without associated flat dysplasia, given the young age of the patient and his long duration of disease, proctocolectomy was advised. The patient refused. So far, in subsequent follow-up exams every 6 months for 18 months, no additional dysplasia was identified.

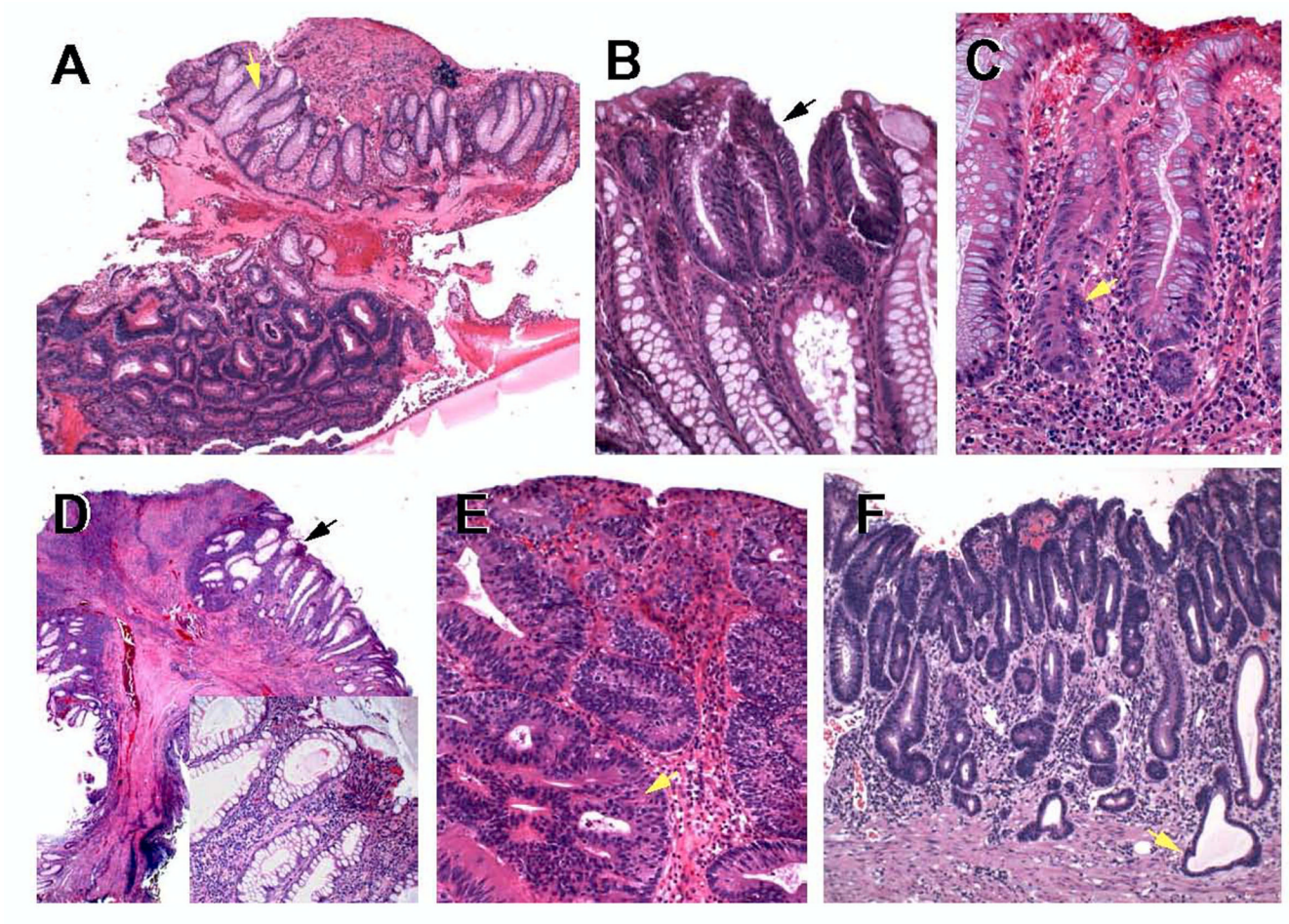

Figure 2.

Histology of representative lesions seen in the setting of colitis. A. One slide from the case presented shows two biopsy fragments. The upper fragment includes obvious architectural features of chronic inflammatory bowel disease, including a branched crypt (arrow), irregular glandular distribution, and a band-like inflammatory infiltrate at the base of the crypts. The lower tissue fragment is obviously hyperchromatic, consistent with low grade dysplasia. B. A higher magnification view of the second focus of dysplasia identified in biopsies from the case presented shows low grade dysplasia (arrow). Note that the hyperchromasia and pseudostratification are present at the surface and involve some glands, but not others. C. A separate focus of active colitis without dysplasia. Note that the hyperchromasia (arrow) is limited to deep proliferative zones, crypt bases, and that cytologic maturation is obvious at the surface. D. A typical inflammatory polyp displays stromal inflammatory infiltrates and reactive epithelial changes (arrow). The inset shows the region indicated by the arrow at higher magnification, confirming the absence of hyperchromasia and other features of dysplasia. E. The resection specimen from the sample case patient included areas of high grade dysplasia, including cribriform (gland-in-gland) architecture (arrow). F. Separate areas in the resection specimen showed superficial invasion of the muscularis mucosa (arrow) beneath low grade dysplasia. Metastasis is extremely rare in colonic adenocarcinoma that does not extend beyond muscularis mucosa.

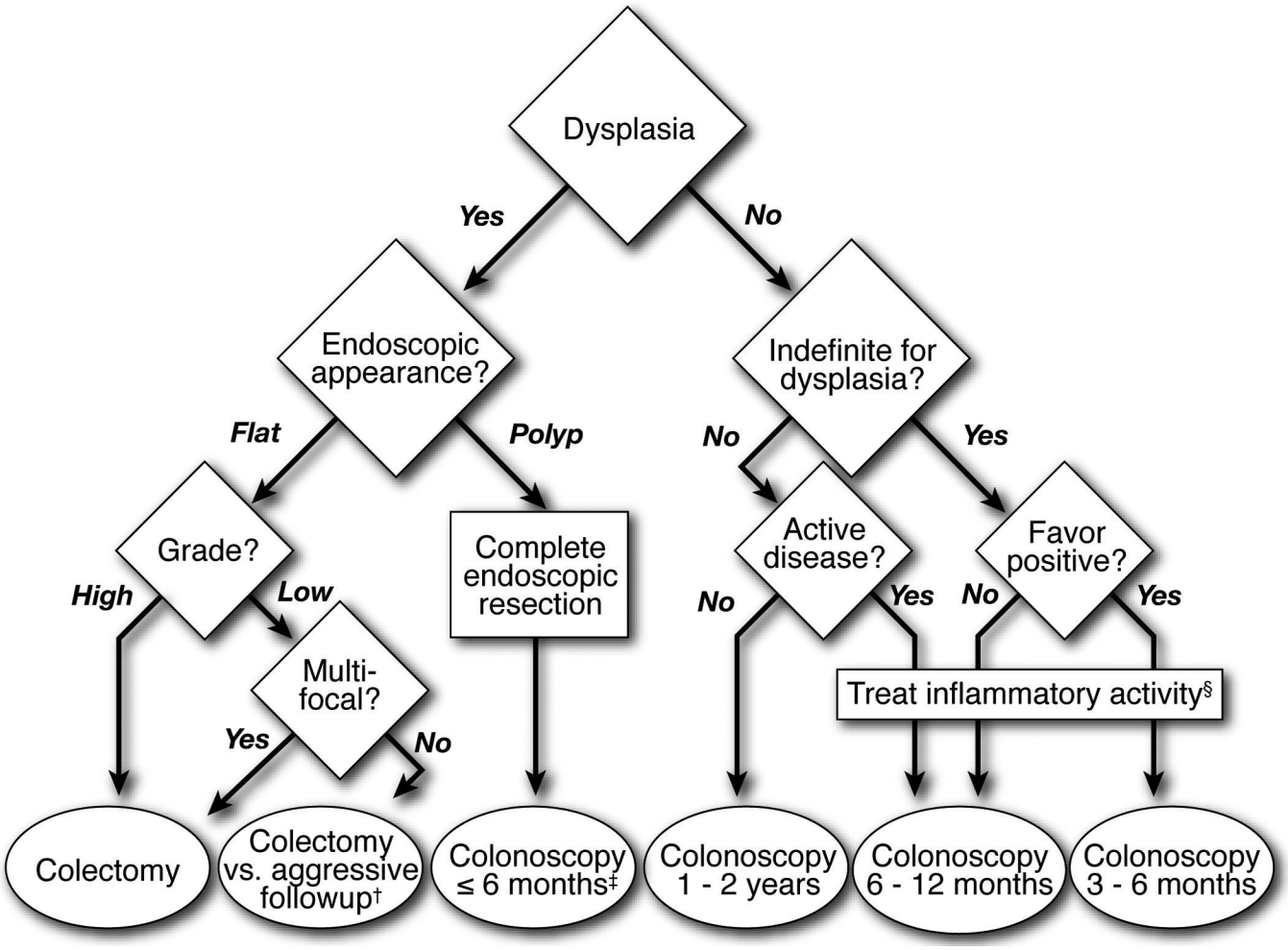

Figure 3.

Algorithm for Dysplasia Management in Ulcerative Colitis. This is a suggested algorithm for the management of dysplasia in patients with UC.

†Management of unifocal low-grade dysplasia remains a controversial area, with debate over whether colectomy or aggressive surveillance is the best approach..

‡ When a resectable polypoid lesion is detected, we recommend that the likely biology of the lesion, including the age of the patient, be given careful consideration (Table 2). Thus, polypoid dysplasia considered likely to be colitis-associated, e.g. in a patient under 40 years old, may prompt consideration of colectomy. On the other hand, a dysplasia-associated polyp in a patient older than 40 without surrounding flat dysplasia may be resected and the patient may continue in surveillance, although possibly more intensive.

§Although not yet proven, there is an evolving recognition that histologically-evident inflammatory activity may be an independent risk for neoplasia. Thus, when histologically active inflammation is identified during a screening or surveillance colonoscopy, it may be appropriate to escalate medical therapy, increase surveillance frequency, or both in order to prevent cancer more effectively.

Table 1

Summary of recommendations for gastroenterologist and pathologist collaboration incancer prevention of ulcerative colitis

1. know an individual patient's risk factors for neoplasia, and encourage adherence to prevention strategies, especially surveillance colonoscopy and biopsies
2. know the approach to specimen processing and review by the pathology department, and limit the number of biopsies per jar
3. place biopsies of polypoid dysplasia and surrounding flat mucosa in separate, clearly labeled jars
4. if possible, include the pathology report at the time of specimen submission and include patient history and risk factors for dysplasia, as well as photographs of any suspicious or concerning findings
5. schedule routine meetings to discuss IBD pathology and review cases and findings
6. obtain a second opinion about possible dysplasia from an experienced GI pathologist

Table 2

Features that can help to distinguish between sporadic adenoma and colitis-associated dysplasia

	Sporadic adenoma	Colitis-associated dysplasia
Patient age	>40-60 years	Any
Duration	Any	>8-10 years
Extent	unrelated	More often pan-colitis
Location	Any	In colitic region
Adjacent mucosa	No dysplasia	Colitis +/- dysplasia
Other dysplastic lesions	Sometimes	Often
Architecture	More often tubular	Occasionally villous
Admixed benign and dysplastic epithelium	Absent	May be present
Immunostains	Not generally helpful in individual cases	