Chapter 10
IBD: Management of Dysplasia in Patients with Ulcerative Colitis

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Introduction

The risk of colorectal cancer (CRC) in the ulcerative colitis (UC) population is real and is the cause of death for up to 15 % of inflammatory bowel disease (IBD) patients [1, 2]. Controversy surrounds the use of prophylactic colectomy when dysplasia is detected. The relatively high risk of progression to CRC must be weighed against the risks associated with total proctocolectomy (TPC) ± ileal pouch anal anastomosis (IPAA), which, in contrast, are relatively low, particularly when performed in an elective setting and by an experienced surgeon. In addition to substantially reducing the CRC risk, TPC results in the elimination of future UC flares and the necessity for medical treatment whilst eliminating the need for frequent CRC surveillance. As more powerful techniques for lesion detection become widespread, the detection of dysplasia will likely increase, increasing the relevance of the question 'What is the most appropriate management of patients with ulcerative colitis and dysplasia?'

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Search Strategy

The PubMed database was searched using the following terms 'dysplasia, carcinoma, neoplasia, DALM, ALM, dysplasia associated mass or lesion, adenoma like lesion or mass and ulcerative colitis or inflammatory bowel disease or IBD.' The search was limited to full length English language manuscripts published between Jan 1, 1980 and Oct 1, 2015. All references in each manuscript identified from the PubMed search were then individually reviewed and examined for relevance and potential inclusion.

Results

Patients, interventions, comparator and outcomes are highlighted in Table 10.1. The most salient studies reviewed are shown in Table 10.2.

Incidences of Dysplasia and Colorectal Cancer (CRC)

Studies on UC dysplasia typically provide incidence rates obtained from the use of conventional endoscopy. Any grade of dysplasia is found in up to 2 % of UC patients at 5 years and 33 % at 15 years [4, 18]. Ten and 15 year rates of high grade dysplasia (HGD) of 7 % and 12 % respectively have been reported. Similar to CRC, incidence is highest in patients with pancolitis [15].

Median time from UC diagnosis to CRC diagnosis varies from 4 to 23 years [4, 19]. Compared to the general population, the relative risk of CRC in UC patients is as high as 16-fold [20]. Meta-analysis inclusive of 116 studies has demonstrated an overall prevalence of CRC in UC patients of 3.7 %, increasing to 5.4 % in the presence of pancolitis [21]. IBD-CRC patients are approximately 7 years younger than sporadic CRC and share the same cancer specific mortality rates on a stage for stage basis [22]. The mean age at CRC diagnosis ranges from 43 to 60 years and the mean interval between diagnosis of UC and CRC is approximately 16 years [17, 23, 24], which is consistent with the majority of UC diagnoses being made in individuals in their 20s to early 30s [21].

Table 10.1 PICO

Patient population	Intervention	Comparator	Outcomes studied
UC patients with dysplasia	Surgery	Expectant management	Cancer risk

Table 10.2 Studies examined

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Choi et al. (2015) [3]	Patients with extensive[a] UC and LGD (median follow up = 48 months) 21 = immediate colectomy 151 = surveillance	33 and 14% of colectomy specimens demonstrated CRC and HGD respectively	13 and 8.6% developed HGD or CRC respectively CRC found in 5 of 11 specimens of patients who developed HGD and underwent colectomy Only 30% of patients who developed CRC had a prior HGD lesion	High-mod
Jess et al. (2006) [4]	29 of 692 IBD registry patients with neoplasia[a] (CD patients included)	NA	0 of 5 with fLGD who underwent surveillance progressed to HGD or CRC (median of 17.8 years) 2 of 18 with ALMs developed LGD or DALM (median 9.3 years) PSC and dysplasia proximal to the splenic flexure were associated with risk for progression	Mod-low
Zisman et al. (2012) [5]	42 with pancolitis ≥8 years' with LGD (mean follow up = 3.9 years)	NA	A higher grade in the colectomy specimen was found in 27% who underwent resection 6 and 2 progressed to HGD and CRC respectively 17% had persistent LGD, 64% had indefinite dysplasia or no dysplasia at the end of the study	High-mod
Ullman et al. (2003) [6]	46 with fLGD (median follow up = 15 months) 11 = immediate colectomy 21 = surveillance	Colectomy specimens showed: LGD n = 7, no dysplasia n = 1, HGD n = 1 and CRC n = 2	19 had LGD and 2 had HGD at the study's end 14 of the 46 progressed to advanced neoplasia (median time to progression = 25 months) 57% of colectomy specimens showed more advanced neoplasia than biopsy specimens 6 DALM patients were managed with polypectomy followed by surveillance. No CRC developed	High-mod

(continued)

Table 10.2 (continued)

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Blackstone et al. (1981) [7]	27 with fLGD in random biopsies 12 with DALMS 9 = immediate colectomy 22 = surveillance	6 colectomy specimens had CRC (including all polypoid lesions). None had a preoperative CRC diagnosis	Of the 2 DALMs that underwent surveillance, 1 developed CRC Of 20 fLGD undergoing surveillance, 6 underwent colectomy. 1 CRC was found. The degree of dysplasia was less severe or absent on follow up in 12	Low
Woolrich et al. (1992) [8]	22 with neoplasia (mean disease duration = 13.5 years)	NA	The first repeat set of biopsies showed dysplasia in six and a CRC in one patient Of the 13 patients with negative first repeat biopsies, who did not undergo colectomy to avoid surveillance: 23 % had CRC in the colectomy specimen (including 1 resection for UC symptoms)	Mod
Befrits et al. (2002) [9]	60 with flGD and UC>years (mean follow up = 10 years)	NA	LGD was only present at index colonoscopy in 16. 73 % had LGD in subsequent colonoscopies. None progressed to HGD in fLGD, except in 2 cases with DALM Five of the 11 with DALMs underwent colectomy. Six underwent endoscopic removal of lesions. None developed HGD or CRC (mean follow-up of 6 years).	Mod
Ullman et al. (2002) [10]	18 with fLGD (median follow up = 32 months)	NA	50 % developed advanced neoplasia (only 1 CRC) Of the patients who underwent colectomy: 2 for DALMs (1 = DALM in colectomy specimen, 1 = no dysplasia) 1 for HGD and 3 for LGD (all had the same results in the colectomy specimen) 5 for refractory disease (1 = DALM, 1 = LGD in the colectomy specimen) The cumulative incidences of progression = 13 % at 1 year, 26 % at 2 years, and 33 % at 5 years All three DALMs that were found on subsequent colonoscopies eventually developed HGD	Mod-Low

Lim et al. (2003) [11]	29 with extensive UC >8 years and LGD and 97 UC without dysplasia	NA	After 10 years, 10 % of LGD patients underwent colectomy for CRC vs 4 % without LGD. No difference in colectomy or death rates between the two groups was seen. Agreement of LGD diagnosis between pathologists was poor	Low
Rutter et al. (2006) [12]	46 with LGD, 19 with HGD, 28 DALMs and 32 ALMs with extensive disease for >8 years (mean follow up = 8.5 years)	CRC was found in 20 and 45 % LGD and HGD colectomies respectively. 30 % of LGD DALM and 33 % HGD DALM patients had CRC in their resection specimen	Of the 36 LGD surveillance patients: 16 = no further dysplasia, 8 = further LGD, 9 = HGD, 3 = CRC. Of the 8 HGD surveillance patients: 1 = developed CRC, 6 = developed HGD, 1 = subsequent LGD. 21 % with LGD DALMs developed CRC, 28 % with HGD DALMs developed CRC, none who had endoscopic resection developed CRC, 6.3 % of 32 ALM patients developed CRC. 13 of the 30 CRCs did not have a preoperative diagnosis of CRC	Mod
Pekow et al. (2010) [13]	28 with LGD (Mean follow up = 50 months)	NA	1 fLGD progressed to HGD and 1 polypoid LGD progressed to CRC. For fLGD, polypoid LGD and PSC the incident rate of advanced neoplasia was 4.3, 1.5 and 10.5 cases per 100 person-years at risk	Mod
Goldstone et al. (2011) [14]	121 with extensive UC>7 years and LGD (median follow up = 37 months)	NA	7.9 % with raised and 25 % with flat dysplasia progressed to advanced neoplasia. The interval for progression was significantly shorter among patients with distal vs. proximal LGD	Mod

(continued)

Table 10.2 (continued)

Study	Ulcerative colitis patients	Typical risk of cancer for immediate surgery when dysplasia is detected	Relative risk of cancer for surveillance	Quality of evidence
Stolwijk et al. (2013) [15]	293 with UC >8 years	NA	Dysplasia of any grade was detected in 24.6 % (LGD n=55) 33 % who had subsequent colonoscopies progressed to HGD and/or CRC. LGD preceded HGD/CRC in 44 % 5.1 % were diagnosed with CRC with a minimal interval from symptom onset to CRC of 10.2 years The cumulative incidence of any dysplasia, HGD and CRC after 10 years was 23.5 %, 6.6 and 4.0 %. After 15 years it was 33.3, 12.1, and 6.8 % In the colectomy specimens, 82 % confirmed the biopsy result, 13 % showed a higher degree of dysplasia	Mod
Provenzale et al. (1995) [16]	A computer generated population of 10,000 30 year old UC patients with pancolitis >10 years	Prophylactic colectomy increased life expectancy by 2–10 months vs surveillance and by 1.1–1.4 years vs. with no surveillance.	Yearly colonoscopic surveillance for LGD increased life expectancy by up to 1.2 years vs no surveillance. If colectomy for LGD is not undertaken, surveillance every 3 years for the first 20 years, every 2 years for the next 8 years, and yearly thereafter and colectomy for HGD or CRC provides the greatest life expectancy.	Poor
Wanders et al. (2014) [17]	Meta-analysis of 10 studies, 376 patients with polypoid dysplasia (combined 1704 years' follow-up)	NA	The pooled CRC and HGD rates were 6.7 and 9 per thousand years of patient follow-up Increased study duration did not correlate with an increase in advanced neoplasia rates	High

UC ulcerative colitis, *LGD* low grade dysplasia, *CRC* colorectal cancer, *HGD* high grade dysplasia, *DALM* dysplasia associated mass or lesion, *ALM* adenoma-like mass or lesion, *CD* Crohn's disease, *fLGD* flat low grade dysplasia, *DALM* dysplasia associated mass or lesion, *ALM* adenoma-like mass or lesion
[a]Extensive UC=UC proximal to the splenic flexure

Disease Defined Risk Factors: Disease Duration, Age of Onset, Disease Extent, PSC

CRC incidence dramatically increases 8–10 years after the onset of UC symptoms. Cumulative probabilities of developing CRC are up to 4 % by 10 years and 8 % by 20 years [15, 21, 25]. Rates after 30 years are less uniformly reported and vary from 2.6 to 34 % [20, 25, 26]. Primary sclerosing cholangitis (PSC) has consistently been shown to increase the risk of CRC through a yet undetermined pathophysiological mechanism. Studies on a potential correlation between young age at UC diagnosis and/or childhood onset and CRC are conflicting with the majority showing no correlation [25]. Dysplasia is typically but not universally found in areas of current or burnt out colitis [27, 28], leading to an increased risk in more extensive disease distribution [20, 25]. An earlier CRC onset has also been suggested in pan vs left sided colitis [29].

Patient Defined Risk Factors: Family History of CRC, Medication Usage, Smoking, Patient Awareness

Family history is a known risk factor for both sporadic carcinoma and IBD associated CRC. CRC risk is at least doubled in UC patients with relatives with CRC and is ninefold greater if the relative is under the age of 50 at CRC diagnosis [23, 30]. Conversely, a family history of IBD does not increase UC-CRC risk [20]. Studies on medication usage in UC and CRC are limited to the older anti-inflammatory drugs, with data on the newer biologics and anti-integrins lacking. Several previous studies including a meta-analysis of 9 studies and 1932 patients, have suggested a protective effect with regular 5-aminosalicylic acid (5-ASA) use [21, 23, 24, 31]. Although a paradoxical effect of smoking and decreased UC incidence and disease severity is well known, the effect of smoking on UC-CRC risk is understudied. Eaden's small case control study demonstrated no association [23].

CRC risk may be underappreciated by UC patients themselves and probably negatively impacts care. The majority of 199 survey respondents with UC for an average of 8 years recognized that CRC risk was increased, however approximately 75 % stated that they were "unlikely" or "very unlikely" to develop CRC within the next 10 years [32].

Classification of UC Dysplasia

Dysplasia in UC has typically been regarded as flat in most cases. When it is raised and found within areas of inflammation, it has been termed a dysplasia associated lesion or mass (DALM) and classically has been viewed as colonoscopically

unresectable. These definitions and concepts are now in question with the development of newer more advanced techniques of endoscopic polyp removal. A polypoid lesion found in an area free of inflammation is termed an adenoma-like mass or lesion (ALM) and is akin to an adenomatous polyp in a non-UC patient.

Grading of dysplasia ranges from mild or low grade (LGD) to more severe or high grade dysplasia (HGD). LGD is histologically similar to inflammation with tall columnar epithelial cells with mild nuclear stratification. HGD is similar to carcinoma in situ [7]. Salient features of HGD include prominent heterochromatin and more irregular nuclear stratification within the epithelial layer. These subtle differences lead to poor interobserver agreement between grading pathologists especially for LGD. When LGD slides are reviewed by a second set of pathologists, agreement with the original LGD diagnosis ranges from 7 to 43 % and varies depending on the number of pathologists reviewing [4, 11, 33, 34]. Dixon et al demonstrated a similarly poor consensus of agreement on HGD, as low as 33 % [35]. Correlation was not improved when specialist gastrointestinal pathologists grated the specimens, compared to general histopathologists [36].

> 1. A second pathologist's opinion for LGD is often necessary (Strong recommendation based on moderate-high quality evidence).

Inadequate tissue sampling during colonoscopy may lead to missed lesions. Mathematical modelling to determine the number of random biopsies required to detect dysplasia with 90 % confidence calculated that 45 biopsies would be required. When the number of biopsies decreases to 10, 26 % confidence was predicted [37, 38]. New enhanced methods of lesion detection including chromoendoscopy which began in the early 2000s, have dramatically increased the sensitivity of surveillance colonoscopy particularly for difficult to detect, flat dysplastic lesions [39–42].

Dysplasia Management

Neoplastic Progression

Unlike sporadic CRC which follows a usual sequence of normal mucosa → adenoma → carcinoma, UC associated CRC does not necessarily follow the expected progression of LGD → HGD → CRC. This makes surgical recommendations problematic, especially in the individual patient. As demonstrated in several studies in Table 10.2, carcinoma is often detected in colectomy specimens in which only LGD or even no dysplasia was detected in prior colonoscopies. In Stolwijk's study of over 290 UC patients undergoing surveillance, LGD preceded HGD or CRC in only 44 % of cases [15]. None of the 5 of 46 flat LGD (fLGD) patients that progressed to CRC had an interval finding of HGD in Ullman's study [43]. In Rutter's

surveillance program of 600 patients with extensive colitis, CRC was found in 20 % of specimens that were resected for only LGD [12]. Choi and Zisman report similar rates of unexpected CRC in resections performed for LGD [3, 5].

A focus of UC dysplasia, especially HGD has been suggested to be a marker for synchronous lesions, including CRC [44–46]. An early study of 590 UC TPC specimens demonstrated that patients with a focus of HGD or LGD were 36 times more likely to have a concomitant CRC found as compared to UC specimens without dysplasia. Up to a 25 % synchronous tumor rate and 55 % synchronous dysplasia rate has been demonstrated in other TPC studies [19, 47].

Flat LGD

In patients with LGD and extensive UC for over 8 years, progression to CRC has been reported to be 13 % at 1 year to 33 % at 5 years [3, 5, 6, 10, 12, 15, 18] with a mean time to progression of 1.8–2.3 years [5, 6, 10]. Woolrich determined LGD to be an indicator of future carcinoma in 18 % of 121 patients [8]. A meta-analysis of 20 studies with 508 LGD patients provided a calculated positive predictive value (PPV) of 22 % for flat LGD (fLGD) as a predictor of CRC [48]. Zisman determined nonpolyoid dysplasia, size >1 cm, previous history of indefinite dysplasia and the presence of a stricture as risk factors for LGD progression. He stratified patients showing that CRC risk at 5 years ranged from 1.8 % in patients with no risk factors to over 60 % with three risk factors [3]. Befrits' study, the only study which has shown no progression of LGD to subsequent HGD or CRC was small with only 16 patients with LGD [9]. Multiple retrospective studies and Thomas' meta-analysis did not demonstrate differences in characteristics between patients with and without LGD prior to HGD and/or CRC [6, 15, 48] again showing the difficulty in making care recommendations in the specific patient.

> 2. Flat LGD warrants colectomy in the otherwise healthy patient due to the increased risk of unrecognized synchronous high risk lesions and the likelihood of developing subsequent HGD or CRC (Strong recommendation based on moderate-high quality evidence).

High Grade Dysplasia

Recent studies on long term HGD surveillance are lacking as patients typically undergo resection due an inordinately high risk of synchronous CRC, as high as 45 % in earlier studies [49, 50]. In a systematic review, 32 % (of 47 patients) with HGD on colonoscopy had CRC discovered on resection pathology [50]. Some smaller studies report lower rates, [27] but sampling errors, the need for repetitive

colonoscopy, and the fear of synchronous CRC or progression over time has led to TPC being the immediate recommendation in the otherwise healthy UC patient with HGD. HGD identified on random biopsies represents an especially concerning circumstance, since overt signs of polyp formation that would focus the attention of the examiner is lacking. Similarly, multiple areas of dysplasia, especially when flat, can only be addressed by colectomy.

3. HGD, multifocality and flat dysplasia are all high risk features for the development of CRC in the UC patient and warrants total proctocolectomy in the surgically fit patient (Strong recommendation based on moderate-high quality evidence).

DALMS

The PPV for DALMs as predictors of CRC is 41 % as calculated by meta-analysis [48]. 43 % of 47 DALM patients in the small systematic review described above were found to ultimately have CRC [50]. Blackstone et al described a series of 12 resected DALMs. CRC was found in 7, including all 5 single polypoid masses. None had invasive carcinoma on preoperative biopsy [7]. Selective resection of DALMs in the form of polypectomy was proposed by one meta-analysis of 10 studies and 376 UC patients, but with a mean follow up of only 2.8 colonoscopies after resection. Many of these studies had very low patient numbers and mean follow up and number of colonscopies varied greatly across the study cohorts included [17]. Kisiel reported higher rates in 77 of 95 DALM patients who underwent polypectomy with cumulative incidences of cancer of 2 % at 1 year and 13 % at 5 years cited [51]. The value of more advanced colon sparing techniques such as endoscopic mucosal resection, has not been fully evaluated in this high risk group of patients. Thus close colonoscopic surveillance is required after colonoscopic excision.

4. DALMS should be viewed as very high risk lesions in the UC patient justifying TPC in most fit individuals. If able to be completely removed colonoscopically, aggressive subsequent surveillance is necessary (Strong recommendation based on moderate-high quality evidence).

ALMS

By definition, ALMs are within areas of the colon without inflammation. Thus they may be treated similarly to sporadic adenomas due to a low risk of CRC. Hurlstone followed ALMs and DALMs in over 180 patients over a median follow-up of

4.1 years as compared with over 1600 non-UC Controls who had undergone endoscopic mucosal resection (EMR) or polypectomy for lesions. Recurrence rates were low in both groups [52]. Torres et al studied ALMs and DALMs in 59 CD and UC patients and found that CRC only developed in DALMs. However, the group was highly selected leading to the recommendation of endoscopic resection with close, 6 monthly surveillance with colonoscopy [30].

> 5. ALMs can be viewed as typical polyps, amenable to polypectomy (Weak recommendation based on low quality evidence).

A Personal View of the Data

Due to the lack of consistent progression of inflammation to LGD to HGD to CRC, recommendations for surgical management of UC dysplasia leans towards treating the worst case scenario. This is especially the case since UC patients with dysplasia are frequently middle aged with a life expectancy that should not be foreshortened by preventable malignancy. Couple this with the above described poor concordance between pathologists and one is frequently led to the recommendation of early resection when any form of dysplasia is found on colonoscopy, but especially when HGD or flat dysplasia is found on random sampling. The high incidence of unexpected synchronous CRC when TPC is done for dysplasia further justifies an aggressive surgical approach.

Recently, chromoendoscopy has suggested itself to be a more sensitive and accurate method of following the equivocal patient; however this has not been thoroughly studied. Similarly the use of EMR for DALMs is also understudied, but really is only considered in highly specialized centers by very committed caregivers, and then only with intense colonoscopic follow up (every 6 months). This surveillance itself becomes an added burden, with attendant complications, costs and potential difficulty with patient compliance.

Thus, in the surgically fit patient we advocate TPC in all patients with any grade of pathologically confirmed dysplasia [45]. In the patient with LGD, this may sometimes require a second colonoscopy (frequently chromoendoscopy) for confirmatory biopsies, possibly after a period of intense medical management to minimize inflammation. However, any single confirmed focus of HGD should send the otherwise healthy and consenting patient directly to surgery. Besides eliminating the risk of CRC, patients are effectively "cured" of their colitis by TPC, with elimination of most medications and their attendant side effects and costs, improvement in bowel habit (especially with the IPAA) and elimination of burdensome surveillance colonoscopies [53]. The more difficult dilemma is the surgical high risk or elderly patient or patient refusing surgery, who has a less compelling indication for surgery, a single focus of LGD for example. After thorough counselling, such a patient can be considered for close surveillance using chromoendoscopy and/or EMR if a lesion

is visualized. If the dysplasia is colonic (not rectal), and localized as can be best determined, a subtotal colectomy and ileorectal anastomosis, or even segmental colectomy will decrease the risk of synchronous or metachronous lesions, and will be surgically less morbid. The patient will still need close colonoscopic surveillance, however. Similarly, a segmental resection (or even TAC/IRA) for DALM is possible in the higher risk patient. It avoids a stoma, but any procedure less that TPC needs preoperative confirmation of a dysplasia free rectum which then requires continued surveillance after this more limited surgery.

Editor's Note The concepts and controversies surrounding the identification and management of dysplasia in IBD are evolving rapidly. It appears that most areas of dysplasia are actually grossly visible with high definition scopes and enhancement techniques (e.g., chromoendoscopy). If lesions can be clearly defined, they can be more readily removed endoscopically and followed carefully with serial endoscopy.

The authors have outlined an aggressive approach, especially to the management of low grade dysplasia; many IBD specialists may espouse a more nuanced view with careful endoscopic surveillance offered as an alternative for many of these patients.

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