Surveillance for colorectal cancer in patients with inflammatory bowel disease

Surveillance for colorectal cancer is necessary in patients with inflammatory bowel disease. This article summarizes the rationale for surveillance in this patient group and gives an overview of updated national guidelines.

Ulcerative colitis was first recognized as a risk factor for colorectal cancer nearly 80 years ago by Crohn and Rosenberg (1925). Later in 1948, colorectal cancer was found to have developed in a patient with Crohn's disease (Warren and Sommers, 1948). Surveillance for colorectal cancer is now accepted as being necessary for patients with inflammatory bowel disease, and patients with Crohn's colitis are at an equal risk as patients with ulcerative colitis who have a similar extent and duration of colonic disease. There are a number of controversies that remain, however, including how best to manage low grade dysplasia when detected, how to define lesions that arise within areas of inflammation and, despite the updated guidance, the optimal surveillance intervals. This article provides an overview of surveillance for colorectal cancer in the inflammatory bowel disease population and subsequent management with reference to the recently published guidance from the British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland (Cairns et al, 2010).

Colorectal cancer and inflammatory bowel disease

Although it is accepted that patients with inflammatory bowel disease are at risk of developing colorectal cancer, it has been difficult to estimate the magnitude of that risk. Data from St Mark's Hospital have shown a cumulative incidence rate of cancer and dysplasia of 7.7% at 20 years and 15.8% at 30 years in patients with ulcerative colitis (Rutter et al, 2006). Patients with Crohn's colitis were initially thought to be at a lower risk of cancer, but it is now believed that the risks are equal in both conditions, with absolute cumulative colon cancer frequencies of 8% for ulcerative colitis and 7% for Crohn's disease after 20 years (Gillen et al, 1994).

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The risk of patients developing colorectal cancer appears to be related to total disease duration and to the extent of disease – most cancers arise in patients with subtotal colitis or pancolitis (generally defined as extension beyond the hepatic flexure) (Farraye et al, 2010). Other well-known risk factors for colorectal cancer development in inflammatory bowel disease are a family history of sporadic colorectal cancer and the presence of primary sclerosing cholangitis (*Table 1*). The relationship between ulcerative colitis and primary sclerosing cholangitis is so strong that 70% of patients initially diagnosed with primary sclerosing cholangitis will subsequently be found to have underlying ulcerative colitis.

Askling et al (2001) demonstrated that a family history of colorectal cancer doubles the risk of developing cancer compared to other inflammatory bowel disease patients without such a family history. Further to this, if the affected family member was diagnosed before the age of 50 years, this risk is increased nine-fold compared to other inflammatory bowel disease patients without a family history. Although a history of severe and frequent attacks of colitis has not been shown to be a risk factor for colorectal cancer (likely to be because these patients often undergo colectomy early in the course of their disease), there is evidence that ongoing microscopic inflammation in the colon may confer a higher risk of colorectal cancer development (Rutter et al, 2004a). Perianal fistulae and strictures in patients with Crohn's disease have yielded higher than expected frequencies of

Table 1. Risk factors for colitis-associated cancer

Presence of dysplasia
Disease duration
Extent of disease
Primary sclerosing cholangitis
Family history of sporadic colorectal cancer
Histological and endoscopic inflammation
Folate deficiency
Post-inflammatory polyps and strictures
Young age at colitis diagnosis (possibly)

adapted from Askling et al (2001); Eaden et al (2001); Cairns et al (2010)

malignant lesions, and there is a doubled risk of colorectal cancer in patients with multiple post-inflammatory pseudopolyps (Connell et al, 1994). Surveillance is thought to be less effective in this context as it is more difficult to visualize dysplastic lesions in a colon with multiple pseudopolyps. However, not all risk factors confer the same magnitude of risk.

The presence of a single dysplastic or even malignant lesion in a patient with inflammatory bowel disease is not necessarily an isolated find. Up to 26% of inflammatory bowel disease patients who develop colorectal cancer will have multifocal disease, in comparison to just 2% of the general population (Eaden and Mayberry, 2002). Morson and Pang (1967) found that in a case series of nine inflammatory bowel disease patients who had undergone colectomy for dysplasia found on rectal biopsies, five had a malignancy elsewhere in the colon. The key differences between inflammatory bowel disease-associated cancers and sporadic colorectal cancers are outlined in *Table 2*.

The need for surveillance guidelines

Guidelines were developed after surveillance strategies were shown to reduce the incidence of colorectal cancer in these patients (Itzkowitz and Harpaz, 2004). Surveillance is carried out by colonoscopy with either random or targeted biopsies. Previously, British Society of Gastroenterology guidelines published in 2002 advised quadrantic biopsies every 10 cm from the entire colon with additional samples of suspicious areas including irregular plaques, ulcers and strictures (Eaden and Mayberry, 2002). Hence an average of 40–50 biopsies may have been taken during surveillance for patients with pancolitis.

Patients with Crohn's disease limited to the small bowel are at no increased risk of developing bowel cancer and therefore do not require colorectal surveillance. However, Crohn's disease is a well-recognized risk factor for the development of small bowel adenocarcinoma, with a cumulative risk of 0.2% at 10 years and 2.2% at 25 years in patients where disease is limited to the small bowel (Feldstein et al, 2008). In contrast to colorectal disease, dysplasia in the small bowel is poorly understood in Crohn's disease and there are no recommendations for screening in this context.

Small bowel lymphoma can also complicate Crohn's disease, but although the available data suggest that the disease alone is not a risk factor for lymphoma development, it remains unclear whether or not patients with more severe and prolonged disease activity are at greater risk (Jones and Loftus, 2007). Patients with ulcerative colitis or Crohn's disease on thiopurine medication have a four-fold increased risk of lymphoma, but it could not be elucidated whether the risk was the result of the medications themselves or underlying disease severity (Kandiel et al, 2005). There is also a very small increased risk of lymphoma in inflammatory bowel disease patients receiving anti-tumour necrosis factor therapy, although this risk has not been clearly quantified. The incidence of small bowel malignancies is too low to advocate small bowel screening.

Patients with proctitis alone appear to have no increased risk of cancer and do not require regular surveillance. However, it is suggested that they should undergo at least one screening or index colonoscopy 10 years after diagnosis, to ensure that the disease has not extended proximally from the time of diagnosis. There is no evidence to support a surveillance strategy based on the maximum extent of disease seen at any one time in an individual, as disease extent may change over time in ulcerative colitis. Thus a clinician may wish to cease surveillance if there is proctitis only at two consecutive colonoscopies (Cairns et al, 2010). All other patients with ulcerative colitis and all patients with

Table 2. Key differences and similarities between inflammatory bowel disease-associated colon cancer and sporadic colon cancer

	Inflammatory bowel disease-associated colorectal cancer	Sporadic colorectal cancer
Differences	Typically arises from flat dysplastic mucosa	Typically arises from adenomatous polyps
	Affects a younger age group (mean age <50 years)	Occurs at greater age (mean age >65 years)
	Often characterized by multiple lesions	Rare to have multiple lesions
	P53 mutations occur early in the development of cancer	P53 mutations occur much later in the development of cancer
	Adenomatous polyposis coli gene mutations occur late in the development of cancer	Adenomatous polyposis coli gene mutations occur early in the development of cancer
	Higher proportion of mucinous or signet cell type tumours	Most commonly adenocarcinoma
	Surgical treatment involves total colectomy	Surgical options depend on the location of the cancer
Similarities	Develop by a dysplasia-cancer sequence	Develop by a dysplasia-cancer sequence
	Multistep mutations present	Multistep mutations present
	Preventable by salicylates (5-aminosalicylic acids)	Preventable by salicylates (aspirin)

Crohn's colitis should undergo surveillance. The figure of 8–10 years after diagnosis has been internationally agreed to be the best time to start screening eligible patients, as meta-analyses have shown that the risk of malignancy at this point is 2%, rising thereafter (Lewis et al, 1999).

Although surveillance is an important aspect of the management of patients with inflammatory bowel disease, not all patients will want to participate. The implications of discovering dysplasia together with the potential complications that can occur when performing colonoscopy, such as pain, bleeding and perforation, need to be fully explored with the patient (Bowles et al, 2004). Although opinion among professionals who care for patients with inflammatory bowel disease is that surveillance programmes are worthwhile and effective, there have been no randomized control trials performed to quantify just how useful such programmes are (Lewis et al, 1999).

A Cochrane review concluded that there was no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis, but there was evidence that cancers were detected at an earlier stage in patients undergoing a surveillance programme (Collins et al, 2006). Indirect data have shown that patients whose cancer was detected through surveillance have a higher 5-year survival rate than those whose cancer was diagnosed incidentally or only when it became symptomatic (Choi et al, 1993).

Management of dysplasia

It is thought that colorectal cancer may develop in patients with chronic colitis through a chronic inflammatory–dysplasia–carcinoma sequence (Hurlstone and Brown, 2007). The presence of dysplasia is thought to be the most reliable marker of an increased risk of malignancy in inflammatory bowel disease patients, but the actual management of dysplasia when found is an area of continuing discourse (Thomas et al, 2007). Although dysplastic lesions have the potential to develop into cancers, not all will do so. Conversely, a patient can develop cancer without any prior history of dysplasia.

If dysplasia of any grade is found, a second opinion from an expert gastrointestinal histopathologist is essential. The next step should be a repeat colonoscopy by a colonoscopist with experience in colitis surveillance. The presence of further synchronous lesions can be detected where possible by dye spraying the entire colon using the techniques described later (Rutter et al, 2004a).

Dysplasia in the colon can be divided into two groups: flat lesions and elevated lesions. In general, flat lesions are lesions that are not visible endoscopically, and can be low grade or high grade. The discovery of high grade dysplasia is an indication for urgent panproctocolectomy. Evidence from St Mark's Hospital demonstrated that 5 of 11 (45%) patients that had an immediate colectomy for high grade dysplasia revealed a synchronous cancer (Rutter et al, 2006). The management of low grade dysplasia is more controversial, in part as a result of difficulties in distinguishing between regenerative changes and true dysplasia. Previous data had suggested 16–29% of patients with untreated low grade dysplasia progress to high grade dysplasia or cancer, resulting in advocation of panproctocolectomy in these patients (Askling et al, 2001). However, more recent data demonstrated that progression to high grade dysplasia or cancer only occurred in 10% of patients with low grade dysplasia (Lim et al, 2003), concluding that low grade dysplasia is not associated with a higher risk of colorectal cancer. If flat low grade dysplasia is detected in biopsy specimens on more than one occasion and in more than one site in the colon, prophylactic colectomy should be strongly considered.

Elevated lesions are often referred to as dysplasia-associated lesions or masses. These have been further categorized into adenoma-like dysplasia-associated lesions (masses that appear similar to sporadic adenomas) or non-adenoma-like dysplasia-associated lesions or masses which include irregular bumps and nodules, wart-like thickenings, stricturing lesions and broad-based masses. This classification is somewhat arbitrary as there is no real endoscopic or histological discriminator – the most crucial factor should be whether the lesion can be removed in its entirety endoscopically, as the prognosis is excellent when endoscopic resection is complete (Odze et al, 2004). The surrounding mucosa should be biopsied to rule out any field change, and if dysplastic tissue is present in the surrounding flat mucosa, colectomy should be recommended as full lesion removal will not be possible endoscopically (Cairns et al, 2010). Lesions that cannot be resected endoscopically usually harbour malignancy, and surgery should be undertaken (Rutter et al, 2004b).

A visible dysplastic lesion detected proximally to the extent of colitis can be considered a sporadic adenoma, and be removed endoscopically with the patient then followed up on standard non-colitic adenoma surveillance protocols (Blackstone et al, 1981). Similarly, a visible dysplastic lesion located within an area of colitis can be treated conservatively with complete endoscopic removal and continued surveillance. The management of visible dysplastic lesions applies to patients regardless of age, duration and extent of colitis (*Figure 1*).

Chromoendoscopy

Chromoendoscopy, or dye spraying, is the use of dyes in the gastrointestinal tract to highlight and delineate abnormal areas, with particular benefits in the detection of more subtle, flat mucosal lesions (Hurlstone and Brown, 2007) (*Figure 2*). The two main dyes used in colitis surveillance are indigo carmine and methylene blue. However, concerns have been raised over the use of methylene blue because of a theoretical carcinogenic risk (Davies et al, 2007). Indigo carmine is a contrast stain

that pools in the pits and grooves of the mucosal surface, but is not absorbed by the cells. Methylene blue is termed a vital stain which is actively absorbed into the colonic epithelium, staining the colonic crypt edges (Canto, 1999).

A spray catheter is passed through the biopsy port of the colonoscope. Injection of dye through this catheter creates a mist used to coat the colonic mucosa. Systematic inspection of each segment of the colon is then undertaken to assess for mucosal irregularities. The use of a magnification colonoscope allows a more detailed assessment of the mucosal surface to help distinguish neoplastic changes. The only contraindication to chromoendoscopy is allergy to the dye used.

The main limitations of this technique are inadequate bowel preparation, mucus layers and procedural experience of the endoscopist. These factors are incorporated into the SURFACE guidelines which also recommend use of a spasmolytic agent such as buscopan, where necessary, to maximize visualization of the colonic mucosa (Kiesslich and Neurath, 2004).

The benefits of chromoendoscopy have been highlighted in several studies. Rutter et al (2004c) compared the use of quadrantic, non-targeted biopsies every 10 cm, with targeted biopsies of mucosal abnormalities after indigo carmine pancolonic dye spraying in patients with chronic ulcerative colitis. They found that chromoendoscopy with targeted biopsies increased the detection rates for dysplasia. No dysplasia was identified in over 2900 biopsies taken in the non-targeted group. The time taken for both surveillance approaches was the same. Similar results have been identified using methylene blue dye and in patients with Crohn's disease as well as ulcerative colitis (Kiesslich et al, 2003; Marion et al, 2008). It allows more accurate diagnosis of the extent and severity of inflammation (Kiesslich et al, 2003). The reduced number of targeted biopsies required with chromoendoscopy also reduces the costs relating to histopathological analysis.

Surveillance guidelines 2010

In May 2010, the British Society of Gastroenterology updated the guidelines for colorectal cancer screening and surveillance in moderate and high risk groups taking into account other recognized risk factors for colorectal cancer in inflammatory bowel disease and use of chromoendoscopy (Cairns et al, 2010). A screening colonoscopy is recommended 10 years after diagnosis in all patients to assess disease extent and other endoscopic risk factors, in light of data demonstrating that endoscopic appearance is an important predictor of future dysplasia or cancer development (Mathy et al, 2003). The surveillance interval varies depending upon these factors, and although it is recognized that the optimal surveillance intervals are yet to be defined, the guidance draws on current data on the natural history of dysplasia and efficacy of surveillance. Higher risk patients are advised to undergo annual colonoscopy, intermediate risk patients 3-yearly and lower risk patients 5-yearly colonoscopy (*Table 3*).

In a single centre, 30-year analysis of the UK surveillance programme, Rutter et al (2006) found that 16 of 30 cancers detected were interval cancers, suggesting that it may be possible to reduce the risk of interval cancers by intensifying surveillance for patients with known additional risk factors for colorectal cancer development. In total 1 in 21 patients benefitted from surveillance, or 1 per 175 patient surveillance years in this study. In the new guidelines, it is estimated that in a population of 300 000 people, approximately 100 patients would need surveillance – of these 15 will be high risk, 30 intermedi-

Figure 1. Management of dysplasia-associated lesions or masses. Adapted from Odze (1999).

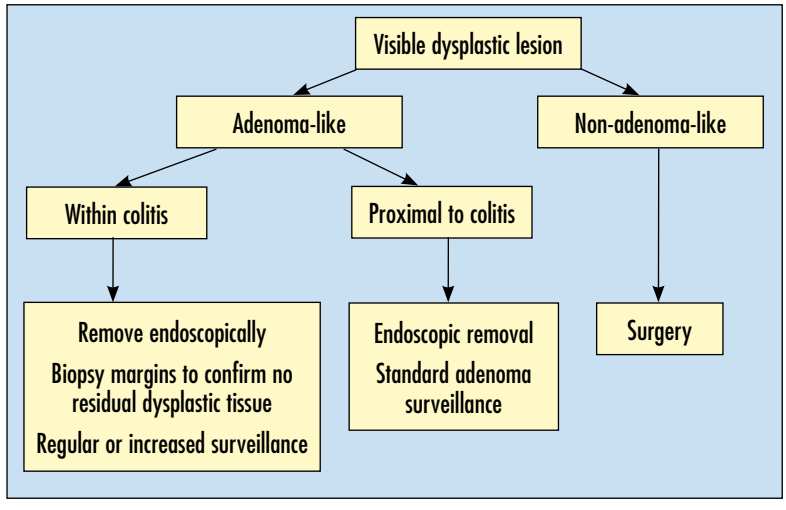
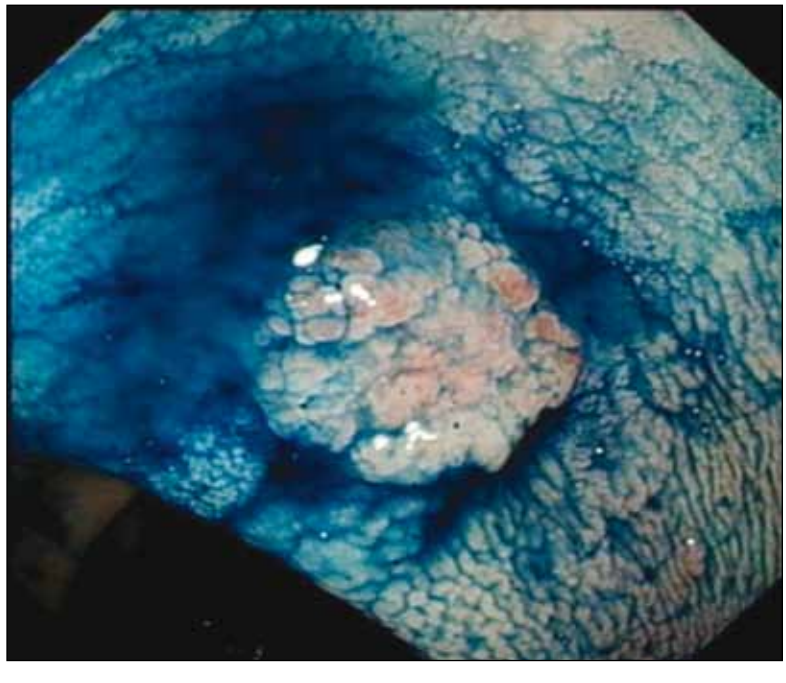


Figure 2. Chromoendoscopy clearly outlining a visible dysplastic lesion within an area of mild inflammation. High grade dysplasia was seen on endoscopic biopsy, confirmed as adenocarcinoma (pT1) following colectomy.



ate risk and 55 low risk patients, which would equate to 36 colonoscopies required per annum. Regular audit should be undertaken to determine whether the revised strategy improves cancer detection rates.

Chromoendoscopy and targeted biopsies are recommended as the preferred method of surveillance, but if this technique is not used then two to four random biopsy specimens from every 10 cm of the colon with additional biopsies of suspicious areas are advised. For patients who have undergone a restorative proctocolectomy with ileal pouch anal anastomosis there is no clear evidence that pouch surveillance is of benefit, and it is not strongly recommended in the new guidelines. Dysplasia can arise in the pouch ileal mucosa or in any retained anorectal mucosa, but this is extremely rare. Risk factors for cancer development – there have only been a few cases of cancer reported in the literature – include presence of previous rectal dysplasia, dysplasia or colorectal cancer at the time of pouch surgery, primary sclerosing cholangitis, refractory pouchitis and type C mucosa (permanent persistent atrophy and severe inflammation). If a patient has any of these risk factors, the guidelines suggest yearly flexible sigmoidoscopy with four proximal and four distal biopsies may be reasonable. If none of these risk factors are present, surveillance can be performed on a 5-yearly basis.

The new guidelines also note the mounting evidence for the chemoprotective role of 5-aminosalicylic acid, and recommend that patients are kept on a dose of at least 1.2 g daily (Eaden, 2004). The studies and epidemiological data relate to the reduction of risk of neoplasia in ulcerative colitis, so far no studies have evaluated the use of 5-aminosalicylic acids in Crohn's colitis. A number of studies have found that there is no chemoprotective benefit from azathioprine or 6-mercaptopurine (Fraser et al, 2002; Matula et al, 2005) in ulcerative colitis or Crohn's colitis, and it may be beneficial for patients to remain on a 5-aminosalicylic acid preparation even if their disease is well controlled with a thiopurine. The use of calcium and probiotics cannot be recommended given the lack of current data (Croog et al, 2003).

Table 3. Risk stratification for patients with inflammatory bowel disease after index colonoscopy 10 years after diagnosis

Low risk	Extensive colitis with no active endoscopic or histological inflammation
	Left-sided colitis
	Crohn's colitis affecting <50% surface area of the colon
Intermediate risk	Extensive colitis with mild active endoscopic or histological inflammation
	Post inflammatory polyps
	Family history of colorectal cancer in a first degree relative aged 50+ years
High risk	Extensive colitis with moderate or severe active endoscopic or histological inflammation
	Stricture within previous 5 years
	Confirmed dysplasia in previous 5 years (in a patient who declines surgery)
	Primary sclerosing cholangitis or post-liver transplant for primary sclerosing cholangitis
	Family history of colorectal cancer in first degree relative <50 years

From Cairns et al (2010)

KEY POINTS

- Patients with inflammatory bowel disease have up to a one in six chance of developing colorectal cancer after 30 years.
- There are associated factors that increase an individual's risk of developing colorectal cancer.
- The presence of dysplasia on biopsies should be confirmed by a second expert gastrointestinal pathologist.
- Chromoendoscopy and targeted biopsy yields higher detection rates for dysplasia and cancer.
- The management of dysplasia is influenced by whether it is high or low grade, and whether it is found in a flat or elevated lesion.
- If a dysplastic polyp is found within an area of inflammation and can be completely removed, a colectomy need not be recommended.
- The new British Society of Gastroenterology guidelines for surveillance intervals take into account risk factors as well as the endoscopic and histological appearances at colonoscopy.

Conclusions

Surveillance colonoscopy is recommended for patients with inflammatory bowel disease at increased risk of developing colorectal cancer despite a lack of randomized controlled trials. New guidance from the British Society of Gastroenterology should help to improve current surveillance techniques and lesion detection rates. In combination with advances in endoscopic removal of lesions, many patients may be able to avoid colectomy. The management of colorectal dysplasia in colitis remains controversial, but better understanding of its natural history has aided clinical decision making.

There are many remaining research questions in this interesting and complex area and further studies are needed to help improve the management of patients at increased risk of colorectal cancer. **BJHM**

Conflict of interest: none.

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