MINIREVIEWS

Role of endoscopy in the surveillance and management of colorectal neoplasia in inflammatory bowel disease

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Abstract

Endoscopy has become increasingly fundamental in the management of patients with inflammatory bowel disease (IBD). It is required for diagnosis, assessment of therapeutic response, postoperative follow up and in the surveillance of dysplasia. With rapid advances in technology, including high definition colonoscopy and chromoendoscopy, questions have arisen regarding the most appropriate surveillance and management strategies of colorectal neoplasia in IBD. We aim to review current surveillance strategies, explore the utility of new technologies, and examine the role of endoscopic resection, with the aim of clarifying these questions.

Key words: Inflammatory bowel disease; Colorectal cancer; High definition endoscopy; Chromoendoscopy

Core tip: With the use of new generation, high definition endoscopy, most dysplasia is visually identifiable and hence targeted biopsies are advised. Random biopsies may be utilised in patients with a personal history of neoplasia, primary sclerosis cholangitis, and a tubular colon. Any lesion deemed to be endoscopically resectable should be referred to centres with expertise to do so whilst invisible dysplasia should prompt consideration towards a colectomy.

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INTRODUCTION

Endoscopy has increasingly become a fundamental investigation in the management of patients with inflammatory bowel disease (IBD). It is required for initial diagnosis, assessment of therapeutic response, postoperative follow up and in the surveillance of dysplasia. It is estimated that up to 10% of deaths amongst those with IBD may be attributed to the development of colorectal cancer (CRC). The cumulative risk of CRC in IBD is approximately 2% at 10 years of disease duration, 5% to 8 % after 20 years, and as high as 20% to 30% by the 30-year mark[1-3]. The risk of developing CRC in ulcerative colitis (UC) is similar to that in Crohn's disease (CD) if adjusted for the area of colonic involvement[4]. Improvements in therapy and refinements in surveillance methodology has seen an overall reduction in CRC in patients with IBD[5]. With rapid advances in technology, including high definition colonoscopy and chromoendoscopy, questions have arisen regarding the most appropriate surveillance and management strategies of colorectal neoplasia in IBD. This article aims to review and clarify these questions.

SURVEILLANCE

According to a 2006 Cochrane review, there was no evidence to support surveillance programs conferring survival benefit[6]. The authors attributed this to a lead-time bias, noting earlier malignancy detection and improved prognosis. Nevertheless, due to the inherent risk of developing CRC, many gastroenterological societies still endorse surveillance programs. The recognized risk factors for the development of malignancy include disease duration, extent of bowel involvement, early age of onset, severity of inflammation, family history of CRC in a first degree relative and presence of primary sclerosing cholangitis (PSC)[1-3] (Table 1). Of these, the strongest predictor is duration of disease, although cancer rarely occurs within the first 7 years. Additional potential risk factors are post inflammatory polyps, backwash ileitis and the presence of strictures. Proctitis, where inflammation is limited to the rectum and anus, is thought to not confer increased risk of cancer, hence such patients should undergo normal CRC screening[5]. All patients diagnosed with either UC or CD should be enrolled into a screening program. Neoplasia surveillance has three goals; first is to define the extent of mucosal healing and response to treatment; second is to identify premalignant lesions and facilitate endoscopic resection; and third is to allow for prompt diagnosis of colitis associated malignancy[4].

There are several recognized guidelines regarding surveillance including the European Crohn's and Colitis Organization (2017) guideline, the American Gastroenterological Association (2010) guideline and the British Society of Gastroenterology (2010) guideline (Table 2). Timing and surveillance intervals vary between these. Typically, surveillance is recommended to begin approximately 8 to 10 years after either the beginning of symptoms or diagnosis. Surveillance intervals range from 1 to 5 years, and is often determined by an individual patient's risk profile for the development of colorectal neoplasia. High risk features, warranting annual surveillance, include active extensive disease, a history of dysplasia or stricture, a personal history of PSC and a strong family history of CRC. Intermediate risk patients may be screened every 3 years. Low risk features, allowing for up to 5 years of surveillance intervals, include endoscopic and histological remission, no history of neoplasia and no family history of CRC[5,7]. Table 3 summarizes low, intermediate and high risk features. Pseudopolyps are not considered a risk factor for the development of neoplasia, however do reflect chronic inflammation which may impact upon the quality of mucosal visualization and examination during endoscopic surveillance[4].

Ideal conditions for surveillance include thorough bowel preparation and a non-inflamed mucosa during a quiescent disease period given the difficulty in distinguishing inflammatory from early dysplastic changes both visually endoscopically and on histology[4]. Inadequate bowel preparation may obscure non polypoid lesions and is associated with reduced dysplasia detection and increased

Table 1 Risk factors for the development of dysplasia in inflammatory bowel disease	
Risk factors	**Endoscopic factors**
Disease duration	Active disease
Disease extent	Presence of strictures in ulcerative colitis
Disease severity	Post inflammatory polyps
Past dysplasia	Tubular appearance of colon with loss of colonic haustration
Primary sclerosing cholangitis	
Family history of colorectal cancer	

need for repeat procedures[5]. It is important to note that surveillance should not be delayed indeterminately in waiting for disease quiescence. Some guidelines may recommend the use of random biopsies; however, the current gold standard is the use of targeted biopsies as discussed below.

IBD associated dysplasia is often visually flat and may be quite subtle[3]. A fundamental new concept which has recently developed is that of visible and invisible dysplasia. Visible dysplasia, by definition, is histopathological proven dysplasia on a targeted biopsy of a specific, concerning area recognized on colonoscopic visualization. Invisible dysplasia is histopathological proven dysplasia on a random biopsy, from a visually unremarkable colonic region[8].

With traditional standard definition white light colonoscopy, conventional screening recommendations incorporated random biopsies to increase the pick-up rate of endoscopically invisible dysplasia[4,7]. Random 4 quadrant biopsies were performed every 10 cm from rectum to cecum, with a total of at least 33 samples. This benchmark was estimated to have approximately 90% confidence of detecting dysplasia in the presence of pancolitis. Two major drawbacks of random biopsies are the significant prolongation of procedure time as well as the relatively poor diagnostic yield. One trial comparing targeted and random biopsies in the surveillance of CRC in patients with UC noted the random group had a longer examination time of 41.7 min compared with 26.6 min in the targeted biopsy group[9]. They also found the mean number of biopsies in the random group to be 34.8 compared with 3.1 amongst the targeted biopsy study arm. Targeted biopsies were also reported to have improved neoplastic detection, with improvements in neoplasia detection per colonoscopy (0.211 vs 0.168) as well as a 2.1% improvement in identification of patients with neoplasia. Van den Broek *et al*. demonstrated neoplasia detection in up to 85% of targeted biopsies, with neoplasia identified in 5.7% of random biopsies in only 7.5% of cases[10]. They also demonstrated neoplasia to be macroscopically visible in 94% of cases. A review by Moussata and colleagues noted random biopsies added an additional 15% detection rate of neoplasia compared to chromoendoscopy with targeted biopsy, and that this was exclusively in patients with either a personal history of neoplasia (OR = 5.3; CI: 3.3-8.8, *P* < 0.001), concomitant PSC (OR = 2.3; CI: 1.2-4.2, *P* = 0.006) or had a tubular appearing colon (OR = 1.5, CI: 0.7-3.5, *P* = 0.303)[11]. The authors also noted that when these 3 risk factors were absent, neoplasia was not detected on random biopsies. Taken together, this study suggests that judicial use of random biopsies has a role in detecting invisible dysplasia, and can be considered in patients with either a personal history of neoplasia, concomitant PSC, or noted to have a tubular appearing colon.

With the new era of high definition and image enhanced colonoscopy, the utility of random biopsies has come into question. It is now generally regarded that most colonic neoplasia may be identified through high definition or image enhanced endoscopy[7]. In a retrospective analysis, comparing standard definition, the new generation endoscopes have been estimated to offer a higher ratio both in terms of prevalence (2.21, CI: 1.09-4.45) and in detecting dysplasia on targeted biopsy (2.99, CI: 1.16-7.79)[12]. Large, prospective trials would be required to better appreciate the difference between standard definition and the new generation endoscopes, however such trials are unlikely given many centers have already shifted to high definition imaging modalities.

Chromoendoscopy is an endoscopic technique utilizing dyes to emphasize mucosal characteristics and highlight pathologically abnormal areas. The utility of dyes to enhance mucosal abnormalities was first developed in the 1990s[3]. Initially contrast dyes were applied via a spraying catheter and foot pump[4]. Chromoendoscopy with targeted biopsies is now regarded as the preferred surveillance technique[7,13]. It has been reported to have up to a 3 fold increase in per patient dysplasia detection, and up to 5 fold increase in per lesion dysplasia detection. Dilution of contrast agents must

Table 2 Commonly used guidelines for the screening of neoplasia in inflammatory bowel disease

Society	Commencement	Risk stratification	Interval
ECCO, 2017	8 yr post symptom onset	Stricture or dysplasia, PSC, extensive colitis, severe active inflammation	Annual
		Mild to moderate active inflammation, post inflammatory polyps, or first degree relative with CRC	2-3 yr
		None of the above features	5 yr
AGA, 2010	8 yr post diagnosis	Active inflammation, stricture, post inflammatory polyps, history of dysplasia, first degree relative with CRC, PSC	Annual
		After 2 negative colonoscopies	1-3 yr
ACG, 2010	8-10 yr post diagnosis	No risk stratification	1-2 yr
BSG, 2010	10 yr post symptom onset	Moderate/severe active inflammation on the prior colonoscopy, stricture, dysplasia, PSC, first degree relative with CRC aged < 50 yr	Annual
		Mild active inflammation on prior colonoscopy, post inflammatory polyps, first degree relative with CRC aged > 50 yr	3 yr
		Nil prior inflammation, left sided colitis or CD colitis affecting > 50% surface area of the colon	5 yr

ECCO: European Crohn's and Colitis Organisation; AGA: American Gastroenterological Association; ACG: American College of Gastroenterology; BSG: British Society of Gastroenterology.

be appropriate to allow for adequate mucosal staining without being too intense and visually obscuring subtle mucosal abnormalities. Topical contrast agents commonly used include 0.1% methylene blue or 0.02% to 0.5% indigo carmine[4,7]. The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) guidelines recommend the use of either 0.03% Indigocarmine or 0.04% Methylene blue applied through biopsy or water jet channels. Identified lesions should be first evaluated as resectable or non resectable. Resectable lesions should be referred for Endoscopic Mucosal Resection and/or Endoscopic Submucosal Dissection. Targeted biopsies should be performed on non resectable lesions and those of uncertain significance. The major limitations of chromoendoscopy are the prolonged procedure times, the additional training required on the part of the proceduralist, and the additional costs, all of which act as barriers to the widespread uptake of this technique[3,5,8].

Random biopsies are not recommended from areas which appear macroscopically normal on chromoendoscopy[4]. In addition to targeted biopsies, some guidelines recommend two biopsies from each colon segment to further define disease extent and the severity of inflammation[7]. Chromoendoscopy has an 83.3% (CI: 35.9-99.6) sensitivity and a 91.3% (CI: 43.8-100) specificity for the detection of dysplasia[14]. Its yield may be reduced by severe inflammation, significant pseudopolyposis or poor bowel preparation. In these conditions, or if chromoendoscopy is not available, previous recommendations of standard definition colonoscopy with combined targeted and random biopsies is regarded as an appropriate approach (Figure 1).

If chromoendoscopy is not available, high definition endoscopy is recommended over standard definition endoscopy[7,8]. Iannone *et al*[15] reviewed 10 randomized controlled trials and found chromoendoscopy to be superior to standard definition white light endoscopy, with a relative rate of 2.12 of detecting dysplasia. The major drawback of chromoendoscopy was the longer procedure times. The authors also commented there was no direct evidence of benefit in terms of all cause or cancer specific mortality, nor in the time interval to the development of neoplasia. With further technological improvements there have been significant advancement in endoscopy resolution however most trials have compared chromoendoscopy to standard definition endoscopy. Iacucci *et al*[16] performed a randomised, non-inferiority study to compare high definition endoscopy, chromoendoscopy and iSCAN image enhanced virtual chromoendoscopy. This paper concluded that virtual

Table 3 Low, intermediate, and high risk features to risk stratify patients and guide surveillance intervals

Low risk	Intermediate risk	High risk
Quiescent disease, even with extensive colonic involvement; left sided IBD	Extensive colonic involvement with mild inflammation; post inflammatory polyps; CRC in 1st degree relative aged > 50	Extensive colitis with moderate/severe inflammation; primary sclerosing cholangitis; colonic strictures[1]; dysplasia of any grade[1]; CRC in 1st degree relative aged < 50

[1]In particular if in the prior 5 years.

chromoendoscopy and high definition endoscopy were non inferior to chromoendoscopy in the detection of neoplasia during surveillance. In actual fact, they found high definition endoscopy alone to be adequate in detecting dysplasia without the drawback of the longer procedure times of chromoendoscopy.

An area of interest is the utility of virtual chromoendoscopy or the utility of digital image enhancement, such as narrow band imaging (NBI, Olympus, Japan), Fujifilm Intelligent Colour Enhancement (FICE, Fujifilm, Japan), i-scan OE (Pentax, Japan), CBI (Aohua Photoelectricity, China), VIST (Sonoscape, China), Storz Professional Image Enhancement System (SPIES, Storz, Germany). These optical techniques allow for visual enhancement of the mucosal images through the utility of optical filters, rather than the use of physical contrast dyes, however unlike dye chromoendoscopy, optical filters attempt to narrow the red light spectrum, which preferentially emphasizes vascular patterns[3].

NBI has been demonstrated to have less withdrawal times compared to chromoendoscopy, with mean times of 15.74 min and 26.87 min respectively. However, although NBI has a similar true positive rate compared to chromoendoscopy and an inferior false positive biopsy rate, NBI has a higher percentage rate of missed dysplasia. As a consequence, at present, NBI is not recommended in place of standard or high definition endoscopy or chromoendoscopy[7,8,17].

I-Scan is a new generation hybrid virtual chromoendoscopy system integrated with a EPKi high definition unit (Pentax, Japan) allowing for a combination of optical and virtual enhancements in the single entity. It can enhance surface characteristics through modification of light-dark contrast, can digitally enhance blue areas to emphasize vascular abnormalities, and can provide real time modification of the red-green-blue spectrum of the high definition images to highlight fine mucosal abnormalities[18,19]. This is a digital technique of chromoendoscopy, without the need for contrast dyes. Other digital options include the FICE and SPIES systems. At present, there is no conclusive evidence for the utility of I-Scan, FICE or SPIES in the surveillance of colorectal neoplasia in IBD, however there is ongoing research which will have to be followed closely[3]. Due to the inherent limitations of xenon light sources, novel approaches have been to utilize laser based systems, such as the Blue Laser Imaging (Fujifilm, Japan), or light-emitting diodes such as Blue Light Imaging (Fujifilm, Japan) or Linked Colour Imaging (Fujifilm, Japan). One report suggested Linked Colour Imaging technology to be superior in the diagnosis of residual inflammation, especially where the Mayo endoscopic subscore was 0[3,20]. These are however novel approaches and further research and refinement will be required before they become standard of care. At present, virtual chromoendoscopy has not been demonstrated to be superior to conventional chromoendoscopy. This lack of superiority may perhaps be related to virtual techniques generating less light intensity as well as enhancing vasculature patterns whilst chromoendoscopy emphasizes changes in crypt patterns[4].

Current evidence indicates optimum surveillance modality is through the use of conventional chromoendoscopy or high definition endoscopy with targeted biopsies of concerning mucosal areas. It must be acknowledged that with further technological advances and clinical trials, the preferred modality may change. It should be highlighted that irrespective of modality, the time for withdrawal when performing surveillance for neoplasia in IBD is often higher given dysplastic changes may be very subtle and elusive. Furthermore, it must be emphasized that irrespective of modality, quality is largely impacted upon by mucosal interrogation, with longer and more detailed examinations conferring improvements in neoplasia detection[4].

ENDOSCOPIC RESECTION

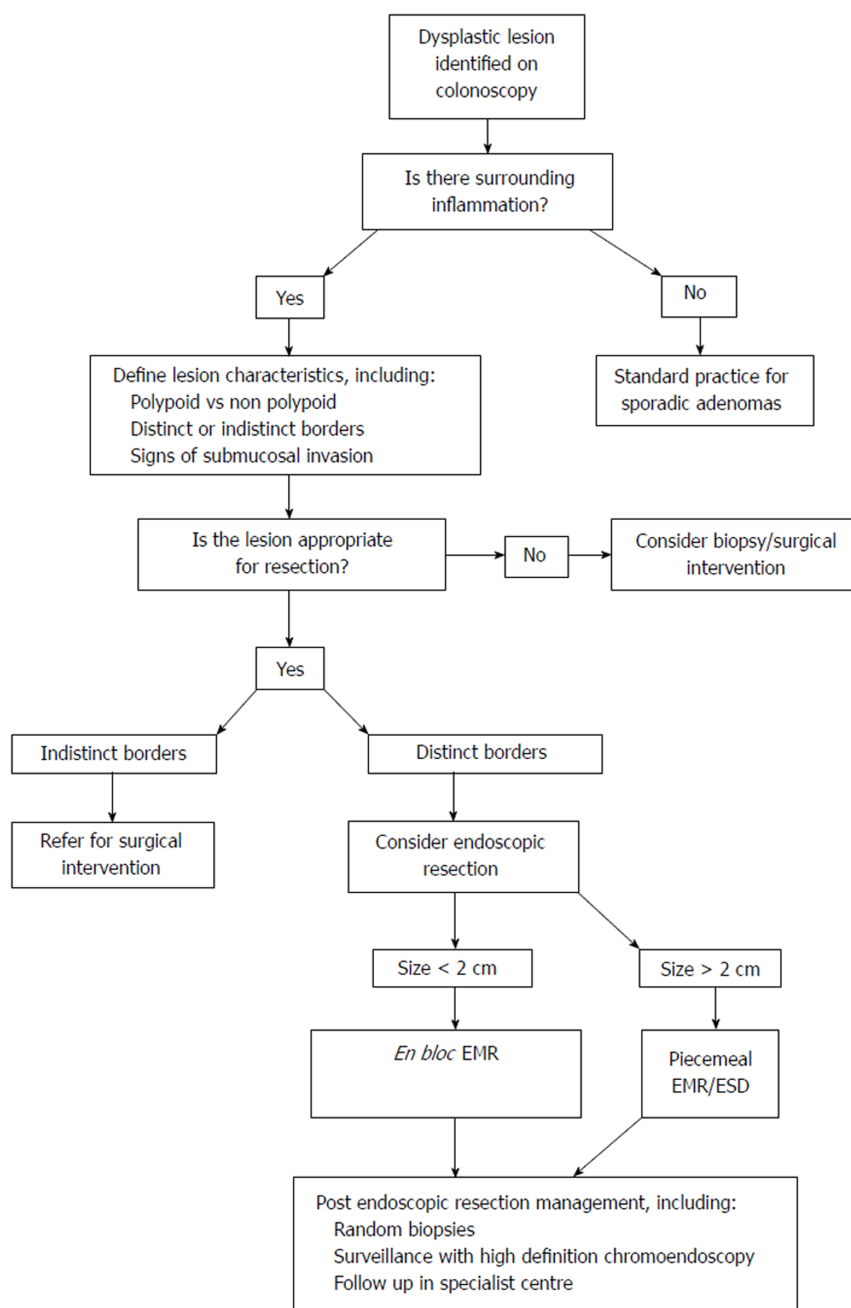Table 4 summarizes the SCENIC consensus nomenclature of dysplasia in

Figure 1 An approach to dysplasia. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

inflammatory bowel disease[5]. On visualization of a lesion, it is imperative to first recognize whether it is within an area of colitis or not. Key features to appreciate include the morphology, margin definition, surface characteristics, size, background mucosa characteristics, and endoscopic access. The lesion should be categorized as either polypoid, *i.e.*, pedunculated or sessile, or non-polypoid, *i.e.*, slightly elevated, flat or depressed. Borders should be classified as distinct or indistinct. It is important to note any suggestions of submucosal invasion, such as the presence of ulceration, depression or failure to lift following submucosal injection[7].

On identification of an area of dysplasia, it is important to determine if the lesion is endoscopically resectable. Performing a biopsy can result in fibrosis, a major risk factor for complications of subsequent future resection strategies such as endoscopic submucosal dissection[21]. Therefore, if it is felt to be technically safe and appropriate, areas of dysplasia should be endoscopically resected[4] rather than undergo unnecessary biopsy. A lesion should be biopsied if the lesion is considered inappropriate for immediate resection or from surrounding tissue post endoscopic resection to assess for invisible dysplasia[3].

A lesion with distinct borders may be considered for endoscopic resection whilst

Table 4 SCENIC consensus nomenclature of dysplasia in inflammatory bowel disease	
Term	**Definition**
Visible dysplasia	Dysplasia confirmed histologically on a targeted biopsy
Invisible dysplasia	Dysplasia on a random biopsy
Polypoid	Lesion protruding ≥ 2.5 mm into the lumen
Non polypoid	Lesion protruding < 2.5 mm into the lumen or not protruding
Superficial elevated	Protrusion < 2.5 mm
Pedunculated	Attached to mucosa via stalk
Sessile	Not attacked via stalk; base contiguous with mucosa
Flat	No protrusion above mucosa
Depressed	At least a portion of lesion depressed below mucosa
Ulcerated	Fibrinous appearing base within lesion
Distinct border	Easily identified from surrounding mucosa
Indistinct border	Not discrete; difficult to distinguish from surrounding mucosa

indistinct borders are preferably surgically managed. An important caveat is that inflammation can impact upon margin visualization. Nevertheless, any well-defined lesion should be endoscopically resected, regardless of the grade of dysplasia[4]. Surface features should be categorized according to standard grading systems such as the Kudo Pit pattern, JNET or MS classification. Lesions identified in areas distinct from areas of colitis should be treated as per standard practice for spontaneous adenomas.

The risk and benefit profile of an individual case will guide the appropriateness of endoscopic management against definitive colectomy. Features favorable for colectomy include ill-defined margins, submucosal invasion, asymmetrical lift not attributable to fibrosis, ulceration or large depression and flat neoplastic changes adjacent to the lesion. It is also important to highlight that if performing endoscopic resection in inflammatory bowel disease, submucosal injection may be difficult, hence careful marking (APC/tip of snare) is essential and one may require a stiffer snare such as a braided or "Histolock" snare. Following endoscopic resection, biopsies of surrounding tissues help evaluate the margins.

Standard snaring is acceptable for small, polypoid or protuberant lesions less than 10 mm in size. Extra care must be taken to ensure complete resection and retrieval. For larger lesions up to 2 cm in size, one may consider *en bloc* endoscopic mucosal resection. If it is larger than 2 cm, then one may consider piecemeal endoscopic mucosal resection unless there is suspicion of submucosal invasion. Endoscopic submucosal dissection (ESD) is an alternative however this may be technically very challenging. Current guidelines recommend random biopsies of peri-resection areas to ensure complete resection, however the diagnostic yield of this is questionable given the development of high definition and chromoendoscopy, as previously discussed[5].

Following endoscopic resection, current guidelines recommend surveillance high definition chromoendoscopy by a specialized IBD proceduralist, rather than colectomy, annually for 5 years. If surveillance is not an option, colectomy may be considered[4].

With regards to invisible dysplasia, once confirmed by a specialist gastrointestinal pathologist, cases should be referred to an IBD specialist and surveillance performed with chromoendoscopy with high definition colonoscopy[3]. Low grade endoscopically invisible dysplasia should be referred for multidisciplinary team review. Given factors such as disease activity and overall patient specific CRC risk factors, a patient centered management plan must be determined and may involve 6 monthly to yearly surveillance or may warrant referral for colectomy. Before the development of high definition and chromoendoscopy, high grade invisible dysplasia would warrant prompt referral for colectomy[22-24]. With the new generation of endoscopic techniques, the management of invisible high grade dysplasia is similar to that of invisible low grade dysplasia, with emphasis being on a multidisciplinary team, patient centered approach to determine whether close surveillance or colectomy is more appropriate[5].

CONCLUSION

With the improvement in endoscopic imaging technologies, surveillance of patients

with IBD have reached new frontiers. Huge progress has also been made in the management of dysplastic lesions. Many of the flat or 'targeted biopsy-only' detected dysplasia that had historically warranted a colectomy can now be visualised as circumscribed lesions with the help of high definition scopes and chromoendoscopy. These lesions are now amenable to endoscopic excision with close subsequent endoscopic follow-up. However, management decisions should be balanced with the risks and benefits of endoscopic, medical, and surgical treatments, during clinical decision making.

Key points

Most colonic dysplasia is visually identifiable with current high definition endoscopic imaging modalities and hence targeted biopsies is advised. Random biopsies may be utilized in patients with a personal history of neoplasia, PSC, or a tubular appearing colon. Lesions deemed to be endoscopically resectable should be referred to centers with expertise to do so and be endoscopically resected rather than undergo unnecessary biopsy. Invisible dysplasia should referred to an IBD specialist and surveillance performed with chromoendoscopy with high definition colonoscopy

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