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MINIREVIEWS

Colorectal cancer surveillance in inflammatory bowel disease: A critical analysis

Devendra Desai, Nutan Desai

Devendra Desai, Division of Medical Gastroenterology, P D Hinduja Hospital, Veer Savarkar Marg, Mahim, Mumbai 400016, India
Nutan Desai, Department of Gastroenterology, Fortis Hospital, Mulund, Mumbai 400016, India
Author contributions: Desai D and Desai N contributed equally to concept and design, acquisition and interpretation of data and final drafting; both authors accepted the final draft.
Correspondence to: Devendra Desai, MD, DNB (Gastroenterology), Division of Medical Gastroenterology, P D Hinduja Hospital, Veer Savarkar Marg, Mahim, Mumbai 400016, India. devendracdesai@gmail.com
Telephone: +91-22-24447106 Fax: +91-22-24440425
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Abstract

Colonoscopic surveillance is advocated in patients with inflammatory bowel disease (IBD) for detection of dysplasia. There are many issues regarding surveillance in IBD: the risk of colorectal cancer seems to be decreasing in the majority of recently published studies, necessitating revisions of surveillance strategy; surveillance guidelines are not based on concrete evidence; commencement and frequency of surveillance, cost-effectiveness and adherence to surveillance have been issues that are only partly answered. The traditional technique of random biopsy is neither evidence-based nor easy to practice. Therefore, highlighting abnormal areas with newer technology and biopsy from these areas are the way forward. Of the newer technology, digital mucosal enhancement, such as high-definition white light endoscopy and chromoendoscopy (with magnification) have been incorporated in guidelines. Dyeless chromoendoscopy (narrow band imaging) has not yet shown potential, whereas some forms of digital chromoendoscopy (i-Scan more than Fujinon intelligent color enhancement) have shown promise for colonoscopic surveillance in IBD. Other techniques such as autofluorescence imaging, endomicroscopy and endocytoscopy need further evidence. Surveillance with genetic markers (tissue, serum or stool) is at an early stage. This article discusses changing epidemiology of colorectal cancer development in IBD and critically evaluates issues regarding colonoscopic surveillance in IBD.

Key words: Advanced imaging; Chromoendoscopy; Colorectal cancer; Colorectal cancer surveillance; Inflammatory bowel disease

Core tip: There is an increase in the risk of colorectal cancer in patients suffering from inflammatory bowel disease. Recent studies have suggested that this risk may be decreasing. In view of the risk, colonoscopic surveillance is recommended in order to detect cancer early. Instead of using previous methods of colonoscopy and random biopsy, newer technology such as chromoendoscopy and biopsy from abnormal mucosa is preferable.

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CHANGING EPIDEMIOLOGY OF COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

The risk of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) was recognized as far back as 1925 for ulcerative colitis (UC) and 1948 for

Crohn's disease (CD)[1,2]. In the second half of the last century, attempts were made to quantify the actual risk of CRC in this population. Earlier studies, mainly in UC patients, tended to overestimate the risk, with cumulative cancer rates reportedly ranging from 16% to 43%[3-7]. A widely cited meta-analysis of 116 studies with age stratified data by Eaden *et al*[8] in 2001 estimated CRC risk as 2% at 10 years, 8% at 20 years and 18% at 30 years. In 2006, two landmark studies suggested a decreasing trend of CRC in IBD. Jess *et al*[9] reported a population-based estimate of CRC in IBD from Olmsted County, Minnesota, US. They reported that the risk of CRC was not increased in UC as compared to the general population [standardized incidence rate (SIR) 1.1; 95%CI: 0.4-2.4], but the risk of CRC was increased in CD (SIR 1.9; 95%CI: 0.7-4.1); the cumulative cancer risk was 2% at 20 years. The other study by Rutter *et al*[10] from St. Marks Hospital, United Kingdom, reported a CRC risk of 2.5% at 20 years, 7.6% at 30 years and 10.8% at 40 years, which was less than that reported by Eaden *et al*[8]. The lower risk of CRC was confined to a location proximal to the splenic flexure, but not at other locations. There were two subsequent meta-analyses. The study by Jess *et al*[11] in 2012 shortlisted eight population-based studies from 1958 to 2004 and reported a risk of 1.6% in patients with UC over 14 years of follow-up; UC increased the risk of CRC 2.4-fold (pooled SIR 2.4, range: 1.05-3.1; 95%CI: 2.1-2.7). The meta-analysis by Lutgens *et al*[12] also shortlisted eight studies from 1988 to 2009 and reported that the risk of CRC was increased in IBD, but was not as high as reported in earlier studies; the pooled SIR was 1.7 (CI: 1.2-2.2). Two recent studies came to different conclusions. In a population-based study from Denmark, Jess *et al*[13] suggested that the risk of colon cancer in UC is not as high as previously reported and in fact may not differ from the general population. To the contrary, Herrinton *et al*[14] showed that the risk of CRC in UC is 60% higher than in age- and gender-matched cohorts of people without IBD from California, and the risk remained the same throughout the study period of 14.5 years. Studies from Asia on CRC in UC are few, and report that the likelihood ranges from 0.87% to 1.8% in general, and can be as high as 13.5% in patients with extensive colitis[15-21].

The risk of CRC in CD was initially underestimated because of failure to evaluate cases of colitis as a separate risk group and to account for the effect of early colectomy. It is now established that patients with colonic or ileocolonic CD have an increased risk of CRC compared to the general population. A meta-analysis of 12 population- and hospital-based studies published in 2006 confirmed an overall relative risk (RR) of 2.5 (95%CI: 1.3-4.7) and an RR of 4.5 in those with colonic CD (95%CI: 1.3-14.7)[13]. The risk for those with ileal disease only was the same as the general population. Regardless of disease distribution, the cumulative risk of CRC was 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years of disease.

Thus, the risk of CRC is increased in IBD, though there is variation due to various factors such as referral center bias, population- or hospital-based data, and small numbers of patients. Prevalence rates of CRC in UC vary from 0.7% to 3.3%[9,22-28] and the cumulative risk is 1%, 2% and 5% for 10, 20, and > 20 years of disease duration, respectively, and a pooled SIR of 1.7 in all patients with IBD in population-based studies[13]. Table 1 summarizes the risk of CRC in IBD in various population groups. The surveillance strategy needs to take into account this decreasing risk of CRC in IBD.

GUIDELINES FOR SURVEILLANCE OF CRC IN IBD

Guidelines by various societies suggest that surveillance for CRC should begin after 8-10 years of disease duration. The guidelines include those from the American Gastroenterological Association (AGA; 2004 and 2010), Association of Coloproctology for Great Britain and Ireland (2004 and 2010), British Society of Gastroenterology (BSG; 2002 and 2010), National Institute for Health and Clinical Excellence (2011), European Crohn's and Colitis Organization (2013), and Australian (2011) and Austrian societies[29-34]. Table 2 summarizes the guidelines with changes over time. The salient features of the guidelines include that surveillance is advised 8-10 years after the onset of symptoms, irrespective of the extent (surveillance is not advised in patients with proctitis and proctosigmoiditis). The frequency of surveillance varies amongst the guidelines: AGA guidelines initially suggest surveillances every 1-2 years, and if two examinations are negative, then every 1-3 years up to the end of the second decade, after which the surveillance is again every 1-2 years. In the BSG guidelines, the frequency of surveillance depends upon the risk. Lower risk requires surveillance every 5 years, which includes extensive colitis with no endoscopic or histologic inflammation, left-sided colitis or crohn' s colitis (involving < 50% colon). Surveillance every three years is recommended for intermediate risk, which includes extensive colitis with mild active endoscopic, histologic inflammation, post inflammatory polyps, or family history of CRC in first-degree relatives over 50 years of age. Yearly surveillance is needed for those with higher risk, including extensive colitis with moderate or severe endoscopic or histologic inflammation, stricture or dysplasia in the past five years where patients have declined surgery, primary sclerosing cholangitis, or family history of CRC in a first-degree relative less than 50 years of age (surveillance yearly). The method of surveillance also varies, from random biopsy every 10 cm, which is still advocated, though the preferred method is to use chromoendoscopy and magnification and take biopsies from the abnormal areas.

Comparison of American and British guidelines

Mooiweer *et al*[35] from the Netherlands compared the American and British guidelines in a retrospective study of 1018 patients. They concluded that BSG surveillance intervals offer the advantage of a lower colonoscopic

Table 1 Risk of colorectal cancer in inflammatory bowel disease

Ref.	Type of study	Risk in UC	Risk in CD	Odds ratio (95%CI)	Comments
Eaden *et al*[8] 2001	Meta-analysis 116 studies; 41 mentioned duration of UC	3.7%		NA	2% at 10 yr, 8% at 20 yr, 18% at 30 yr
Jess *et al*[9] 2006	Population-based	6/378 (1.6%)	6/314 (1.9%)	SIR UC: 1.1 (0.4-2.4) CD: 1.9 (0.7-4.1)	Cumulative cancer risk 2% at 20 yr
Rutter *et al*[10] 2006	Hospital-based retrospective	3/600 (0.5%)	NA	NA	2.5% at 20 yr, 7.6% at 30 yr, 10.8% at 40 yr
Jess *et al*[11] 2012	Meta-analysis of 8 population-based (1958-2004)	1.6% (14 yr follow-up)	NA	Pooled SIR: 2.4 (2.1-2.7)	Risk of in patients with UC over
Lutgens *et al*[12] 2013	Meta-analysis (1988-2009)			IBD pooled SIR Population based: 1.7 (1.2-2.2) Referral based: 5.3 (2.8-7.8)	
Jess *et al*[13] 2012	Population-based			RR for CRC- UC 1979-1988: 1.34 (1.13-1.58) 1989-1998: 1.09 (0.9-1.33) 1999-2008: 0.57 (0.41-0.80) RR for CRC in CD: 0.85 (0.67-1.07), which did not change over time	CRC risk in UC reduced over three decades and comparable to general population; CD no change
Herrinton *et al*[14] 2012	Hospital-based	UC 53 /10895 CD 29/5603		UC: 1.6 (1.3-2.0) CD: 1.6 (1.2-2.0)	CRC risk in UC and CD 60% higher than population
Asian studies					
Gilat *et al*[15] 1988	Population-based (central Israel)		NA		CRC risk in UC: 0.2% at 10 yr, 5.5% at 20 yr, 13.5% at 30 yr
Kochhar *et al*[16] 1992	Hospital-based (India)	UC 1.8%	NA		
Venkataraman *et al*[17] 2005	Hospital-based (India)	UC 0.94%			
Kim *et al*[19] 2009	Population-based (South Korea)	UC 0.50%			
Kekilli *et al*[20] 2010	Hospital-based (Turkey)	UC 1.10%			
Gong *et al*[21] 2012	Hospital-based (China)	UC 0.87%			

CD: Crohn's disease; FH: Family history; IBD: Inflammatory bowel disease; NA: Not applicable; PSC: Primary sclerosing cholangitis; RR: Relative risk; SIR: Standardized incidence rate; UC: Ulcerative colitis.

workload (421 colonoscopies as per BSG guidelines and 541 colonoscopies as per AGA guidelines). However, the risk stratification of the AGA appears superior in distinguishing patients at higher risk of colitis-associated neoplasia (AGA: 5.3 and 20.3% in low and high risk groups, respectively; BSG: 3.6, 6.9 and 10.8% in low, intermediate and high-risk groups, respectively).

ISSUES WITH SURVEILLANCE

Is surveillance really necessary?

Most of the above guidelines suggest that surveillance is recommended based on the high risk of CRC in IBD[8]. However, a recent study by Jess *et al*[13] suggested that the incidence of CRC in UC in a Dannish population decreased over 30 years (1979-2008), and the risk was not different from the general population during the period of 1999-2008 (RR 0.8). There is no systematic surveillance in Denmark. In their population-based study from patients in the US, Jess *et al*[9] reported no overall increase in CRC in all UC patients but only in patients with extensive colitis. A Dannish article commented that, based on Dannish epidemiologic data, the American and British recommendations were dubious and surveillance may be recommended in patients with extensive, uncontrolled inflammation and patients with primary sclerosing cholangitis, and not on the disease duration[36]. Thus, although surveillance is recommended by all societies, routine surveillance may not be beneficial and surveillance strategies should be reviewed due to the reduction in risk of CRC in UC.

When should surveillance begin?

The guidelines suggest that surveillance for CRC should begin after 8-10 years of disease duration. However, if these recommendations are followed, CRC is likely to be missed. In the study by Gilat *et al*[15], 2/26 patients who developed CRC in UC had a disease duration less than ten years (six and nine years)[16]. The cumulative risk of CRC in the first decade was 1.15% in the study by Gong *et al*[21], and 1.6% in the meta-analysis by Eaden *et al*[8]. Lutgens *et al*[37] reported that 15% of their patients with UC developed CRC before the recommended surveillance period. Kocher *et al*[16] reported that 2/8 patients developed CRC at seven and eight years of disease duration. Thus, we are faced with a dilemma: on one hand, the incidence seems to be decreasing, whereas on the other hand, we are likely to miss about 15%-20% of patients who develop CRC before the recommended commencement of surveillance.

Table 2 Guidelines of various societies on surveillance for colorectal cancer in ulcerative colitis

Society	Year	Beginning of surveillance	Frequency	Technique	Biopsy protocol	Risk	Change
BSG	2002	All patients have colonoscopy screening at 8-10 yr; surveillance begins 8-10 yr after onset for pancolitis, 15-20 yr for left-sided colitis	Decrease in surveillance interval with increase in disease duration for pancolitis: Every 3 yr: 2nd decade Every 2 yr: 3rd decade Every 1 yr: 4th decade	Nil	2-4 random biopsies every 10 cm from the entire colon	Patients with PSC, including those with OLT, should have annual screening	
AGA	2004	8-10 yr	Every 1-2 yr	Nil			
ACG	2004	8-10 yr	Every 1-2 yr	Nil			
ECCO	2008	8 yr for pancolitis, 15 yr for left-sided colitis	Every 2 yr: 1st two decades Every 1 yr: 3rd decade	CE			
BSG	2010	10 yr	Based on extent of disease, endoscopic and histologic activity, FH of CRC, presence of PSC, pseudopolyps, stricture, dysplasia on biopsy: Every 3 yr: low risk Every 2 yr: intermediate risk Every 1 yr: high risk	CE	Random biopsies every 10 cm and biopsies from raised/ suspicious areas on CE	Patients with PSC, including those with OLT, should have annual screening	If dysplastic polyp within area of inflammation can be removed entirely, colectomy is not necessary
AGA	2010	8-10 yr	Every 1-2 yr If two examinations are negative, then every 1-3 yr up to 20 yr, then every 1-2/yr	CE		Patients with PSC, including those with OLT, should have annual screening	
NICE	2011	10 yr	As per BSG 2010 guidelines	CE			
Australian	2011	8-10 yr	As per BSG 2010 guidelines	CE			
ECCO	2013	6-8 yr, 8-10 yr	Same as BSG	CE			

ACG: Association of Coloproctology for Great Britain and Ireland; AGA: American Gastroenterological Association; BSG: British Society of Gastroenterology; CE: Chromoendoscopy; CRC: Colorectal cancer; ECCO: European Crohn's and Colitis Organization; FH: Family history; NICE: National Institute for Health and Clinical Excellence; OLT: Orthotopic liver transplantation; PSC: Primary sclerosing cholangitis.

ROLE OF NEWER MODALITIES FOR SURVEILLANCE IN IBD

There are clear lapses in the present form of colonoscopic surveillance. The random biopsy technique is not very useful for detecting dysplasia. In a retrospective analysis of 11772 biopsies in 466 colonoscopies in 167 patients over ten years, this technique had a much lower yield of dysplasia as compared to targeted biopsies and did not significantly change the management[38,39]. Two retrospective studies have shown that dysplasia in IBD is macroscopically visible in 72%-77% of patients[40,41]. Based on a single retrospective study, high-definition endoscopy is three times more likely to detect dysplastic lesions as compared to standard-definition endoscopy[42].

Chromoendoscopy and magnification chromoendoscopy have been used for the detection of dysplastic lesions that are likely to be missed by white light endoscopy. A meta-analysis of six studies showed that the yield with chromoendoscopy was 7% greater than that of white light endoscopy, and the pooled increase in targeted dysplasia detection of chromoendoscopy over white light endoscopy was 44% (95%CI: 28.6-59.1)[43]. The difference in detection of flat dysplastic lesions was 27% (95%CI: 11.2-41.9). Chromoendoscopy has been incorporated in the recent guidelines.

Dyeless chromoendoscopy includes compound-band imaging and narrow-band imaging, which fails to detect dysplasia in patients with IBD and has not been recommended for surveillance in its present form[39]. Digital chormoendoscopy includes i-Scan and Fuji intelligent chromoendoscopy, which have not been studied in clinical trials in IBD patients to detect dysplasias. They have been used to detect adenomas in surveillance programs in CRC in a non-IBD population, where only i-Scan demonstrated some positive results[39]. Studies using autofluorescence imaging have shown that it is a sensitive modality to detect dysplastic lesions in IBD[44]. Confocal laser endomicroscopy and endocytoscopy allow for magnification of up to 1390-fold. Confocal laser endomicroscopy detects more dysplasia than white light and chromoendoscopy, but requires special training and takes twice as much time[45,46]. Table 3 summarizes the important features of these modalities.

Although the pathogenesis of CRC in IBD differs from sporadic CRC, polyposis syndromes and hereditary non-polyposis colon cancers, the pathways include chromosomal instability, microsatellite instability and CpG island methylation pathways. Tissue-based markers, such as aneuploidy, p53, and microsatellite instability, are associated with the development of dysplasia or CRC[30]. They cannnot be included in the guidelines for surveillance for CRC in IBD at present.

NON-COLONOSCOPIC APPROACHES FOR CANCER SURVEILLANCE IN IBD

Non-colonoscopic techniques that are noninvasive are

Table 3 Endoscopic dysplasia-detection modalities in patients with inflammatory bowel disease and recommendations for use[39]

	Demonstrated accuracy in IBD	Supporting evidence in IBD	Incorporated into guidelines	Practicality of use in practice	Should be used in 2013?
Random biopsy	-	-	+	±	±
HD WLE	+	±	+	+	+
Chromoendoscopy	+	+	+	+	+
NBI	-	-	-	±	-
FICE	NA	NA	-	±	-
i-Scan	NA	NA	-	±	-
AFI	+	+	-	-	-

AFI: Auto-fluorescence imaging; HD WLE: High-definition white light endoscopy; FICE: Fuji intelligent chromoendoscopy; IBD: Inflammatory bowel disease; NA: Not available; NBI: Narrow-band imaging. Reproduced with permission[39].

more appealing to patients than the repeated invasive colonoscopic approach, with the potential to reduce the high cost associated with surveillance. Stool examination has been used for surveillance for sporadic CRC and stool DNA testing has recently been incorporated[47]. Studies by Kisiel and others suggest that stool DNA testing is feasible to detect CRC in patients with IBD[48,49]. Although this approach is not recommended for surveillance at present, it has the potential to radically change the approach to surveillance.

IS SURVEILLANC EFFECTIVE? DOES SURVEILLANCE SAVE LIVES? IS IT COST-EFFECTIVE?

Multiple case series and case control studies have suggested that surveillance leads to improvement in survival in UC, which was not supported by a Cochrane systematic review[50-58]. The data from the Cochrane analysis suggests that there is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. In patients undergoing surveillance, CRC is detected at an earlier stage, which may lead to a better prognosis (which may actually be due to lead-time bias). Surveillance may be effective in reducing the risk of death and it may be cost-effective. These findings have to be taken with the facts that these pivotal studies were in the 1990s, and the Cochrane analysis was in 2004. Studies showing a reduction in CRC have been published after these studies and this analysis may not hold true in the situation with reduced risk of CRC in UC. Surveillance is advocated in CD but there is no data to support it[30].

ADHERENCE OF PHYSICIANS AND PATIENTS TO SURVEILLANCE COLONOSCOPY

There is a wide variation in conducting colonoscopic surveillance by gastroenterologists. Eaden *et al*[59] reported that all British gastroenterologists perform colonoscopic surveillance in pancolitis, but only 24% practiced surveillance in left-sided colitis, and only 2% took more than 20 biopsies. In a survey from the Netherlands, 95% of gastroenterologists performed colonoscopic surveillance in UC and 65% in CD; a majority (73%) of gastroenterologists took fewer than 30 biopsies, and only 27% followed AGA guidelines[60]. From this and similar data, it is clear that the concept of colonoscopic surveillance is accepted by gastroenterologists in general, but there are lapses in the frequency of surveillance and in taking the requisite number of biopsies. Targeted biopsies may reduce this problem. Friedman *et al*[61] studied patient-related factors in colonoscopic surveillance and reported that only one-fourth of their patients underwent surveillance colonoscopy at an interval of less than three years; the factors related to non-adherence were logistics, health perceptions, stress regarding procedure, job or personal life, and procedural problems. The most frequent patient-related reason was difficulty with bowel preparation.

CONCLUSION

Should surveillance be continued in same way today or should we change it? It is clear that colonoscopic surveillance in the present form is neither an ideal nor practical approach. We feel that in the light of new data, the guidelines need to be re-examined. The surveillance should likely begin at six years after the onset of symptoms. It should consist of high-definition white light endoscopy with magnification chromendoscopy and with targeted, rather than random, biopsies. The frequency of surveillance is not clear. In view of the recent comparison of American and British guidelines, further studies are necessary to decide frequency of surveillance. At present, British guidelines are useful, considering the fact that the risk of CRC is decreasing in UC. But there are ambuguities in both guidelines. As the techology evolves, it should be incorporated in surveillance (after considering cost-effectiveness): digital chromoendoscopy seems to come close to this. Other new technologies seem many years away.

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