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**Colorectal cancer surveillance in inflammatory bowel disease: A critical analysis**

Desai D *et al.* Colorectal cancer surveillance in IBD

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:** Both authors contributed equally to concept and design, acquisition and interpretation of data and final drafting; both had 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](mailto: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 (CRC) seems to be decreasing in majority of recently published studies, thereby needing a rethink on surveillance strategy; surveillance guidelines are not based on concrete evidence; Commencement of surveillance, 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 the highlighting of abnormal areas with newer technology and biopsy from these areas are the way forward. Of the newer technology, digital mucosal enhancement like high definition white light endoscopy and chromoendoscopy (with magnification) have been incorporated in guidelines; Dyeless chromoendoscopy (narrow band imaging) has not yet showed potential where as some forms of digital chromoendoscopy (i-scan more than Fujinon intelligent color enhancement have showed promise for colonoscopic surveillance in IBD. Other techniques like autofluorescence imaging, endomicroscopy and endocytoscopy need further evidence. Surveillance with genetic markers (tissue, serum or stool) is at evanescent stage. This article discusses changing epidemiology of CRC development in IBD and critically evaluates issues regarding colonoscopic surveillance in IBD.

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

**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 this risk of colorectal cancers, colonoscopic surveillance is recommended in order to detect cancer early. Instead of earlier method of colonoscopy and random biopsy, newer technology like chromoendoscopy and biopsy from abnormal mucosa is preferable.

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**INTRODUCTION**

Changing epidemiology of colorectal cancer (CRC) in inflammatory bowel disease (IBD)

Risk of colorectal cancer in patients with 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 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 rate reportedly ranging from 16% to 43%[3-7]. A widely cited metaanalyses of 116 studies by Eaden *et al*[8] with age stratified data, 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 decreasing trend of CRC in IBD. Jess *et al*[9] reported a population-based estimate of CRC in IBD from Olmsted County, Minnesota, United States. They reported the risk of CRC was not increased in UC as compared to general population (Standardized incidence rate (SIR) 1.1; 95% confidence interval (CI): 0.4 -2.4; 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, UK, reported 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 in study by Eaden *et al*[8]. The lower risk of CRC was confined to location proximal to splenic flexure but not at other locations. There were 2 subsequent metaanalyses: A meta-analysis by Jess *et al*[11] (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 to 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 is increased in IBD but is 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. Jess *et al*[13], in a population-based study from Denmark, suggested that the risk of colon cancer in UC is not as high as previously reported and in fact may not be different than that in the general population. To the contrary, Herrington *et al*[14] from California showed that the risk of CRC in UC is 60% higher than in age- and gender-matched cohorts of people without IBD, 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 as high as 13.5% in patients with extensive colitis[15-21].

The risk of CRC in CD was underestimated initially because of failure to evaluate cases of colitis as a separate risk group and to account for effect of early colectomy. It is now established that patients with colonic or ileocolonic CD have a increased risk of CRC compared to general population. A metaanalysis of 12 population based and hospital based studies published in 2006 confirmed an overall RR of 2.5 (95%CI: 1.3-4.7) and a 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 same as 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 colorectal cancer is increased in IBD, although there is variation due to various factors such as referral center bias, population or hospital based data and small number 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 standardized incidence ratio of 1.7 in all patients of IBD in population based studies[13]. Table 1 summarizes the risk of colorectal cancer in IBD in various population groups. The surveillance strategy needs to take in to account this decreasing risk of CRC in IBD.

**GUIDELINES FOR SURVEILLANCE FOR CRC IN IBD**

The guidelines include AGA guidelines (2004 and 2010), ACG guidelines (2004and 2010), BSG guidelines (2002 and 2010), NICE guidelines (2011), ECCO guidelines (2013), guidelines by Australian (2011) and Austrian societies[29-34]. Guidelines by various societies suggest that surveillance for CRC should begin after 8 to 10 years of disease duration. Table summarizes the guidelines with changes over time. The salient features of the guidelines include: (1) The surveillance is advised 8 to 10 years after the onset of symptoms, irrespective of the extent (the surveillance is not advised in patients with proctitis and proctosigmoiditis); (2) The frequency of surveillance varies amongst the guidelines: AGA guidelines suggest surveillance initially 1 to 2 yearly and if 2 examination are negative, every 1 to 3 yearly upto end of second decade, after which again the surveillance is 1 to 2 yearly. In the BSG guidelines, frequency of surveillance depends on the risk. Lower risk includes extensive colitis with no endoscopic or histologic inflammation or left sided colitis or crohn’s colitis with involving < 50% colon (surveillance every 5 years). Intermediate risk includes extensive colitis with mild active endoscopic or histologic inflammation or post inflammatory polyps or family history of CRC in first degree relatives age more than 50 years (surveillance every 3 years). Higher risk include extensive colitis with moderate or severe endoscopic or histologic inflammation or stricture in past 5 years or dysplasia in past 5 years where patients has declined surgery or primary sclerosing cholangitis or family history of CRC in a first degre relative < 50 years of age (surveillance yearly); and (3) The way the surveillance is done is changing. From random biopsy every 10 centimeters, the preferred method is to use chromoendoscopy and magnification and take biopsies from the abnormal areas. However random biopsies are still advocated (Table 2).

**COMPARISON OF AMERICAN AND BRITISH GUIDELINES**

Mooiweer *et al*[35] from Netherlands compared the American and British Guidelines in 1018 patients in a retrospective study. They concluded that BSG surveillance intervals offer the advantage of a lower colonoscopic workload (421 colonoscopies as per BSG guidelines and 541 colonoscopies as per AGA guidelines), the risk stratification of the AGA seems superior in distinguishing patients at higher risk of colitis associated neoplasia (AGA guidelines: the cancer associated neoplasia was 5.3% and 20.3% in low and high risk groups, respectively; BSG guidelines: cancer associated neoplasia was 3.6% (low risk), 6.9% (intermediate risk) and 10.8% (high-risk) groups.

**ISSUES WITH SURVEILLANCE**

***Is surveillance really necessary?***

Most of the above guidelines suggest that surveillance is recommended. These were based on paper showing high risk of CRC in IBD[8]. However the recent study by Jess *et al*[9] suggested that the incidence of CRC in ulcerative colitis in Dannish population decreased over 30 years (1979 to 2008) and during the period 1999 to 2008, the risk was not different from the general population (Relative risk 0.8)[13]. There is no systematic surveillance in Denmark. Jess *et al*[9] in a population based study from study from Olmsted county, Minnesota, reported no overall increase in CRC in all UC patients but only in patients with extensive colitis. A Dannish article, commented that, the based on Dannish epidemiological data, the American and British recommendations were dubious and surveillance may be recommended in patients with extensive uncontrolled inflammation and patients with PSC and not on the disease duration[36].

Thus, although surveillance is recommended by all societies, routine surveillance may not be beneficial and surveillance strategy needs to be reviewed in face of reduction in risk of CRC in UC.

***When should surveillance begin?***

Guidelines by various societies suggest that surveillance for CRC should begin after 8 to 10 years of disease duration. However, if these recommendations are followed, CRC is likely to be missed. In the study by Gilat *et al*[16], 2 of 26 patients who developed CRC in UC had disease duration less than 10 years (6 and 9 years). 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]. Lutgen *et al*[37] reported that 15% of their patients with UC developed CRC before the recommended surveillance. Kocher *et al*[16] reported that 2 of 8 patients developed CRC at 7 and 8 years of disease duration.Thus we are faced with dual challenge: On one hand the incidence seems to be decreasing where as on the other hand we are likely to miss about 15 to 20% of patients who develop CRC before the recommended commencement of surveillance.

**ROLE OF NEWER MODALITIES FOR THE SURVEILLANCE IN IBD**

Clearly there are lacunae in the preset form of colonoscopic surveillance. Random biopsy techique is not much useful for detecting dysplasia. In a retrospective analysis of 11772 biopsies in 466 colonoscopies in 167 patients over 10 years, random biopsy 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% to 77% patients[40,41]. Based on single retrospective study, high definition endoscopy is likely to detect dysplastic lesions 3 times as compared to standard definition endoscopy[42].

Chromoendoscopy and magnification chromoendoscopy has been used for the detection for dysplastic lesion which are likely to be missed by white light endoscopy. A metanlysis of 6 studies showed that chromoendoscopy yield was 7% more than that of white light endoscopy and 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 lesion was 27% (95%CI: 11.2-41.9). Chromoendoscopy has been incorporated in the recent guidelines.

Dyeless chromoendoscopy includes narrow band imaging and compound band imaging and digital chormoendoscopy includes i-scan and FICE.

Narrow Band Imaging (NBI): Studies using NBI have shown that it has failed to detect dysplasia in patients with IBD and has not been recommended for surveillance in present form[39]. FICE and i-scan 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 non IBD population where i-scan has shown some positive results whereas FICE has not shown encouraging results[39].

Autofluorescence imaging: studies using autofluorrescence imaging have shown that it is a sensitive modality to detect dysplastic lesions in IBD[44].

Confocal laser endomicroscopy (CLE) and endocytoscopy: This technique allows magnification upto 1390 folds. CLE has detected more dysplasia than WLE and chromoendoscopy but need a special training and takes twice as much time as chromoendoscopy[45,46]. Table 3 summarizes the important features of these modalities.

Molecular markers: Although pathogenesis of CRC in IBD is not exactly similar to that in sporadic CRC, polyposis syndromes and hereditary non polyposis colon cancers, the pathways include chromosomal instability, microsatellite instabilty and CpG island methylation pathway. The tissue based markers like aneuploidy, p53, microsatellite instabilty have shown association 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 include non invasive and much more appealing approach to patients than the repeated invasive colonoscopic approach, with potential to reduce high cost associated with surveillance. Stool examination has been used for surveillance for sporadic CRC and stool DNA testing has been incorporated recently[47]. A study by Kisiel *et al*[48,49] suggested that stool DNA testing was feasible to detect CRC in patients with IBD. Although this approach is not recommended for surveillance at present, it has potential to change the approach to surveillance radically.

**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 ulcerative colitis, which was not supported by Cochrane systematic review[50-58]. The data from Cochrane analysis suggests that there is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis. In patients undergoing surveillance, CRCs tend to be detected at an earlier stage, which may lead to 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 3 pivotal studies were in 1990s and Cochrane analysis in 2004. Studies showing reduction in colorectal cancers 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 the gastroenterologists. Eaden *et al*[59] reported that all British gastroenterologist performed colonoscopic surveillance in pancolitis but only 24 % practiced aurveillance in left sided colitis and only 2% took more than 20 biopsies. In a survey from The Netherlands 95% gastroenterologist performed colonoscopic surveillance in UC and 65% in CD; majority (73%) of gastroenterologists took < 30 biopsies. Only 27% followed AGA guidelines[60]. From this and similar data, it is clear that the concept of colonoscopic surveillance is accepted by gastroenterologist in general but there are lacunae 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 < 3 years interval; the factors related to non adherence were logistics, health perceptions, stress regarding procedure, job or personal life and procedural problems[61]. The most frequent patient related reason was difficulty with bowel preparation.

**CONCLUSION**

Should surveillance be continued in same way today or should we change the way that we do surveillance?

It is clear that colonoscopic surveillance in the present form is neither ideal nor practical approach. We feel that in the light of new data, the guidelines need to be relooked at. The surveillance should begin probably at 6 years after the onset of symptoms. It should consist of high definition white light endoscopy with magnification chromendoscopy and targeted biosies 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 probably 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 seems many years away.

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**Table 1 The risk of colorectal cancers in inflammatory bowel disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of study** | **Risk in UC** | **Risk in CD** | **Odds ratio (95%CI)** | **Comments** |
| Eden *et al*[8] 2001 | Metaanalysis 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 (0.42.4)  CD: 1.9 (0.7-4.1) | Cumulative cancer risk 2% at 20 yr |
| [Rutter *et al*[10]](http://www.ncbi.nlm.nih.gov/pubmed?term=Rutter%20MD%5BAuthor%5D&cauthor=true&cauthor_uid=16618396) 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 | Metaanalyses 8 population-based studies 1958 to 2004 | 1.6% (14 yr of follow-up) | NA | pooled SIR: 2.4  (2.1-2.7) | risk of in patients with UC over |
| [Lutgens *et al*[12]](http://www.ncbi.nlm.nih.gov/pubmed?term=Lutgens%20MW%5BAuthor%5D&cauthor=true&cauthor_uid=23448792) 2013 | Metaanalyses 1988 to 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 study |  |  | 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 3 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 study (central Israel) |  | NA |  | CRC risk in UC  10 yr 0.2%, 20 yr 5.5%, 30 yr 13.5% |
| 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% |  |  |  |
| Kekili *et al*[20] 2010 | Hospital based (Turkey) | UC 1.10% |  |  |  |
| Gong *et al*[21] 2012 | Hospital based (China) | UC 0.87% |  |  |  |

UC: Ulcerative colitis; CD: Crohn’s disease; SIR: Standardized incidence rate; CI Confidence interval; NA: Not applicable; FH: Family history; PSC: Primary sclerosing cholangitis.

**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 to have screening colonoscopy at 8-10 yr, surveillance to begin at 8-10 yr after onset for pancolitis  15-20 yr -left sided colitis | Decrease in surveillance interval with increase in disease duration for pancolitis 3 yearly -2nd decade  2 yearly- 3rd decade  1 yearly- 4th decade | Nil | 2-4 random biopsies every 10cm from entire colon | Patients with PSC including those with OLT should have annual screening |  |
| AGA | 2004 | 8 to 10 yr | 1 to 2 yr | Nil |  |  |  |
| ACG | 2004 | 8 to 10 yr | 1 to 2 yr | Nil |  |  |  |
| ECCO | 2008 | 8 yr –pancolitis  15 yr - left sided colitis | 2 yearly-1st and 2nd decade  1 yearly 3rd decade | Chromo-endoscopy |  |  |  |
| BSG | 2010 | 10 yr | 3 yearly – low risk  2 yearly - intermediate risk  1 yearly - high risk  Risk stratification based on extent of diease, endoscopic and histological activity, FH of CRC, presence of PSC, pseudopolyps, stricture, dysplasia on biopsy | Chromo-endoscopy | Random biopsies every 10 cm +biopsies from raised / suspicious areas on chromoendoscopy | Patients with PSC including those with OLT should have annual screening | If dysplastic polyp within area of inflammation can be removed entirely, colectomy not necessary |
| AGA | 2010 | 8 to 10 yr | 1 to 2 yr  If 2 examinations are –ve, 1 to 3 yr upto 20 yr After 20 yr, 1 to 2 yearly | Chromo  endoscopy |  | Patients with PSC including those with OLT should have annual screening |  |
| NICE | 2011 | 10 yr | As per BSG 2010 guidelines | Chromo  endoscopy |  |  |  |
| Australian | 2011 | 8 – 10 yr | As per BSG 2010 guidelines | Chromo  endoscopy |  |  |  |
| ECCO | 2013 | (6-8 yr)  8 to 10 yr | Same as BSG | Chromo  endoscopy |  |  |  |

**Table 3 Summary of 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 | N/A | N/A | - | ± | - |
| i-Scan | N/A | N/A | - | ± | - |
| AFI | + | + | - | - | - |

IBD: Inflammatory bowel disease;AFI: Autofluorescence imaging; FICE: Fuji Intelligent Chromoendoscopy; DH WLE: high-definition white-light endoscopy; N/A: Not available; NBI: Narrow-band imaging. Reproduced with permission ref.[39].

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