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Review Article

Comparison of Clinical Guidelines for Ulcerative Colitis: ECCO, BSG, US and Japanese Guidelines with Reference to Surveillance Program

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Abstract

Surveillance colonoscopy with random and targeted biopsies has been recommended to detect early neoplasia in ulcerative colitis. Different national and international gastroenterological societies, including the ECCO, BSG, AGA, ASGE and the Japanese research group, have published similar surveillance guidelines for early detection of dysplasia/cancer. The purpose of this study is to compare the concordance and differences in the following sections of the guidelines, including the surveillance colonoscopy and biopsy protocols, of these international and national guidelines for cancer surveillance in ulcerative colitis patients. Surveillance colonoscopy and biopsy protocol are evaluated as below: 1) Risk of CRC; 2) High risk status of cancer; 3) Candidates for surveillance; 4) Screening colonoscopy;5) Interval of surveillance colonoscopies; 6) Number of biopsies recommended; 7) Random or targeted biopsies; 8) Method of random biopsy; 9) Method of targeted biopsy; 10) Use of chromoendoscopy/magnifying colonoscopy.

Chromoendoscopy and high-resolution endoscopy may have superior ability for the detection of neoplasia. Discussion should begin about further development of the existing guidelines to give more effective strategies, so that patients can hope to receive adequate surveillance in the future.

ABBREVIATIONS

UC: Ulcerative Colitis; CRC: Colorectal Cancer; ECCO: European Crohn's and Colitis Organization; BSG: British Society of Gastroenterology; AGA: American Gastroenterological Association; ASGE: American Society for Gastrointestinal Endoscopy; PSC: Primary Sclerosing Cholangitis, Study concept and design, HS: acquisition of data; HO: analysis and interpretation of data; AN: drafting of the manuscript; MS: critical revision of the manuscript for important intellectual content; HT: study supervision; MS

INTRODUCTION

Patients with longstanding Ulcerative Colitis (UC) are at an increased risk of developing Colorectal Cancer (CRC) [1]. In an attempt to reduce the CRC mortality in UC patients, surveillance colonoscopy with random and targeted biopsies has been recommended for the early detection of neoplasia. Increasing introduction of novel endoscopic techniques such as magnifying colonoscopy and virtual chromoendoscopy to facilitate targeted biopsies, and high-resolution endoscopy to further characterize suspicious lesions has come to be associated with enhanced

neoplasia detection. However, there is only indirect evidence to suggest that such surveillance strategies are likely to be effective in reducing the risk of death from colitis-associated cancer. It is sometimes considered difficult to conduct randomized controlled studies for ethical reasons, because expert consensus in this field was formed and became widely employed in practicing surveillance programs, long before the call for establishment of evidence-based medicine.

Surveillance of colitis-associated cancer is widely practiced, and is recommended by the European Crohn's and Colitis Organization (ECCO), the British Society of Gastroenterology (BSG), American Gastroenterological Association (AGA), American Society for Gastrointestinal Endoscopy (ASGE) and Japanese guidelines [2-7]. The purpose of this study is to compare these international and national guidelines for patients of ulcerative colitis, with a special focus on the recommendations for cancer screening, and examine their concordance and differences. The possible reasons for the differences in the guidelines are discussed so as to identify the important issues that need to be addressed in the future.

METHODS

A wide range of guideline programs from different countries were scanned. To widen the scope, well-known guidelines, i.e. those published by the ECCO [2], BSG [3], AGA [4,5], ASGE [6] and the Japanese research group [7] were included. In total, 6 guidelines programs were selected. All of these different national and international gastroenterological societies, including the ECCO, BSG, AGA, ASGE and Japanese have published similar surveillance guidelines for the detection of dysplasia/cancer in IBD patients. According to these guidelines, a surveillance program is recommended in UC patients for the detection of pre-neoplastic lesions at a curable stage, to prevent malignant transformation. The concordance and differences in each of the following sections of the guidelines, including the surveillance colonoscopy and biopsy protocols were compared : 1) Risk of CRC; 2) High risk status of cancer; 3) Candidates for surveillance; 4) Screening colonoscopy; 5) Interval of surveillance colonoscopies; 6) Number of biopsies recommended; 7) Random or targeted biopsies; 8) Method of random biopsy; 9) Method of targeted biopsy; 10) Use of chromoendoscopy/magnifying colonoscopy.

RESULTS

All of the guidelines examined in this study recommend surveillance for the detection of dysplasia or surgically curable cancer, detection at these stages being thought to improve the prognosis. However, the reduction in mortality in patients with IBD and colorectal cancer through surveillance remains to be proven in large prospective randomized controlled trials. Comparisons of the recommendations of international and national guidelines for surveillance of colitis-associated cancer were shown in Tables 1-1, 1-2, 1-3 and 1-4.

Estimation of the cancer risk

All the guidelines cite the report of Eaden et al., of cumulative risks of 2%, 8% and 18% at 10, 20 and 30 years after the disease onset in UC patients[1]. The lifetime prevalence of CRC in patients with UC is estimated to be 2% after 10 years, 8% after 20 years, and as high as 18% after 30 years of extensive disease [1]. All guidelines indicate Primary Sclerosing Cholangitis (PSC) as a high risk factor for CRC, and the ECCO, BSG and US guidelines indicate the disease duration, severity of inflammation and family history as influencing the risk of cancer. The ECCO suggests post-inflammatory polyps as a risk factor. The BSG suggests stricture within the previous 5 years or confirmed dysplasia within previous 5 years in patients who decline surgery as risk factors, while the AGA suggests more extensive disease, colonic strictures and/or a shortened colon and/or multiple post inflammatory pseudopolyps as increasing the risk of colon cancer. The ASGE suggests young age at onset of disease and presence of backwash ileitis as risk factors for colon cancer. The risk factors pointed out in the commentary section of the Japanese guideline were pancolitis, severity of inflammation and the age at onset.

Methods of cancer screening

Patients to be enrolled in surveillance: The ECCO, BSG and AGA suggest that all patients with UC, irrespective of the disease activity should undergo screening, while the recommendations of the ASGE and Japanese guideline are unclear.

Screening colonoscopy: The ECCO suggests that screening be started 6–8 years after the onset of symptoms, the BSG suggests approximately 10 years, the AGA suggests a maximum of 8 years after, and the ASGE and Japanese guideline suggest 8 to 10 years after the onset of symptoms.

Interval of surveillance colonoscopies: The ECCO divides the risk into risk grades and suggests colonoscopy every 1–2 years in high-risk cases and every 3–4 years in low-risk cases. The BSG suggests 5-yearly screening for lower risk cases, 3-yearly screening for intermediate risk cases and yearly screening for higher risk cases; these periods are more specific than those recommended by the ECCO. The AGA suggests screening every 1–3 years, while the ASGE and the Japanese guideline suggest screening colonoscopy every 1–2 years in all patients.

Methods of Biopsies: Since dysplastic lesions in these patients often present as flat or depressed abnormalities, surveillance colonoscopies should be performed with an extensive biopsy protocol in place. The ECCO, BSG, AGA and ASGE recommend random and targeted biopsies, and all of these guidelines suggest that two to four random biopsy specimens be obtained from every 10 cm of the entire colon or from each anatomic section. On the other hand, the Japanese guideline suggests targeted biopsy rather than random biopsy. In relation to the method of obtainment of targeted biopsies, the ECCO, BSG, AGA and ASGE recommend targeted biopsies using chromoendoscopy; especially the ASGE; chromoendoscopy has been more commonly used in Europe and Asia than in the United States to identify nonpolypoid flat and depressed neoplastic lesions in the colon. Chromoendoscopy is recommended by the BSG, AGA and ASGE, however, ASGE adds that chromoendoscopy has not yet been adopted in routine practice. Magnifying colonoscopy is recommended by the AGA, and high-resolution endoscopy is recommended by the ECCO. The Japanese guideline only comments that targeted biopsy rather than random biopsy.

Table 1-1: Comparison of recommendations (Risk estimation and cancer surveillance).

	ECCO (2012)	BSG (2011)	AGA (2010)	ASGE (2006)	Japan (2010)
Title	Second European evidence-based consensus on the diagnosis and management of ulcerative colitis: Special situations [2]	Guidelines for the management of inflammatory bowel disease in adults [3]	AGA Medical Position Statement on the Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease [4] AGA Technical Review on the Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease [5]	ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease [6]	Guidelines for the Management of Ulcerative Colitis in Japan [7]
Author(s)	Van Assche G, et al.	Mowat C, et al.	Farraye FA, et al.	Leighton JA, et al.	Hibi T, et al.
Risk of cancer	Cumulative CRC risks of 2% at 10 years, 8% at 20 years and 18% at 30 years disease duration. (ref: [1,19,20])	Evidence relating to the increased incidence of colorectal carcinoma and the need for surveillance is reviewed in the ECCO consensus document. (ref: [37])	The risk of cancer in patients with UC is estimated at 2% after 10 years, 8% after 20 years, and 18% after 30 years of disease. Data from a UK 30-year surveillance program calculated the risk of cancer and dysplasia to be 7.7% at 20 years and 15.8% at 30 years. (ref: [1])	The risk of CRC increases with longer duration and extensive severe colitis, family history of CRC, young age at onset of disease, presence of backwash ileitis, and personal history of primary sclerosing cholangitis. (ref: [1,49-52])	The rate of development of colorectal cancer is 2%, 8% and 18% at 10, 20 and 30 years after diagnosis, respectively. (ref: [1,43])
High risk status of cancer	The most consistent risk factors reported are primary sclerosing cholangitis (PSC) with a CRC risk up to 31% and histological or clinical disease activity. Post-inflammatory polyps may be markers of previous inflammatory severity and have also been found to be strong risk factors. (ref: [21-28])	Higher risk: -moderate or severe endoscopic/ histological active inflammation on the previous surveillance colonoscopy or -stricture within past 5 years or -confirmed dysplasia within past 5 years in a patient who declines surgery or -primary sclerosing cholangitis/ post-orthotopic liver transplant for PSC or -family history of colorectal cancer in a first-degree (ref: [37,38])	Disease duration, more extensive disease, primary sclerosing cholangitis, and a positive family history of sporadic CRC are all associated with an increased risk of CRC. (ref: [1,41-44])	The risk of CRC increases with longer duration and extensive severe colitis, family history of CRC, young age at onset of disease, presence of backwash ileitis, and personal history of primary sclerosing cholangitis. (ref: [1,49-52])	The risk of colorectal cancer is particularly high in patients complicated with primary sclerosing cholangitis. (ref: [1,43])

Table 1-2: Comparison of recommendations (Screening and interval of cancer surveillance).

	ECCO (2012)	BSG (2011)	AGA (2010)	ASGE (2006)	Japan (2010)
Candidates for surveillance	In all patients with UC irrespective of the disease activity, a screening colonoscopy could be carried out 6–8 years after the beginning of symptoms in order to assess the patient's individual risk profile. (ref:[1])	Index (screening) colonoscopy is advised for all patients with ulcerative colitis or Crohn's disease colitis. (ref: [37,38])	All patients, regardless of the extent of disease at initial diagnosis, should undergo a screening. (ref: [40,45-47])	Individuals with long-standing UC and extensive CD colitis are at increased risk for development of dysplasia and colorectal cancer (CRC) and should undergo colonoscopic surveillance. (ref: [1,49-52])	None

Screening colonoscopy	Screening colonoscopy could be carried out 6–8 years after the beginning of symptoms inorder to assess the patient's individual risk profile. (ref: [1,19,20])	At approximately 10 years after onset of symptoms to reassess disease extent. (ref: [38,39])	All patients, regardless of the extent of disease at initial diagnosis, should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms, with multiple biopsy specimens obtained throughout the entire colon, to assess the true microscopic extent of inflammation. (ref: [40,45-47])	Every 1 to 2 years beginning 8 to 10 years after disease onset. (ref: [46])	Annual or biannual colonoscopy with biopsies is performed, beginning 8-10 years after disease onset. (ref: [47,53,54])
Interval of surveillance colonoscopies	Every 1–2 years (high-risk) or every 3–4 years (low-risk) from the eighth year after the first manifestation in both extensive UC and left-sided UC. (ref: [29-31])	Patients with extensive colitis (ulcerative colitis or Crohn's disease) can be risk stratified as follows: Lower risk: 5-yearly colonoscopy Intermediate risk: 3-yearly colonoscopy Higher risk: yearly colonoscopy (Risk grade is shown as *1) (ref: [38,39])	The optimal surveillance interval has not been clearly defined. After 2 negative examinations (no dysplasia or cancer), further surveillance examinations should be performed every 1 to 3 years. Recent data suggest that increasing the frequency of surveillance colonoscopy to every 1 to 2 years after 20 years of disease is not needed for all patients but should be individualized according to the presence or absence of other risk factors. (ref: [46,47])	Surveillance colonoscopy every 1 to 2 years beginning 8 to 10 years after disease onset. (ref: [46])	Annual or biannual colonoscopy with biopsies. (ref: [47,53,54])

Table 1-3: Comparison of recommendations (Biopsies).

	ECCO (2012)	BSG (2011)	AGA (2010)	ASGE (2006)	Japan (2010)
Number of biopsies recommended	Chromoendoscopy with targeted biopsies is the surveillance procedure of choice for appropriately trained endoscopists. Alternatively, random biopsies (quadrant biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed (ref: [32])	Two to four random biopsy specimens every 10 cm from the entire colon should be taken with additional samples of suspicious areas. (ref: [39,40])	There are no prospective studies that have determined the optimal number of biopsy specimens that should be obtained to detect dysplasia reliably. Representative biopsy specimens from each anatomic section of the colon is recommended. (ref: [32])	In all 4 quadrants every 10 cm from the cecum to the rectum, to obtain a minimum of 32 biopsy samples. (ref: [46])	No well-designed clinical studies have been published on the surveillance protocols. Commentary: At present, a study evaluating the validity of surveillance by detailed observation and targeted biopsy rather than random biopsy is under way. (no reference cited)
Random or targeted biopsies	Random/Target	Random/Target	Random/Target	Random/Target	
Method of random biopsy	Chromoendoscopy with targeted biopsies is the surveillance procedure of choice for appropriately trained endoscopists. Alternatively, random biopsies (quadrant biopsies every 10 cm) and targeted biopsies of any visible lesion should be performed (ref: [32])	Two to four random biopsy specimens every 10 cm from the entire colon should be taken with additional samples of suspicious areas. (ref: [39,40])	Representative biopsy specimens from each anatomic section of the colon is recommended. One study has recommended that a minimum of 33 biopsy specimens be taken in patients with pancolitis. (ref: [32])	Biopsy specimens of the colon in patients with documented pancolitis should be obtained in all 4 quadrants every 10 cm from the cecum to the rectum. (ref: [1,46])	

Method of targeted biopsy	It is very important to take targeted biopsies from all visible suspicious lesions. (ref: [33-35])	Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended. (ref: [39,40])	Chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies for endoscopists who have expertise with this technique. (ref: [32,48])	Chromoendoscopy offers the potential for improved sensitivity during colonoscopic surveillance by allowing for targeted biopsies of enhanced mucosal abnormality. (ref: [12,13])	

Table 1-4: Comparison of recommendations (Chromoendoscopy/magnifying colonoscopy).

	ECCO (2012)	BSG (2011)	AGA (2010)	ASGE (2006)	Japan (2010)
Use of chromoendoscopy/ magnifying colonoscopy	Most intraepithelial neoplasias can be visualised by high-resolution endoscopy, either as irregular mucosa, strictures or mucous membrane elevations. (ref: [36])	Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended. (ref: [39,40])	Chromoendoscopy has been proposed as a method to increase the yield of detecting dysplasia on surveillance colonoscopy and is considered a technique easily applicable to clinical practice. Chromoendoscopy has been more commonly used in Europe and Asia than in the United States to identify nonpolypoid flat and depressed neoplastic lesions in the colon. The use of a magnifying colonoscope may further improve the sensitivity, and specificity of chromoendoscopy. (ref: [32,48])	Chromoendoscopy offers the potential for improved sensitivity during colonoscopic surveillance by allowing for targeted biopsies of enhanced mucosal abnormality. While promising, chromoendoscopy has not yet been adopted in routine practice. (ref: [12,13])	None

*1
< Lower risk: 5-yearly colonoscopy
-no endoscopic/histological active inflammation on the previous colonoscopy (histological chronic or quiescent changes acceptable) or
-left-sided colitis (any grade of inflammation) or
-Crohn's disease colitis affecting <50% surface area of the colon (any grade of inflammation).
< Intermediate risk: 3-yearly colonoscopy
-mild endoscopic/histological active inflammation on the previous surveillance colonoscopy or
-presence of post-inflammatory polyps or
-family history of colorectal cancer in a first-degree relative aged 50 years or over.
< Higher risk: yearly colonoscopy
-moderate or severe endoscopic/histological active inflammation on the previous surveillance colonoscopy or
-stricture within past 5 years or
-confirmed dysplasia within past 5 years in a patient who declines surgery or
-primary sclerosing cholangitis/post-orthotopic liver transplant for PSC or
-family history of colorectal cancer in a first-degree.

DISCUSSION

A review of the major clinical guidelines indicates that the risk of colon cancer associated with ulcerative colitis is widely acknowledged, with recommendations of regular screening, especially of high-risk UC patients. However, the method of the cancer risk, and the recommended schedules and methods of screening appear to differ among the guidelines. The ECCO, BSG, AGA and ASGE surveillance guidelines make two central suggestions: (1) regular surveillance should begin 6–10 years after onset of symptoms; (2) random and/or targeted biopsies should be performed, including the recommendation of 2–4 random biopsy specimens being obtained from every 10 cm of the entire colon during surveillance colonoscopy, and chromoendoscopy with targeted biopsy, are recommended. Differing from the above guidelines, the Japanese guideline suggests targeted biopsy rather than random biopsy in the commentary section. A survey was conducted on the implementation of the recommendation of 40–50 random biopsies on surveillance colonoscopies in several other countries [8-10]. Recently, it has been shown that in more than 50% of cases, 10 biopsies are taken[8]; therefore, the question arises as to why random biopsies are not generally accepted. A typical biopsy sample represents less than 0.05% of the colon; therefore, 33 biopsies are required to detect dysplasia with 90% sensitivity, and 64 biopsies are needed to achieve 95% sensitivity [11]. Dysplasia is detected at a higher sensitivity by biopsies obtained using chromoendoscopy than by those obtained using white-light endoscopy [12,13]. Chromoendoscopy and high-resolution endoscopy may have a better ability to detect neoplasia.

Estimation of the cancer risk

The risk estimation is based on a limited number of epidemiological studies: All the guidelines cite the report of Eaden et al., of cumulative risks of 2%, 8% and 18% at 10, 20 and 30 years after the disease onset in UC patients [1]. A possible reason for this concordance is that there is no certain evidence has been published after the publication of this paper. According to all the guidelines, the risk of colorectal cancer is particularly high in patients with the complication of PSC. Family history has also been indicated as a high-risk factor by all guidelines, except the Japanese guideline, while the incidence of UC is currently increasing at a tremendous rate in Japan. On the other hand,

the guidelines differ somewhat in their mode of estimation/description of the cancer risks associated with UC. The risk status is divided into three grades by the BSG. It is suggested that guidelines include easy-to-follow grading that can directly facilitate treatment.

A study in a national cohort of UC patients revealed that the risk of development of CRC in African Americans was no higher than that in Caucasians. The reasons for this lack of racial difference are not clear, but could be related to access to care, genetic factors, and molecular pathways [14]. On the other hand, the decrease in the risk of CRC from 1979 to 2008 might be the result of the improved therapies in Danish patients with IBD [15]. The evidence for risk grading is based on limited racial or regional studies, and it would seem difficult to establish a universal standard guideline.

Methods of cancer screening

All guidelines recommend the performance of screening colonoscopy 6–10 years after the onset of symptoms. This recommendation was potentially influenced by the data included in the *Risk of cancer* section [1]. The ECCO, BSG, AGA and ASGE recommend random and targeted biopsy, and the recommendations are almost the same, each suggesting two to four random biopsy specimens be obtained from every 10 cm of the entire colon or from each anatomic section. These guidelines suggest chromoendoscopy or magnifying colonoscopy when targeted biopsy is intended; however these procedures involve time, cost and patient discomfort. A unified guideline needs to be established worldwide after examining the efficacy of biopsy.

On the other hand, the guidelines differ in respect of the recommended targets of cancer screening. While the ECCO suggests that biopsy be carried out 6–8 years after the onset of symptoms in all patients with UC, the BSG recommends colonoscopy approximately 10 years after symptom onset for all patients with UC, and the ASGE and Japanese guideline are unclear about the protocol for surveillance colonoscopy. All of these recommendations derive from the same set of scientific reports. AGA Guidelines for colonoscopy surveillance after screening and polypectomy recommend surveillance and screening intervals based on the findings of baseline colonoscopy in sporadic CRC [16]. However, there is limited evidence in relation to ulcerative colitis-related CRC.

Commonly unfulfilled aspects

While the same databases have been employed for searching and selecting scientific evidence, the selection and weighting of papers, and the recommendations seem to differ sometimes. Factors leading to such differences could be related to differences in the clinical philosophy, differences in the characteristics of the guidelines, and differences in the methods used to incorporate various aspects of value judgments (e.g., experts' views, patients' views, economic aspects, and local availability of specific drugs). An awareness of these factors is essential to the understanding and critical (re-)appraisal of each guideline [17].

Most of the guidelines refer to the economic aspects of cancer screening among UC patients. Sometimes, even the way in which the experts' views were used in making recommendations was not clearly disclosed. Furthermore, one of the important omissions is the lack of incorporation of the patients' views in the clinical guidelines. Although GRADE recommends incorporation of the patients' perspectives in making recommendations, none of the guidelines either stated the patients' views, or disclosed how those views were incorporated and reflected in the final recommendations [18].

Potential benefits of comparison of clinical guidelines and practices

Discussion should begin to give more effective strategies an integral part, so that patients can hope to receive sufficient surveillance in the future. The guidelines differed mainly in respect of the guideline objectives and the evidence base and its evaluation for guideline development. There were two main guideline objectives, covering new/advanced measures and covering widely accepted/acceptable ones. Future international guidelines require global harmonization by (1) continuous improvement based on comparative discussion, (2) appropriate international collaborative research, (3) active movements across international borders of patients and doctors, (4) unified disease registry. Comparison of the clinical guidelines to determine their concordance and difference revealed challenges for the future pertaining to cancer surveillance of patients with ulcerative colitis.

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Conflicts of interest

None declared.

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