Interval Colorectal Cancers in Inflammatory Bowel Disease: The Grim Statistics and True Stories

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KEYWORDS

• Colorectal cancer • Interval colorectal cancer • Inflammatory bowel disease
• Ulcerative colitis • Crohn's disease • Surveillance • Colonoscopy

KEY POINTS

- Interval colorectal cancers (CRCs) may account for approximately half of all CRCs identified during IBD surveillance, which highlights the need for improvements.
- The cause of interval CRCs is multifactorial, with procedural factors likely to play an important role.
- Molecular events promoted by inflamed mucosa may augment the cancer risk and perhaps explain some interval CRCs.

The past decade has witnessed considerable progress in the management of inflammatory bowel disease (IBD), including improvements in the quality and effectiveness of colonoscopic surveillance.[1–3] Patients with ulcerative colitis (UC) or Crohn's colitis have a greater risk of colorectal cancers (CRC), which may develop earlier and progress more rapidly than sporadic CRCs. Although most societies now endorse intensive colonoscopic surveillance to reduce the CRC risk,[4–6] the efficacy of this strategy remains controversial. Several recent studies have cast doubt about the limited effectiveness of colonoscopy at reducing the incidence of sporadic CRC in the general population, especially in the proximal part of the colon,[7,8] resulting in the occurrence of interval CRCs. Little is known, however, about the magnitude of this problem in patients with IBD and the most common explanations. Similar to the sporadic interval CRCs, two factors contribute to interval CRCs in IBD: clinician-dependent factors, such as missed, incompletely resected lesions or suboptimal surveillance; and

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molecular features of the inflamed mucosa underlying the development of cancer. The endoscopic knowledge, equipment, and techniques have evolved in recent years, contributing to a paradigm shift in the diagnosis and endoscopic resection of CRC precursors. The nonpolypoid (flat or depressed) colorectal neoplasms (NP-CRNs) play a significant role in the genesis of interval CRCs.[9] Such subtle-appearing lesions are indeed more likely missed or incompletely resected endoscopically than their polypoid counterparts, and a subgroup of them harbor an aggressive biologic behavior.

This article provides insight into the magnitude and most common factors underlying the cause of interval CRCs during surveillance for IBD. Milestones of the literature regarding CRC risk in patients with IBD are reviewed. Specifically examined to the occurrence of interval CRCs are the contribution of missed, incompletely resected lesions; the adherence to surveillance; and distinct biologic features of the inflamed mucosa. Key principles are presented for ensuring the quality of IBD surveillance practice.

INCIDENCE OF CRC AND INTERVAL CRC

A casual glance at the overall incidence of CRC in patients with IBD reveals discrepant outcomes, with a few studies showing similar CRC rates in patients with IBD versus the general population,[10,11] whereas others show greater rates.[12–14] In a nationwide cohort of close to 50,000 Danish patients with IBD who were followed over three decades (1979–2008), CRC was identified in 338 (0.71%) cases (268 in patients with UC and 70 in patients with Crohn's disease).[10] The overall CRC risk among patients with UC in this study was similar to that of the general population (relative risk, 1.07; 95% confidence interval, 0.95–1.21). In contrast, a North American study[15] conducted from 1998 through 2010 found that the incidence of CRC in patients with Crohn's disease or UC was 60% higher than in the general population.

The Danish study found a marked decline in the overall relative risk of CRC among patients with UC over the past decades, from 1.34 (95% confidence interval, 1.13–1.58) in 1979 to 1988 to 0.57 (95% confidence interval, 0.41–0.80) in 1999 to 2008,[10] possibly reflecting refinements in the anti-inflammatory arsenal (ie, immunosuppressive therapy, biologicals), but perhaps also caused by a gradual adoption of CRC screening and surveillance. Conversely, the North American study[15] found a fairly stable CRC rate in patients with IBD over time. Controversies surrounding the time-trends in CRC risk are not surprising, and likely reflect the cumulative effect of several factors, such as advancements in endoscope technology, a greater awareness, and improvements in the quality of colonoscopic performance.

As a common denominator, such epidemiologic studies lack relevant information about the disease duration, degree and extent of inflammation, presence of risk factors (ie, primary sclerosing cholangitis, personal or family history of CRC), and patients' compliance with the recommended follow-up. Although clinical studies provide such details, most have focused on the optimal frequency of surveillance, paying less attention to the quality of examination. A systematic characterization of the lesions phenotype, in particular the location, size, shape, and histology, is often lacking.

Very few data are available about the occurrence of interval cancers during surveillance for IBD. The first paper dates back to 1982.[16] In this surgical review of 676 patients with UC undergoing long-term follow-up, a total of 35 CRCs were identified. Twelve of these were diagnosed because of symptoms, 10 as incidental findings at proctocolectomy, and 13 CRCs were diagnosed during the follow-up at least 1 year after the initial UC diagnosis. This latter subgroup was referred to as "interval CRCs." In a St Mark's study reviewing the UC surveillance program over approximately three decades, a total of 74 patients (12.3% of the total population) developed

neoplasms, including 30 CRCs.[17] The authors defined interval CRCs as "cancers presenting after a negative index-colonoscopy or advanced (Dukes' C/disseminated) cancers detected at surveillance." During a median follow-up of 1.5 years, nine patients were identified with Dukes' C cancers and four patients with disseminated cancers (4 of these 13 cases were diagnosed within 12 months). In three cases, CRC was diagnosed at colonoscopy because of symptoms; one of these was attributable to noncompliance. Of note, more than half (16 out of the 30) of the CRCs identified with this program were interval cancers, raising concerns about the effectiveness of colonoscopic cancer prevention. A statistically significant reduction in CRC rates over time was observed in this study ($r = -0.40$; $P = .04$), especially in the proximal colon.

From these data, we can conclude that there is sparse understanding of the magnitude and clinical significance of interval CRCs in patients with IBD. Indeed, a wide variation exists with regard to the terminology used in endoscopy and pathology diagnostic protocols across countries, IBD centers, and studies.

Standardization of the nomenclature and clinical protocols, and uniformity in reporting on interval CRCs during IBD surveillance, would help to define quality targets. As a first step, a universal terminology is required for dysplasia and interval cancers. Previously used terms, such as flat dysplasia or dysplasia associated lesion or mass, need to be revisited. A rigorous description of the endoscopic shape and histologic features of the detected lesions is required, using international classifications (ie, Paris-Japanese endoscopic classifications[18,19] and the World Health Organization histopathologic classifications[20,21]). Interval cancers should be considered those invasive cancers diagnosed after a negative screening examination, but before the next recommended follow-up colonoscopy, as endorsed by the current international IBD surveillance guidelines.

POTENTIAL ETIOLOGIC FACTORS OF INTERVAL CRCS

Similarly to sporadic CRCs, most interval CRCs in IBD probably can be explained by clinician-dependent factors, such as missed, incompletely resected lesions or deviation from surveillance protocols. The understanding of the underpinnings of such interval CRCs is of importance because it may permit identification of modifiable factors, for example gaps in knowledge and training on the recognition of nonpolypoid neoplasms and their endoscopic resection. In this case, tailored educational programs would improve the awareness and help to shape practical skills, to ultimately safeguard the quality of colonoscopy. Furthermore, it is important to understand whether certain molecular features of the inflamed mucosa could augment the risk of cancer progression. Such information may help to develop personalized (ie, molecular-based) surveillance strategies.

Missed Lesions

Two recent studies exploring the cause of sporadic interval CRCs in the general population found missed lesions represent by far the most important contributor (>50% of all interval CRCs).[22,23] Undoubtedly, missed lesions are likely to account for a significant proportion of interval CRCs in IBD, although a thorough analysis using structured algorithms[24] has not yet been performed. A recent population-based analysis by Wang and colleagues,[25] using SEER cancer registry data from 55,008 older patients with CRC, found rates of early/missed CRCs were three-fold greater in IBD than in patients without IBD (15.1% for Crohn's disease, 15.8% for UC vs 5.8% for patients without IBD; $P<.001$). Early/missed CRCs were defined as CRCs identified

within 6 to 36 months after a colonoscopic examination that did not detect cancer. This study was based on administrative data, and therefore lacked detail about the completeness of colonoscopy, bowel preparation, extent of colitis, characteristics of mucosal lesions identified at the baseline examination, and resection outcomes. Such observations underscore the importance of meticulous inspection of the entire colonic mucosa, which should be ideally clean and free of inflammation, and the need for formal training of the endoscopist in the recognition of IBD neoplasms. Presence of active or chronic background inflammation and the diversity in endoscopic appearance of dysplasia by IBD may, however, increase the complexity of diagnosis. Fig. 1 illustrates a lateral spreading tumor of granular subtype, which could have been missed at a previous examination.

A substantial number of studies demonstrated that indigo carmine– or methylene blue–guided chromoendoscopy (CE) improves the diagnostic yield of dysplasia and

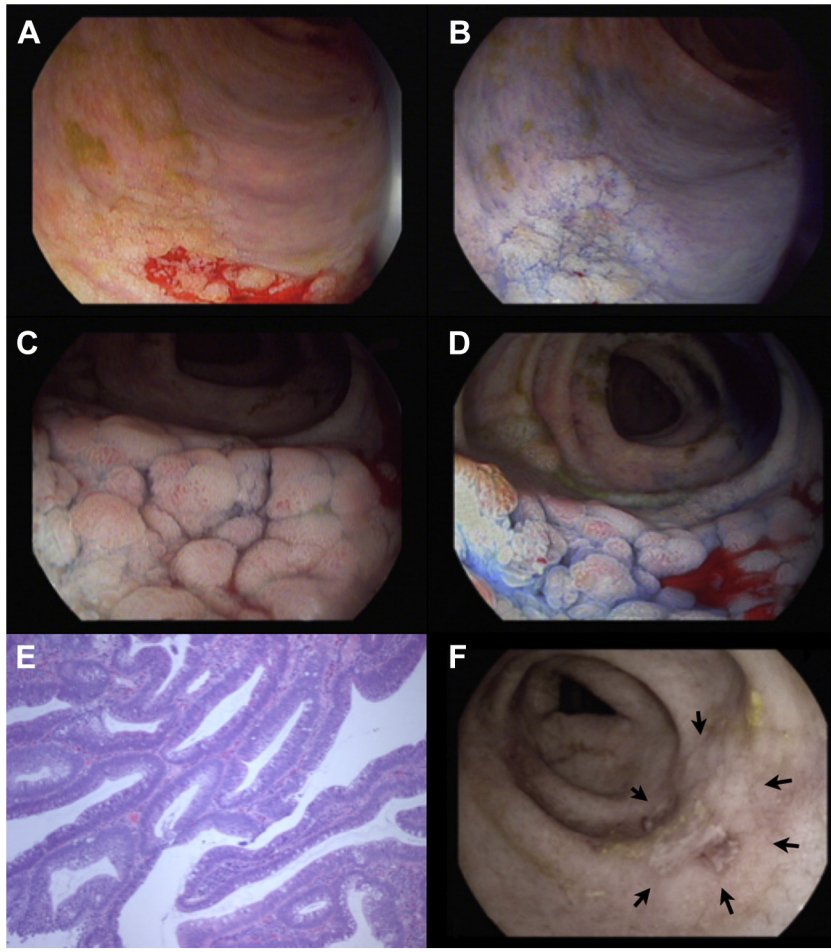

Fig. 1. (*A–D*) Lateral spreading tumor of granular type, located in the descending colon of a patient with a Crohn's pancolitis. (*E*) Histopathology revealed low-grade dysplasia (Hematoxylin and eosin, original magnification ×20). (*F*) Colonoscopic examination 8 months earlier showed Mayo 2 inflammation only at the same anatomic site (*arrows*), suggesting this lesion could have been missed.

invasive CRC during IBD surveillance. This is not surprising, because a significant proportion[26–28] of dysplastic lesions in patients with IBD appear to have a flat appearance, as illustrated in **Table 1**. Pancolonic CE delineates the borders and permits a detailed analysis of the epithelial surface, thus facilitating the diagnosis of subtle lesions and their endoscopic resection. A few meta-analyses now demonstrate CE with targeted biopsies is superior to white-light colonoscopy with random biopsies in the detection of dysplasia and invasive CRCs.[29–31] CE yielded a 7% increase in the detection of any dysplasia.[31] Compared with white-light colonoscopy with random biopsies, the likelihood to detect any dysplasia with CE and targeted biopsies was 8.9-fold greater, and 5.2-fold greater for detecting nonpolypoid dysplasia. In a Mainz study of 165 patients with long-standing UC who were randomized to undergo standard colonoscopy using white light versus CE (0.1% methylene blue), significantly more intraepithelial neoplasms were detected in the CE group (32 vs 10; $P = .003$). CE detected more intraepithelial neoplasms in "flat mucosa" than white-light endoscopy (24 vs 4; $P = .0007$), and more invasive cancers (3 vs 1).[26]

In these studies, colonoscopies were performed by dedicated colonoscopists with expertise in multimodal imaging, and under controlled circumstances (ie, clinical trials), and may preclude generalizability. Recognition of the nonpolypoid dysplasia in a real-world environment remains challenging and requires additional training. In a study conducted at Maastricht University Medical Center, where the endoscopists have been trained on the recognition of nonpolypoid neoplasms,[32] the overall detection rate of sporadic NP-CRNs (defined as lesions of which the height was less than half of the diameter) was 5.7% (diagnostic subgroup, 4.7%; screening subgroup, 4.5%; surveillance subgroup, 15.6%).[33] The learning-curve in the detection of NP-CRNs is, however, tedious, with at least 600 colonoscopies being required to achieve a detection rate of at least 4.5%.[34]

It is highly likely that missed lesions have a major contribution to the development of interval CRCs in patients with IBD, although this needs further investigation. The current data highlight the importance of vigilant inspection and a thorough phenotyping of lesions identified at colonoscopy, including subtle erosions, shallow ulcerations, and their relationship with inflammation or strictures. Such exquisite detail may improve the understanding of the link between inflammation, the occurrence of dysplasia, and interval CRCs. High-quality videos/photodocumentation obtained in a standardized fashion facilitates this process. Challenging cases should be performed by expert endoscopists.

Incompletely Resected Lesions

Endoscopic resection of neoplasms in the context of colitis is clearly fraught with difficulties because of the presence of inflammation and scarring. Such conditions challenge the accurate detection, clear demarcation, and lifting of the lesions. Studies examining the diagnostic yield of CE during surveillance for IBD provided, however, limited information about the effectiveness of the endoscopic resection, which requires further investigation. In a long-term follow-up evaluation, Odze and colleagues[35] compared the outcome after polypectomy among three subgroups: (1) patients with UC with adenoma-like dysplastic lesions, (2) patients with UC with sporadic adenomas, and (3) a non-UC sporadic adenoma subgroup. Prevalence of polyp formation on follow-up, albeit high in this study, did not significantly differ across subgroups (62.5%, 50%, and 49%, respectively) indicating IBD-associated dysplasia may be effectively treated endoscopically. Indeed, over the past few years, endoscopic mucosal resection and endoscopic submucosal dissection resection techniques proved to be increasingly safe and effective in the Western practice.[36–38] A study

Table 1
Detection of flat dysplastic lesions in patients undergoing surveillance for IBD

Study, Author, Year	Design	Endoscopist Experience	Number of Patients	Dye	Number of Patients with IEN	Flat Dysplastic Lesions (Numbers)	Invasive CRCs (Numbers)
Kiesslich et al,[26] 2003	Randomized 1:1, CE vs standard WLE	Several experienced endoscopists	165	MB 0.1%	CE group: 32 IENs in 13 pts WLE group: 10 IENs in 6 pts	CE group: 24 WLE group: 4 ($P = .0007$)	CE group: 3 invasive CRC WLE group: 1 invasive CRC
Matsumoto et al,[27] 2003	Prospective cohort CE	Single experienced endoscopist	57	IC 0.2%	12 pts with 117 IENs	27	4 HGD/invasive CRCs
Rutter et al,[28] 2004	Prospective cohort back-to-back WLE→CE	Single experienced endoscopist	100	IC 0.1%	CE group: 9 pts WLE group: 2 pts	CE group: 75 "flat topped elevated" WLE group: 0	None
Kiesslich et al, 2007	Randomized 1:1 CE (N = 80) vs WLE (N = 73)	Several experienced endoscopists	153	MB 0.1%	CE group: 19 in 11 pts CC group: 4 in 4 pts	CE group: 16 CC group: 2	None
Hlavaty et al, 2011	Tandem colonoscopies	Several experienced endoscopists	30	IC 0.4%	WLE: 2 CE: 4	2	None
Günther et al, 2011	Randomized Group 1: random biopsies; Group 2 CE + biopsies; Group 3 CE + confocal endomicroscopy	Two experienced endoscopists	150	IC 0.1%	Group 1: no IEN Group 2: 2 pts Group 3: 4 pts	Group I (0) Group II (18) Group III (10)	1 (Group 3)

Abbreviations: CC, conventional colonoscopy; HGD, high-grade dysplasia; IC, indigo carmine; MB, methylene blue; WLE, white-light endoscopy.

examining the effectiveness of endoscopic resection of NP-CRNs found that 93% of those larger than 10 mm were successfully resected.[36] Residual neoplasia was identified in 10% of cases on the first follow-up examination, although complete resection was obtained in all cases after one to three follow-up examinations. Likewise, Buchner and colleagues[37] found that large sessile and NP-CRNs could be managed endoscopically in 91% of cases, with a perforation rate of 0.4% and a bleeding rate of 11%. Because 9%[23] to 50%[38] of the sporadic interval CRCs are thought to be caused by an ineffective polyp resection, the precise contribution of this factor to the genesis of interval CRCs in patients with IBD needs further elucidation.

Adherence to Colonoscopic Surveillance

Adherence to colonoscopic surveillance guidelines is indeed vital, but seems to be often problematic.[39–42] There are several caveats to keep in mind, foremost of which is the patient's understanding of the cancer risk.[43,44] Disease flares and presence of comorbidity may further reduce the compliance to surveillance. Because the presence of disease activity challenges the endoscopic and histologic appreciation of dysplasia, colonoscopic surveillance should be ideally performed in the quiescent phase. However, surveillance should not be delayed too long, because those with more active disease carry a greater risk of developing CRC. With regard to bowel preparation, a low-residue diet the days before the procedure in conjunction with split-dose polyethylene glycol solutions is often sufficient for adequate cleansing, without inducing inflammation.

Biologic Features

The precise biologic events underlying chronic inflammation and leading to a faster progression to CRC are presently unknown and need further exploration. A subset of dysplastic lesions identified in patients with IBD harbor a villous phenotype, as illustrated in **Fig. 2**. Such macroscopic features have been suggested to represent a red flag for the presence of invasive CRC, especially of colloid subtype.[45] Other CRCs harbor signet ring cells, features associated with a more aggressive biologic behavior. **Fig. 3** illustrates a small signet ring cell carcinoma that displayed clear signs of local invasion. Approximately 6% of the cancers in patients with IBD are small flat invasive CRCs, without adjacent adenomatous tissue,[30] suggesting that progression to CRC may involve a pathway different from the classic adenoma-carcinoma sequence.

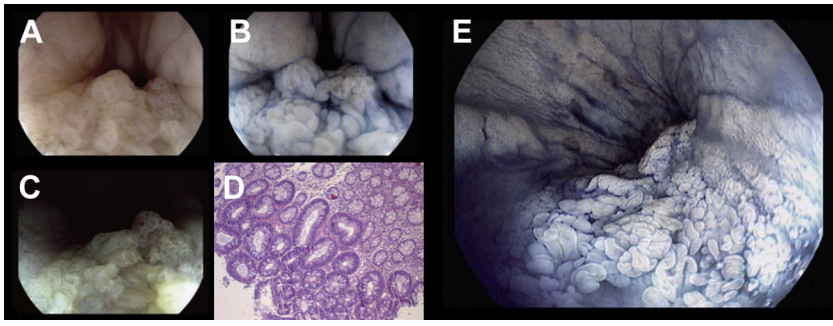

Fig. 2. (*A–C*) Lateral spreading tumor of the rectum in a patient with distal ulcerative colitis. Examination using high-definition endoscopy in conjunction with chromoendoscopy clearly showed a villous appearance. (*D*) Histopathology revealed low-grade dysplasia (Hematoxylin and eosin, original magnification ×20). (*E*) Fuller view of lesion with indigo carmine chromoendoscopy.

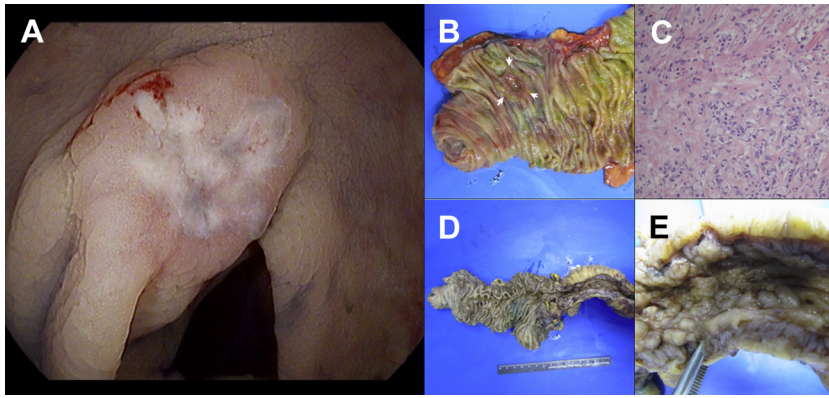

Fig. 3. (*A*) A 10-mm sized, Paris type IIa+IIc lesion, with a central ulceration that has been identified at the hepatic flexure of a patient with Crohn's colitis. (*B*) Examination of the surgical specimen showed the small cancer (*arrows*). (*C*) Histopathology revealed a poorly differentiated signet ring cell adenocarcinoma, with signs of lymphangioinvasion. The lesion was located near a stricture (Hematoxylin and eosin, original magnification ×30) (*D*, *E*) and staged pT3N1Mx.

The newly described serrated neoplastic pathway may also explain a subset of interval CRCs in patients with IBD.[46] Interestingly, a recent study by Voorham and colleagues[47] found that sporadic nonpolypoid neoplasms are likely to herald 5q loss, and less likely MSI and APC mutations, features resembling the carcinogenesis process in inflammatory conditions, such as IBD.

In summary, clinician-dependent factors and biologic factors intermingle in the genesis of interval CRCs by IBD. It is important to understand whether presence of NP (flat or depressed)-CRNs in patients with IBD signifies a diagnostic and therapeutic challenge alone. The most effective filter of missed or incompletely resected lesions would then be training for improving the education and endoscopic skills. Clinical decisional algorithms, including the characterization of shape, epithelial surface of lesions, and their relation with inflammation,[31] have the potential to steer the diagnostic and therapeutic process and optimize outcomes. If a subset of the NP-CRNs contains molecular features associated with a greater risk of CRC, such patients need to be identified and closely surveyed to prevent CRC.

CONCLUDING REMARKS

Interval CRCs may account for approximately 50% of the CRCs identified during IBD surveillance, favoring the idea that clinical consent should include information about cancer risk. Improvements in the quality of colonoscopic examinations are vital for minimizing the CRC risk of patients with IBD. **Box 1** summarizes basic concepts for achieving that goal. Standardization of clinical protocols is required, including the use of high-definition and high-resolution colonoscopes coupled with the application of pancolonic CE with targeted biopsies. Surveillance colonoscopy using white light with random biopsies should be abandoned. Formal training in recognition of NP-CRNs and proficiency in endoscopic resection techniques should be compulsory for providers who perform surveillance in patients with IBD. Comprehensive colonoscopy and pathology data reporting using a standardized nomenclature and interpretation of findings using tailored algorithms may ultimately shed light on the cause of interval CRCs and the required improvements.

Box 1
Principles for quality colonoscopy during surveillance for IBD: The Six Ts

- Timing

  Ideally, surveillance should be performed in the quiescent phase.

- Tolerance

  Tolerance of bowel preparation is key for adequate cleansing; a low-residue diet can be added to standard split-dose bowel preparations.

- Technology

  High-definition/high-resolution colonoscopes should be used.

- Technique

  Pancolonic chromoendoscopy with targeted biopsies should be considered the standard of care.

- Training

  The IBD specialist and pathologist needs to be formally trained on detection, classification, and diagnosis of nonpolypoid (flat or depressed) colorectal neoplasms.

- Traits

  A thorough registration of patient and lesion characteristics may help identify the most likely cause:

  - Patient with IBD: duration and extent of disease, presence of primary sclerosing cholangitis, family history of CRC, personal history of colorectal polyps (including postinflammatory polyps), history of medication, compliance and response to therapy
  - Lesions at baseline examination: location, size, shape, histology, and the relationship with inflammation and strictures
  - Interval CRCs: recommended surveillance intervals, time to CRC diagnosis, location of tumor, histology, and tumor stage

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