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**Interval colorectal carcinoma: An unsolved debate**

Benedict M *et al.* Interval colorectal carcinoma

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**Abstract**

Colorectal carcinoma (CRC), as the third most common new cancer diagnosis, poses a significant health risk to the population. Interval CRCs are those that appear after a negative screening test or examination. The development of interval CRCs has been shown to be multifactorial: location of exam-academic institution versus community hospital, experience of the endoscopist, quality of the procedure, age of the patient, flat versus polypoid neoplasia, genetics, hereditary gastrointestinal neoplasia, and most significantly missed or incompletely excised lesions. The rate of interval CRCs has decreased in the last decade, which has been ascribed to an increased understanding of interval disease and technological advances in the screening of high risk individuals. In this article, we aim to review the literature with regard to the multifactorial nature of interval CRCs and provide the most recent developments regarding this important gastrointestinal entity.

**Key words:** Colorectal carcinoma; Interval colorectal carcinoma; Postcolonoscopy colorectal cancer; Detection; Screening

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**Core tip:** Interval colorectal cancers (CRCs) represent a small but important subgroup of colorectal cancers. Interval CRCs are those that appear after a negative screening test or examination. The development of interval CRCs has been shown to be multifactorial. We aim to review the multifactorial nature of interval CRCs and provide the most recent developments regarding this important entity.

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**INTRODUCTION**

Colorectal carcinoma (CRC) is the third most common new cancer diagnosis as well as the third most common cause of death due to cancer[1]. An estimated 96090 new cases of colorectal cancer with 49700 deaths are expected to occur in the United States for 2015[1]. The 5-year survival rate for CRC that is localized at the time of diagnosis is 90% with a decrease to 68% with regional involvement and a precipitous decline to 10% if distant metastases are discovered[2]. Colonoscopy has been an effective measure in the screening and ultimate prevention of CRC with a 30-year decline in new cases and deaths as a result of CRC[3]. There are over 12 million colonoscopic procedures performed in the USA each year with roughly half occurring due to CRC prevention[3]. The current prevention strategy dictates that at 50 years of age a screening colonoscopy be performed and every ten years subsequent to a negative exam[4]. The U.S. Preventative Services Task Force recommends against the routine screening of any individual after the age of 75[5]. Adenomatous as well as serrated polyps harbor malignant potential and require additional early screening for the development of CRC[5]. Those patients with two or more tubular adenomas that measure less than 10 mm should have a colonoscopic exam every 5 years[5]. A three year repeat colonoscopy is required for patients that have three to 10 adenomas, an adenoma or serrated polyp greater than or equal to 10mm, an adenoma with villous features or high grade dysplasia, a dysplastic serrated adenoma, or a traditional serrated adenoma[5]. Endoscopic surveillance becomes more tenuous in cases of inflammatory bowel disease (IBD). Inflammatory bowel diseases, specifically ulcerative colitis and Crohn’s disease, are damaging processes that result from the constant assault on the bowel by inflammation. Ulcerative colitis characteristically involves the rectum with proximal extension to involve all or just a portion of the colon. However, Crohn’s disease is characterized by its patchy involvement of the gastrointestinal tract from the mouth to the anus. There is a bimodal age distribution for inflammatory bowel disease with peak incidences in the age range of 15-30 years and 50-80 years[6]. Inflammatory bowel disease shows its highest prevalence in western countries, with nearly 1.4 million Americans affected[7]. Patients with inflammatory bowel disease are at increased risk for CRC as well as a more rapid progression to CRC[8]. However, the overall incidence of IBD-related CRC has decreased in recent years[9]. Of the conditions which are risk factors for the development of CRC, IBD ranks third behind familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer syndrome (HNPCC/Lynch syndrome)[10]. In the general population, screening colonoscopy seeks to identify dysplastic or premalignant conditions, namely colon polyps, which are typically easily visualized and resected [11]. In stark contrast, dysplasia in IBD is difficult to recognize at colonoscopy, as it is often seen to arise from flat, plaque-like, or occasionally raised polypoid lesions defined as dysplasia-associated lesion or masses (DALM)[11]. In addition to the difficulties posed by flat dysplasia, operator-dependent variability and the quality of examination contribute to the inconsistent effectiveness of colonoscopy, especially in the proximal colon[12]. All of these factors, as well as additional contributing factors that will be subsequently discussed, contribute to what is called interval colorectal carcinoma.

**DEFINITION AND INCIDENCE OF INTERVAL COLORECTAL CARCINOMA**

The definition of interval CRC is varied and complex. Therefore, the Expert Working Group on interval CRC of the Colorectal Cancer Screening Committee of the World Endoscopy Organization (WEO) has set out to standardize the nomenclature for its definition[12]. After a literature review, the WEO has defined an interval CRC as “colorectal cancer diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the next recommended exam”[12]. Samadder *et al*. conducted a population based-study of Utah residents and observed that 3.4% of all CRCs occurred in 6-36 mo from their index colonoscopy[10]. Singh *et al*[13] looked at 4883 cases of CRCs and concluded that 1 in 13 CRCs may be an early or missed CRC, diagnosed after an index colonoscopy. Whereas, additional data suggests that 1 in 45 of CRCs are of the interval type[14]. Several studies site incidence rates of interval CRC to be as high as 9% of all diagnosed CRCs[14]. Site specific interval CRCs were identified and include (based on nine studies): 4615 proximal interval CRCs out of 53847 total proximal CRCs and 2726 distal interval CRCs out of a total 77922 distal CRCs[10]. This corresponds to 1 in 15 proximal CRCs being interval and 1 in 34 distal CRCs being interval[10]. Proximal interval CRCs are 2.4 times more likely when compared to distal interval CRCs[10]. Sanduleanu *et al*[14] calculated the magnitude of threat posed by interval CRCs to be in the range of 30000 out of one million new cases of CRC diagnosed worldwide each year, based on an average-risk scenario of 1 out of 30 diagnosed CRCs.

**RISK FACTORS**

There are several factors that have been implicated in the development of interval CRCs including: technical factors, biology-related, nonpolypoid colorectal neoplasms, serrated lesions, hereditary cancer syndromes (for example Lynch Syndrome), among others[14].

***Technical factors***

Colonoscopy value, defined using both health outcomes and cost, is intimately linked to the physician performing the procedure, university facility versus community practice, site of service, and the engagement of the patient in the colonoscopy sequence[3]. Physician factors have proved most directly related to the risk of an interval CRC. The use of three quality metrics: adenoma detection rate, use of recommended screening and surveillance intervals, and cecal intubation rate are measures which are used to establish this link[3]. A great deal of data exists to support the notion that colonoscopy is less effective in preventing right sided CRCs and that those trained in proper colonoscopic techniques, specifically gastroenterologists, are more effective in the prevention of CRC when compared to other types of physicians[15-21].

Early colorectal neoplasia has been increasingly treated by conventional endoscopic resection, including endoscopic mucosal resection (EMR) and polypectomy[22]. Piecemeal EMR is an accepted treatment option for large adenomatous colorectal neoplasms (> 20 mm) in diameter, however it is more advantageous to resect neoplasia with *en bloc* resection, which results in a more accurate histological assessment[22]. With that being said, endoscopic submucosal dissection (ESD) is an effective, safe, and convenient approach that has gradually been established and has now in more general use[22]. ESD, like polypectomy (discussed subsequently), also falls prey to the problem of incomplete resection and local recurrence[22]. Shiro *et al*[22], using data from a multicenter prospective cohort, showed that piecemeal resection is the most important risk factor for a local recurrence after endoscopic resection (ER), irrespective of the method of ER used. They report local recurrence rates of 0-17.9% for *en bloc* resection and 4.8%-31.4% for piecemeal resection [22]. Hence, the guidelines for CRC screening and surveillance recommend a follow-up colonoscopy at 3-6 mo after piecemeal EMR[22]. Like endoscopic resection, incomplete polypectomy and missed lesions are evolving as a substantial risk factor for the development of interval CRCs. Robertson *et al*[23] showed that 26% of interval CRCs developed in the same anatomical area as where the patient’s previous polypectomy occurred. Chen *et al*[24] also showed similar results of interval CRC after incomplete polypectomy. In a study performed by Atkin *et al*[25], 31 of 842 patients with tubulovillous adenomas, specifically of the rectosigmoid, which were most likely incompletely excised, ended up developing interval CRCs. Missed lesions were the most probable cause of interval CRC in 15 out of 28 patients as revealed by le Clercq *et al*[26]. Additionally, using pooled data on 9167 adenoma patients, Robertson *et al*[27] showed that 58 people were diagnosed with CRC within 4 years of colonoscopy and three quarters were likely the result of a missed lesion, incomplete adenoma resection or failed biopsy detection.

Patient related factors also contribute to the risk of interval CRC. Patients with interval CRCs are on average 6 years older than those with non-interval colon cancer and typically have substantial co-morbidities, such as cardiovascular disease or a history of diverticulosis[14]. Patients who are older, frail, and have co-morbidities are more prone to have inadequate bowel preparations, which may explain the increased risk of interval CRCs seen in these individuals[14]. Colonoscopic examination can be difficult in patients with diverticular disease and when coupled with the fact that patients with diverticular disease have a higher risk of harboring adenomas and advanced adenomas in the sigmoid colon, may increase the risk of interval CRC in these persons[28].

***Sessile serrated adenoma/polyps***

In order for interval CRCs to occur several conditions need to be fulfilled; namely, a precursor lesion that is rapidly progressive, evades detection, and is difficult to resect[29]. Sessile serrated adenomas (SSA) are the perfect precursor that fulfills these criteria. SSAs without dysplasia are often difficult for endoscopists to detect due to their flat and indistinct nature. SSA prevalence at colonoscopy has always been accepted to be in the realm of 2%, however, recent evidence suggests that these lesions may be more common than previously thought, specifically 4-6 fold higher[30]. Endoscopically, sessile serrated adenomas with dysplasia (SSA-D) are identifiable due to their dysplastic component, which appears to the endoscopist as a typical adenoma; however, when the endoscopist resects the polyp, the dysplastic component is removed leaving the nondysplastic component behind[29]. Endoscopic snare resection of SSAs are often incomplete with studies suggesting that in 31% of cases residual SSAs are left behind, when compared to conventional adenomas, a residual rate of only 7.2% is seen[31]. Large SSAs (1-2 cm) show even greater rates of residual tumor, with one study showing up to 48% of large SSA polypectomies resulting in residual disease[31]. The reason for such concern over an incomplete SSA polypectomy lies in the genetic make-up of these neoplasms. Sessile serrated adenomas commonly have activating mutations of the BRAF proto-oncogene, and develop hypermethylation of the CpG promoter regions of mismatch repair genes (*i.e.,* MLH-1), which leads to microsatellite instability (MSI) and is a well-recognized path to CRC[29]. As discussed earlier, many interval CRCs are proximal in location and are CIMP-H as well as MSI positive, which strongly suggests a role for SSA in the development of interval CRC[29,32]. SSAs have been associated with proximal MSI CRCs as well as rapid progression times to CRC diagnosis[33]. Sessile serrated adenomas are not only problematic for the endoscopist, they also pose a problem for the pathologist. The frequency of SSA diagnosis varies greatly in the literature and the diagnostic difficulty becomes more apparent due to the fact that the histologic features of microvesicular hyperplastic polyp and SSA overlap[34]. Bettington *et al*[34] showed that in applying strict histologic criteria for the diagnosis of SSA, a 14.7% rate of detection can be achieved with a high rate of reproducibility among pathologists. However, SSAs continue to be underdiagnosed and will lead to inadequate surveillance and will likely contribute to the rate of interval CRCs[34].

***Interval CRC in inflammatory bowel disease***

Colonoscopy, as described earlier, is the predominant screening and diagnostic test for CRC in the general population. Likewise, colonoscopic examination among those patients with inflammatory bowel disease, specifically Crohn Disease and Ulcerative Colitis, is pivotal in screening this high risk population for CRC. Patients with long-standing inflammatory bowel disease have typically been excluded from studies investigating the rate of early/missed lesions leading to CRC, hence, the rate of early and missed CRCs in this population is still largely unknown[35]. However, in the largest and longest running UC surveillance program in the world (42 year history) has revealed that advanced cancer incidence rate (IR) has consistently decreased over the past four decades, suggesting that the efficacy and use of advanced imaging techniques has led to a greater detection of early neoplasia[36]. Additionally, there has also been a reduction in the incidence rate of high grade dysplasia and low grade dysplasia in the current decade, now 2.1 per 1000 patient-years, down from 4.6 per 1000 patient years[36]. They also found that the risk of interval cancer has rapidly decreased with the steepest decline coming in the last decade, which may be related to the increased use of chromoendoscopy[36]. Chromoendoscopy is the use of image-enhanced techniques, such as the use of dye spraying or optical, to improve the visualization of mucosal structures, and thus improve the recognition of the borders, microvasculature, and surface topography of neoplasia[37]. Patients who underwent chromoendoscopy were found to have a lower risk of developing CRC when compared to those who had never had the procedure[36]. However, other studies do not confirm the benefit of using chromoendoscopy. In a large retrospective study, it was shown that the use of chromoendoscopy with targeted biopsies did not result in an increased neoplasia detection rate when compared to white light endoscopy with random biopsies[38]. With that being said, the majority of the literature seems to suggest a benefit from using chromoendoscopy when compared to standard white light endoscopy[39-42]. Wang *et al*[35] investigated the rate of early/missed CRCs in both IBD patients as well as non-IBD patients. Their findings showed that out of 3589 early/missed lesions, 54 were seen in Crohn’s patients, 103 in UC patients, and 3432 in non-IBD patients. Patient’s without IBD showed a rate of early/missed CRCs after colonoscopy in the range of 5.8%; however, the rate increased substantially in those patients with IBD to 15.1% for Crohn’s and 15.8% for UC[35]. Similar to our discussion of sporadic interval CRC in non-IBD patients, interval CRCs in patients with IBD may be explained again by clinician-dependent factors including: missed lesions, incomplete resection, or deviation from set surveillance protocols[43]. In contrast to non-IBD interval CRC, the presence of active or chronic background inflammation seen in patients with IBD causes diversity in the appearance of dysplastic lesions and thus increases the complexity of the study for the endoscopist[43]. Like SSA, dysplastic lesions in patients with IBD are often flat and easily missed on colonoscopy[43]. The difficulties presented by flat dysplasia in IBD led Maastricht University Medical Center to perform a study where endoscopists were trained on the recognition of nonpolypoid colorectal neoplasms (NP-CRN)[44]. They determined that intensive training with regard to NP-CRNs lead to similar detection rates among their staff gastroenterologists and GI trainees, suggesting that clinical awareness was more important than experience in the detection of flat lesions[44]. Strict adherence to the prescribed colonoscopic surveillance in IBD patients can be tenuous due to a multitude of factors such as: the patient’s understanding of cancer risk, disease flares and associated co-morbidity, and disease activity causing a delay in surveillance[43]. Therefore, patient education to include disease course and risk of CRC, adherence to treatment protocols to limit disease flares, and surveillance during quiescent phase may contribute to the reduction of interval CRC in patients with IBD. The biologic factors which underpin the molecular events that underlie the development of CRC in a background of inflammation are still under active investigation. It has been shown that nearly 6% of CRCs arising in those with IBD are small flat invasive lesions with no adjacent adenomatous tissue, which suggests that the progression to CRC may not follow the classic adenoma-carcinoma sequence[43]. Srivastava *et al*[45] looked at the molecular features of 3 unique patients with long standing IBD who developed numerous hyperplastic/serrated colonic polyps. The group revealed that all 3 patients showed retention of MLH-1 and MSH-2 within these polyps, one case showing a loss of MGMT, and no BRAF mutations were present[45]. They proposed that the findings were suggestive of a serrated pathway of carcinogenesis in those with IBD, which is characterized by silencing of MGMT[45].

***Lynch syndrome and interval CRC***

Lynch syndrome (LS), an autosomal dominant disorder, is characterized by mutations in mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6), which causes an increased lifetime risk of developing CRCs as well as other cancers (*i.e.,* endometrial) in the affected host[46]. The recommended surveillance programs for these patients include colonoscopic examination at an interval of 1-2 years starting at the age of 20-25 years[46]. Many factors contribute to the development of an interval CRC in patients with Lynch Syndrome, including compliance to the recommended surveillance protocols. Newton *et al*[47] investigated compliance with large bowel screening in Lynch Syndrome mutation carriers amongst patients in the United Kingdom and found that in only 62% of the cases was the screening colonoscopy performed during the suggest screening interval. They also found a reduced cumulative incidence of CRC, to the age of 70 years, when screening protocols were adhered to; a reduction from 81% in non-screened patients to 25% in screened individuals[47]. Haanstra *et al*[46] showed that in 29 LS patients (all mutational carriers), a total of 31 interval cancers were found within or at 24 mo of previous colonoscopic examination. In 16 of 19 patients with LS, the interval carcinoma was located in a proximal location and when considering all detected interval carcinomas, 65% are found within the right colon[46]. Their study revealed that in all LS patients who developed an interval CRC a MLH1 or MSH2 mutation was identified, and 90% of these CRCs were diagnosed in the 1-2 years after previous colonoscopy[46]. Richter *et al*[48] looked at 42 interval CRCs and showed that 41% of these tumors exhibited DNA microsatellite instability (MSI) and of these 54% exhibited somatic hypermethylation of the MLH1 promoter. They concluded that interval CRCs cannot be distinguished by activation of KRAS, NRAS, BRAF, or PIK3CA oncogenic pathways, however, MSI pathway defects represent a large proportion of interval CRCs with an underlying LS possibly explaining half of these cases[48].

**BIOLOGIC AGGRESSIVENESS AND SURVIVIAL IN INTERVAL-CRCS**

As previously discussed, interval CRCs are seen most often in the proximal colon and as demonstrated by Arain *et al*[32], are 2.5 times more likely than non-interval CRCs to be CIMP+ and 2.7 times more likely to show MSI positivity. Other studies as well posit that interval CRC may represent a rapidly growing and aggressive cancer[49-52]. However, other studies have not shown any difference in survival between interval CRC and those with no prior colonoscopic surveillance[13,53]. Erichsen *et al*[49] conducted a population based study among the Danish population from 2000-2009 and found out of 38064 CRC patients, a total of 982 (3%) were interval. When compared to non-interval CRC, interval carcinomas were more often women, were proximal in location, displayed mucinous histology, and had co-morbid conditions (IBD and diverticular disease)[49]. The one year survival rate was similar for those patients with interval CRCs when compared to those who developed CRC after a ten year period from their last colposcopy (68%: interval; 72%: > 10 years before CRC diagnosis, and 71% sporadic)[49]. The five-year survival was close to 40% in all groups[49]. Additionally, interval CRC were less likely to be diagnosed at an advanced stage and interval CRCs were just as likely as detected CRCs to be well-to-moderately differentiated[10]. Interval CRCs, when compared to detected CRCs, were seen to have a 37% lower risk of mortality, which held true for both early-stage and advanced stage cancer[53].

**CONCLUSION**

Interval colorectal carcinoma poses a distinct threat, not only to the general population, but also to other population groups such as those with inflammatory bowel disease, hereditary predisposition to gastrointestinal neoplasia, as well as those patients who are more advanced in years with multiple co-morbidities. With a rate that could be as high as nine percent of newly diagnosed CRC being an interval CRC, an estimated 8648 patients will develop a CRC after being screened with colonoscopy in 2015. The etiology of these lesions has been shown to be multifactorial in nature with perhaps the largest risk coming from missed or incompletely excised lesions. There appears to be some disagreement in the literature as to whether interval CRCs are more biologically aggressive due to changes in their molecular make-up. However, there are biological factors that seem to contribute to the development of interval CRC with evidence to suggest that the sessile serrated neoplasia pathway may promote a more rapid development of carcinoma after a screening colonoscopy. Regardless, the overall survival irrespective of tumor biology appears to be similar between interval and detected CRCs. Non-polypoid neoplasia presents a well-defined challenge to the endoscopist as well as the pathologist. Flat lesions are challenging for the endoscopist to discern, but when biopsied, may be miss diagnosed by the pathologist if strict criteria are not adhered to. Improvements in the quality of the endoscopic procedure through the education of the endoscopist is a worthwhile endeavor with a focus on flat lesion recognition. The more widespread use of chromoendoscopy may also be advantageous to many patient groups, most especially those with inflammatory bowel disease. Finally, a greater understanding of the molecular features and biologic behavior of interval CRCs, when coupled with increased endoscopic recognition and complete removal of neoplasia, will likely lead to the greatest improvement and reduction in the rate of diagnosis of carcinoma after a negative colonoscopy.

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