Clinical and Biological Features of Interval Colorectal Cancer

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide, with the highest incidence rate of 45.7 per 100,000 found in Australia and New Zealand. Most CRCs develop from adenomatous polyps with an observed sojourn time. The entire colorectal mucosa can be viewed via colonoscopy; thus, colonoscopy may be used to detect and simultaneously remove premalignant adenomas before they become invasive cancers. Although many physicians consider colonoscopy as the best diagnostic modality for detecting CRCs, there are some questions regarding whether it is truly the most ideal procedure to use. Several studies reported that 5% to 8% of all CRCs were diagnosed in patients who had undergone colonoscopies 3 to 5 years before the diagnosis. These cancers are usually called interval CRCs (I-CRCs) or post-colonoscopy CRCs. The cancers were named “I-CRCs” because the diagnosis was usually made during the interval periods between colonoscopies.

An I-CRC is defined as a CRC that is diagnosed within 60 months of a negative colonoscopy, taking into account that 5 years is the “mean sojourn time” (i.e., the estimated interval between the preclinical [screen] phase and the detectable period) in previous studies. However, some studies defined I-CRC as a CRC diagnosed within 36 months of a negative colonoscopy. The definite time period between a negative colonoscopy and the detection of I-CRCs needs to be elucidated.

This article provides an overview and a review of recent updates on the clinical and biological characteristics of I-CRCs.
The underlying reasons why the I-CRCs were more frequently found in the proximal colon are not apparent. However, three possible reasons could be suggested. First, proximal and distal lesions show differences in gene expression and tumor phenotypes. For instance, a mucinous histology, microsatellite instability (MSI), and CpG island methylation are more common in proximal CRCs, whereas chromosomal instability (CIN) is a prominent feature of distal CRCs. These differences imply that separate mechanisms may be responsible for the development and growth of tumors arising from different anatomic locations. Second, compared with those in the distal colon, lesions arising from the proximal colon tend to be smaller and morphologically nonpolypoid and flat, which make their detection with colonoscopy more difficult. Third, a wide variation exists in adenomatous polyp detection rate, even among experienced gastroenterologists. Successful detection of I-CRCs is associated with the quality of the colonoscopy. Lesions may be easily missed when endoscopists fail to reach the cecum during colonoscopy and/or if the lesion is nonpolypoid, as it is more common in the proximal colon, which is more difficult to examine with colonoscopy. Additionally, although adequate bowel preparation is important to facilitate examination, it is not as sufficiently done in the proximal colon as in the distal colon in many patients.

Although a meta-analysis study reported that there was no difference in the development of I-CRCs between female and male patients, several studies showed that I-CRCs are more commonly found in female than in male patients. Women especially have a higher proportion of CRCs of the proximal colon. Several reasons have been proposed to explain such tendency in women. First, older age correlates with a higher prevalence of proximal CRCs. As women generally live longer than men, a larger proportion of living patients with CRC may be women, resulting in the higher prevalence among women. Second, estrogen might increase the risk of proximal CRC. Finally, some factors such as diet and exercise might influence motility and the exposure time to toxic materials in the colon. As colorectal neoplasms in women occur more frequently in the proximal colon, they often can be missed during colonoscopy examinations. In Singh et al’s population-based study, during the first 3 years immediately after a negative colonoscopy, there was no sex difference in terms of the risk of CRC development. Nonetheless, after the first 3 years, the risk was lower in women than in men. Such findings showed that women might be at a risk of missed detection of neoplasms in previous colonoscopies. Therefore, colonoscopists should take extra-care during examinations in women in order to avoid missed detection of lesions.

**RISK FACTORS OF I-CRC**

**Patient-related factors**

Patients with I-CRCs were older than patients with sporadic CRCs (Sp-CRCs). In addition, patients with I-CRCs have a family history of CRC 1.6 times more often than those with Sp-CRCs. These results supported the idea that some fraction of I-CRCs may have genetic and epigenetic biological factors associated with their development. Consequently, it is important to take a thorough family history and to strictly adhere to surveillance guidelines in high-risk groups.

Patients with I-CRC had a diverticular disease 4.3 times more often than those with Sp-CRCs, and had a higher prevalence of comorbidities such as cardiovascular diseases. It is possible that insufficient bowel preparation, which is more common in older and fragile patients with comorbidities, increases the risk of detection failure.

Furthermore, index colonoscopy revealed that patients with I-CRC had adenomatous polyps. Compared to patients with Sp-CRCs, those with I-CRCs were 1.6 times more likely to have undergone a polypectomy during their index colonoscopies. In addition, the greater the number of polyps in a patient, the higher the rate of incomplete resection, leading to more numbers of missed lesions.

**Endoscopy-related factors**

Compared with patients with Sp-CRCs, a greater number of patients with I-CRCs have had their index colonoscopies done by non-gastroenterologists, such as an intern or a family practitioner. Surprisingly, in a study in Manitoba, colonoscopy performed by a general physician was related to a 60% higher risk of missed CRCs compared with that performed by gastroenterologists. A more detailed look into such finding led to the conclusion that the specialty of the physician performing the index colonoscopy was also related to the risk of interval cancer; that is, index colonoscopy performed by gastroenterologists was associated with a lower risk than that performed by primary care physicians, general surgeons, or colorectal surgeons.

The risk was also associated with the setting under which the procedures were done. Colonoscopies undertaken in inpatient settings were much less likely to be associated with interval cancers than those done in outpatient clinics or ambulatory surgical centers. The probability of I-CRC occurrence, in increasing order, is as follows: in-patient setting, hospital outpatient setting, and ambulatory surgery centers.

The complete colonoscopy and polypectomy rates can be used to measure the quality of endoscopists. Endoscopists with lower rates of I-CRCs had higher polypectomy rates. Singh et al’s meta-analysis study reported that endoscopists
who had the highest quartile of polypectomy rate had a significantly lower risk of I-CRC compared with endoscopists who had the lowest quartile of polypectomy rate.

Studies evaluating the association between the number of procedures done and the risk of I-CRCs applied various cutoff values in order to differentiate the level of load on physicians from performing the procedures. There was no clear evidence on whether the amount of load or a higher number of procedures affected the prevalence of I-CRCs. However, in the medicare study of Cooper et al., the physician polypectomy rate, done on noncancer patients, was inversely associated with the risk of I-CRCs, whereas the number of procedures was positively proportional to the risk.

ETIOLOGY OF I-CRC

Generally, I-CRCs are classified as missed lesions, inadequate colonoscopy, incomplete resection, and newly developed cancers (de novo I-CRCs). The definitions of each subgroup are as follows. (1) Missed lesions are considered to be the main etiological factor in I-CRCs when diagnosed within 36 months after the index colonoscopy, and there was no advanced adenoma in the same segment at the previous index colonoscopy. (2) Inadequate examination is defined as failure of colonic intubation to the cecum or poor bowel preparation. (3) Incomplete resection is defined as a cancer diagnosed in the same anatomical segment where an advanced adenoma was previously resected. (4) Newly developed cancers are considered as CRCs detected ≥36 months after the index colonoscopy that revealed no or one component of advanced cancer (advanced stage or large size) and without a previous advanced adenoma in the same segment.

In le Clercq et al.'s study, of the 147 cases of postcolonoscopy CRCs, 29 (19.7%) were ascribed to inadequate examination. Of the remaining 118 cases, 13 (8.8%) were attributed to an incomplete resection of an advanced adenoma and 85 cases (57.8%) were attributed to missed lesions. Twenty cases (13.6%) were attributed to newly developed cancers. Robertson et al. identified 58 I-CRCs, and the putative reason for the interval cancers was missed lesions for 30 cases (52%), incomplete adenoma resection for 11 cases (19%), and new cancer for 14 cases (24%); the remaining three cases (5%) were categorized as failed biopsy detections. The most common cause of I-CRC might be missed lesions.

However, the same classification cannot be used for I-CRCs. This is also the difficulty in I-CRC studies. Moreover, there is no current assay, marker, or definite clinical feature that can specifically ascribe an I-CRC as either a rapidly growing de novo tumor or a tumor belonging to other groups. Consequently, greater insight into the underlying molecular etiology associated with this type of tumor is warranted.

PROGNOSIS OF I-CRC

In study by Farrar et al. who compared interval and sporadic cancers, there were no large differences in overall survival rates between the two groups. Additionally, there were no differences in histology, tumor stage, and carcinoembryonic antigen level. This finding is similar to that of a Danish study. In this nationwide population-based cohort study, the authors found similar survival rates in metastatic behavior (23% vs. 24%), localized stage at diagnosis, and 5-year survival (41% vs. 43%) between interval and sporadic cancers. However, in a population-based study about features of I-CRCs and patient survival, the authors found a statistically significant survival advantage for I-CRCs compared with detected CRCs overall and for advanced stages (stages 3 to 4). The underlying reasons for the observed survival advantage of interval cancers are unclear.

BIOLOGICAL FEATURES OF I-CRC

Molecular biological studies about the development and progression of tumors have been actively progressing during the last two decades. These carcinogenetic processes are associated with a characterized genetic or epigenetic signature. Especially, it has been known that CRC is caused by a variety of pathways at the genetic and epigenetic levels. Furthermore, this biological approach to the classification of CRC has already been attempted. We evaluated the features of I-CRC from a biological point of view.

Background: molecular pathways that contribute to CRC tumorigenesis

Before we review the biological features of I-CRC, we will focus on describing the three aberrant pathways involved in CRC pathogenesis: CIN, MSI, and CpG island methylator phenotype (CIMP). A proportion of I-CRCs have more recently been shown to have one or more of these genomic instability phenotypes.

Chromosomal instability

CIN refers to an increase in the rate at which whole or large parts of chromosomes are gained or lost. CIN can occur numerically (N-CIN) as a result of defects in chromosomal segregation, or structurally (S-CIN) as a result of chromosomal rearrangements, including duplications, deletions, and trans-
locations. This CIN pathway was first reported by Vogelstein et al., and involved the mutated activation of an oncogene and the loss of several tumor suppressor genes. The CIN pathway is called the "microsatellite stable (MSS) pathway" or the "adenomatous polyposis coli (APC)/β-catenin pathway," and is a characterized mutation of the APC gene, which is a known gatekeeper gene. CIN is observed in up to 80% of Sp-CRCs and up to 85% of familial adenomatous polyposis with germ-line mutation.

β-Catenin is involved in various gene translations, and is inactivated by APC protein. In CRC, APC gene mutation results in inactivation by truncation of APC protein. It induces the β-catenin accumulations in the nucleus from the cytosol, and augments cell proliferation. The occurrence of aberrant crypt foci due to APC gene mutation is followed by subsequent mutations in the tumor suppressor genes, DCC, p53, SMAD2, SMAD4, and the proto-oncogene K-ras. These mutations are known to be related to the occurrence of adenomas and adenocarcinomas.

In molecular pathology, loss of heterozygosity of 1p, 2p, 3p, 5q, 17p, and 18q and an aneuploid karyotype are the predominant phenotypic characteristics that define CIN-positive CRCs. The clinical features are predominantly found in the distal colon.

Microsatellite instability
A microsatellite is a tract of repetitive deoxyribonucleic acid (DNA), repeating specific DNA motifs (ranging in length from 2 to 5 base pairs) typically 5 to 50 times. Microsatellites occur in multiple locations in the human genome and are notable for their diversity and high mutation rate in the population. MSI manifests as small increases or decreases ("instability") in the number of repeats in microsatellites throughout the genome because of defects in mismatch repair (MMR) genes. MMR protein is a nuclear enzyme for recognizing and repairing erroneous deletion, insertion, and mis-incorporation of bases that can occur during DNA replication and recombination. MMR has been known to have at least five kinds (hMLH1, hMSH2, hMSH6, hpMS1, and hpMS2).

In 1997, a panel of five markers (BAT25, BAT26, D2S123, D5S346, and D17S) for the uniform detection of MSI tumors was proposed at the National Cancer Institute Workshop meeting. MSI-high (MSI-H) tumors are defined as tumors with instability at two or more of these markers, whereas tumors with instability at one marker and those with no instability are defined as MSI-low and MSS tumors, respectively.

MSI is detected in approximately 15% of all CRCs. Of these, 3% are associated with Lynch syndrome and the remaining 12% are associated with Sp-CRCs due to sporadic or acquired hypermethylation of the promoter of the MLH1 gene, which arise in the neoplasm with the CIMP. MSI was significantly associated with proximal colon cancer and increased survival of patients. MSI-H correlated with a better prognosis compared with low MSI or CIN. Moreover, it is known that the typical mutations observed with CIN (e.g., APC and K-ras) are observed less frequently in MSI+ tumors. This is because MSI+ tumors seldom show gains or losses in large chromosomal segments, which is caused by subtle genomic alterations in MSI tumors. The MSI and CIN pathways were traditionally thought to be mutually exclusive; however, recent evidence suggests that this may not be the case. Ten percent to 15% of CIN+CRCs have been shown to possess MSI-H, and MSI in Sp-CRC is associated with the acquisition of the oncogenic BRAF mutation.

CpG island methylator phenotype
Several papers recently reported that epigenetic changes, which are defined as clonal changes in gene expression without subsequent changes in primary DNA sequence, are the third mechanism of tumorigenesis followed by gene mutations, such as CIN and MSI. DNA methylation and histone acetylation are major epigenetic changes. DNA can be methylated to a cytosine base by the addition of a methyl group. A "CpG island" is a region with a higher frequency of CpG dinucleotides than the rest of the genome, where a cytosine is followed by a guanine in the linear sequence of bases along the 5' to 3' direction. CpG islands are found in the promoter regions of 50% to 60% of all genes. DNA methylation takes place in this short CpG island and hypermethylation of this CpG island results in its transcriptional silencing. Aberrant hypermethylation of these promoter CpG islands has been associated with silencing of genes that encode tumor suppressors, leading to the development of cancer.

Toyota et al. reported the patterns of hypermethylation to be different between a natural progression of colonic epithelial cell aging and tumor types including CRC. Two types of methylation appear in CRCs: type A methylation (age related) and type C methylation (cancer specific). Initially, type A methylation is the result of a function of age in normal colo-rectal epithelial cells. Such methylation affecting genes that control the growth and/or differentiation of cells may result in a predisposition state of tumor formation. By contrast, type C methylation was found exclusively in a subset of cancers that show a CIMP.

Approximately one-third of Sp-CRCs harbor the CIMP, and as with MSI, these tumors occur predominantly within the proximal colon. CIMP positivity is determined by the existence of CIMP markers. Many other CIMP markers exist, some of which further categorize CIMP+ tumors as either CIMP-high (two or more of the five markers exist) or CIMP-
low (only one or none of the five markers exist). These minimum numbers and the choice of genes to be analyzed often vary among studies. This lack of a standardized definition of CIMP is one of the major confounding factors in the evaluation of CIMP-associated CRCs. Samowitz et al. evaluated a large population-based sample of patients with colon cancer and evaluated CIMP with clinicopathologic variables and their relation with K-ras, p53, and BRAF600E. CIMP-high tumors were more likely to be K-ras wild type, p53 wild type, and V600E BRAF mutated. Furthermore, these CIMP-high tumors are also located proximally and occurred in older individuals. CIMP-high tumors are expected to occur in women and to be poorly differentiated; however, these relationships were statistically insignificant.

MOLECULAR PATHWAYS IN I-CRCs

The three pathways have overlapping contributions in sessile serrated adenoma, I-CRCs, and Sp-CRCs.18 I-CRCs may share similar etiological origins as Sp-CRCs, but in very different frequencies. In a study of Sawhney et al.,24 compared with non-I-CRCs, I-CRCs were more likely to have loss of function of MMR genes and consequently demonstrate MSI. Of the 993 CRC patients in this study, 51 (5.1%) were classified as having interval cancer, and MSI was identified in 30.4% of I-CRCs compared with 10.3% of non-I-CRCs (p = 0.003). After adjusting for age, I-CRCs were 3.7 times more likely to present MSI than non-I-CRCs. This relationship was stronger in tumors in the distal colon (odds ratio [OR], 17.5; p = 0.008). More recently, Nishihara et al.11 compared the prevalence of MSI between I-CRC and non-I-CRCs. MSI was detected in 25% of the I-CRCs, compared with only 13.6% of the Sp-CRCs. As compared with cancers diagnosed in patients without any prior endoscopy or at >5 years after colonoscopy, those diagnosed within 5 years after colonoscopy were more likely to be identified as showing MSI (multivariate OR, 2.10; 95% confidence interval, 1.10 to 4.02). Arain et al.1 showed an increase in the prevalence of CIMP within I-CRCs compared with controls. In this study, CIMP was present in 57% of I-CRCs compared with 33% of non-I-CRCs (p = 0.004). It represented a 2.4-fold increase in adjusted multivariate analysis. Nishihara et al.11 also evaluated CIMP in their cohort, and detected a 2-fold increase in the prevalence of CIMP within the I-CRCs compared with the Sp-CRC samples. As shown previously, I-CRCs were more likely to have MSI (29% vs. 11%, p = 0.004) and to occur in the proximal colon than non-I-CRCs (63% vs. 39%, p = 0.002).

At least two specific pathways, the conventional pathway and the serrated pathway, are associated with most CRCs. Approximately 70% are generated through the well-characterized CIN pathway, which is the basis of most screening and treatment decisions. During the last two decades, many of the molecular biological mechanisms of the “serrated pathway,” which caused about 30% of CRCs, have been determined.46,47 The serrated pathway of CRC involves BRAF, CIMP, and MSI mutations and MLH1 methylation, and many of these features are similar to those in I-CRCs.48

There are similar aspects between the serrated pathway and I-CRCs. First, the clinical features of I-CRC are similar to those of sessile serrated adenomas/polyps (SSA/Ps). The SSA/Ps tend to be pale, flat polyps with minimal changes to the vascular network, and are often covered with yellow mucus, rendering them difficult to detect with colonoscopy. Second, SSA/Ps present most frequently in the proximal colon. These clinical factors are similar to those of I-CRCs. Furthermore, their potential relationship with I-CRCs have garnered recent attention. I-CRCs are almost four times as likely as non-I-CRCs to be associated with MSI. Moreover, synchronous CRCs are more frequently CIMP-high and MSI-H, and have more frequent BRAF mutations,49 similar to I-CRCs. Although recent empirical evidence suggests that a subset of I-CRCs may arise due to aberrant molecular biology, studies are required to determine the possible contribution of these molecular features in the development of I-CRCs.

CONCLUSIONS

The prevalence of I-CRCs varies from 2.8% to 4.9% of all CRCs. Compared with Sp-CRCs, I-CRCs were found 2.4 times more frequently in the proximal colon than in the distal colon. The patient-related risk factors include female sex, old age, family history of CRC, diverticulosis, comorbidities, and skill of the endoscopist. The risk factors associated with the endoscopist were low polypectomy rate and low colonoscopy completion rate. The specialty of the endoscopist is another risk factor for I-CRCs.

No major differences were found in overall survival and outcome between interval and sporadic cases, and in markers of aggressive tumor behavior such as histologic grade, carcinoembryonic antigen levels, and stage.

Concerning the molecular pathway of carcinogenesis, SSA/Ps share many genomic features, such as MSI and CIMP, as well as colonic site characteristics with I-CRCs. Consequently, SSA/Ps may be suggested to be precursor lesions for I-CRCs.

Establishment of a consensus definition of I-CRC is essential. Furthermore, specific definitions according to the classification of I-CRC, such as missed lesions, inadequate colonoscopy, incomplete resection, and newly developed can-
cancers, are needed. Beyond missed lesions, aberrant pathways are proposed to have substantial roles in driving the progression of I-CRCs. However, there are few Eastern studies about the biology of I-CRC, and this should be addressed in future studies.

Conflicts of Interest

The authors have no financial conflicts of interest.

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