



Postcolonoscopy Colorectal Cancer: An Overview and Future Directions

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Abstract

Over the past decade, there has been a great interest in postcolonoscopy colorectal cancer (PCCRC). Its etiology is complex and multifactorial. Monitoring for PCCRC is even more complex. The strategies to decrease the incidence of PCCRC start by defining the problem, identifying the factors contributing to its development, followed by an attempt to define methods to decrease its incidence. We believe that the quality of the colonoscopy and the endoscopist's expertise are the key factors in decreasing the incidence of PCCRC.

Keywords

- ▶ postcolonoscopy colorectal cancer
- ▶ colonoscopy
- ▶ colorectal cancer

Introduction

Colorectal cancer (CRC) is a common and lethal disease. Genetic and environmental factors contribute to the development of CRC, with different incidence and mortality rates around the world. This difference in incidence is related to the geographical area, exposure to risk factors, and genetic susceptibility. Globally, CRC is the third most commonly diagnosed cancer in males, and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018, according to the World Health Organization (WHO).

Colonoscopy is used both diagnostically and therapeutically, for it enables the examination and treatment of the rectum, colon, and a portion of the terminal ileum, and is considered the gold standard for colon-cancer screening and surveillance. Having said this, colonoscopy does not always detect CRC; hence, it can be diagnosed months or years after a colonoscopy that is negative for CRC or CRC precursor lesions, leading to what is known as postcolonoscopy colorectal cancer (PCCRC). Therefore, the performance of a high-quality colonoscopy requires understanding and mastery of

cognitive and technical skills and is the key for the effectiveness of CRC screening.

From another perspective, colonoscopy is more effective in preventing left-sided than right-sided CRCs, which could also contribute to a shift in the distribution of colon cancers. It is likely that part of the difference is due to aspects of quality relating to the colonoscopy; however, the biology of the tumor may also differ between CRCs of the proximal and distal colon. Having said this, there is a predilection of PCCRC for the proximal colon when compared with the distal colon.

The aforementioned information, including the effectiveness of the colonoscopy, especially in the proximal colon,¹ to detect and treat right-sided or proximal malignancies, in addition to the difficulties faced during colonoscopy when dealing with flat dysplasia, and the difference in tumor biology between proximal and distal colon cancers has led physicians to miss a certain subset of CRCs during colonoscopy, leading to PCCRC. The present review highlights the current knowledge on PCCRC, the common risk factors, and the potential solutions to this issue, as those will be critical to reduce the incidence of PCCRC, and, consequently, the incidence of CRC and its associated burden across the globe.

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Definition and Incidence of PCCRC

The definition of PCCRC is varied and complex. The World Endoscopy Organization (WEO) has defined PCCRC 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.” Postcolonoscopy CRC can be divided into interval cancers and non-interval cancers. With respect to interval PCCRC, it is identified before the next recommended screening or surveillance examination, which is usually a measure of the quality of the colonoscopy. As for non-interval PCCRC, it may be further subcategorized into those that occur at or after a recommended screening or surveillance interval, and those for which no subsequent screening or surveillance procedure was recommended, which may similarly be a measure of the quality of the colonoscopy, but may also reflect the “correctness” or appropriateness of the current screening or surveillance interval recommendations. Studies from the United States² and Canada³ found incidence rates of PCCRC ranging from 3.4% to 9.0% of all diagnosed CRCs, with a predominant proximal location. Singh et al.⁴ examined 4,883 cases of CRCs, and concluded that 1 in every 13 cases may be an early or missed CRC, diagnosed after an index colonoscopy. On the other hand, additional data suggests that 1 in every 45 CRCs are of the PCCRC type.⁵ Sanduleanu et al. report incidence rates of PCCRC as high as 9% of all diagnosed CRCs.⁵ Furthermore, site-specific PCCRCs have been identified, and include, based on 9 studies reviewed by Singh et al.,⁶ 4,615 proximal PCCRCs out of 5,3847 total proximal CRCs, and 2,726 distal PCCRCs out of a total 77,922 distal CRCs. This means that 1 in every 15 proximal CRCs are PCCRCs, and 1 in every 34 distal CRCs are PCCRCs.⁶ In fact, proximal PCCRCs are 2.4 times more likely when compared with distal PCCRCs.⁶ On the other hand, Sanduleanu et al.⁵ calculated the magnitude of the threat posed by PCCRCs to be in the range of 30,000 out of 1 million new cases of CRCs diagnosed worldwide each year, based on an average-risk scenario of 1 out of 30 diagnosed CRCs. The development of PCCRCs has been shown to be multifactorial. We aim to review the multifactorial nature of PCCRCs, provide the most recent developments regarding this important entity, and explore the potential solutions to this problem.

Risk Factors

There are several factors that have been implicated in the development of PCCRCs.

Tumor Biology

There is a growing body of evidence that states that at least a small percentage of PCCRCs represent a unique subcategory with a specific aberrant biology that drives their de novo and rapid growth. In 2006, Brenner et al. concluded that incomplete colonoscopies is not the only contributing factor for PCCRC and suggested that additional factors such as tumor biology play a role in the development of these

tumors. They are most frequently present in the proximal colon and in women. In fact, data from a Canadian colonoscopy cohort indicates that more than 50% of PCCRCs arise in the proximal colon compared to less than 30% for all sporadic CRCs.⁸ On the other hand, a German population-based study⁹ identified in women a more than 2-fold higher risk of developing PCCRC compared with men.

It is important to note that the biological environment varies considerably throughout the length of the colon; hence, the difference in the biology of proximal and distal colon cancers. During fetal development, for example, the proximal colon originates from the embryonic midgut, whereas the distal colon is derived from the hindgut.¹⁰ Hence, blood supply,¹⁰ mucin pH,¹¹ and the average crypt length¹² are additional biological features that differ along the colonic tract. Consequently, the environmental and physical properties specific to the proximal colon may contribute to the development of PCCRC.

On the molecular level, Sawhney et al.¹³ determined the prevalence of microsatellite instability (MSI) within PCCRCs, and found that it was observed in 30.4% of patients with PCCRCs, as compared with 10.3% of the controls. Furthermore, Nishihara et al.¹⁴ found that MSI was detected in 25% of the PCCRCs compared with only 13.6% of the sporadic CRCs. This represents a 2-fold increase in the prevalence of MSI within PCCRCs. On the other hand, Arain et al.¹⁵ identified an increase in the prevalence of the CpG island methylator phenotype (CIMP) among the cases of PCCRCs compared with the controls, using the same cohort employed by Sawhney et al.¹³ The CIMP was identified in 57% of the cases of PCCRC compared with 33% of the controls, representing a 2.4-fold increase in the adjusted multivariate analysis. Besides, Nishihara et al.¹⁴ also evaluated the CIMP in their cohort, and detected a similar 2-fold increase in its prevalence within the PCCRC group (30.2%) versus 15% among the cases of sporadic CRC. Thus, one can conclude that these pathways are proposed to have a fundamental role in driving the progression of PCCRC, as manifested by the increased prevalence of MSI and CIMP in these tumors.

Technical Factors

Colonoscopy-related

Colonoscopy is the cornerstone for the diagnosis, prevention and surveillance of CRCs, but it does not always detect them; hence, they can be diagnosed months or years after a colonoscopy that is negative for CRC or CRC precursor lesions. In fact, studies suggest^{3,4} that colonoscopy will miss between 2% and 6% of CRCs. Therefore, the performance of a high-quality colonoscopy examination requires understanding and mastery of cognitive and technical skills, and is the key for the effectiveness of CRC screening. Thus, quality indicators were identified by a consensus panel of the American Society of Gastrointestinal Endoscopy and the American College of Gastroenterology in guidelines that were updated in 2015.¹⁶ The goal of applying quality indicators is to improve the performance of colonoscopies and decrease the number of lesions missed during them, consequently decreasing the incidence of PCCRC. Among the

quality indicators that directly affect the incidence of PCCRC are the cecal intubation rate, the adenoma detection rate; the withdrawal time; the use of recommended screening and surveillance intervals; the quality of the colonic preparation; the appropriate number and distribution of biopsy samples obtained from patients undergoing surveillance for inflammatory bowel disease (IBD); and endoscopically-resected mucosa-based pedunculated polyps and sessile polyps < 2 cm, or documentation of unresectability.

Cecal Intubation

The rates of cecal intubation are considered acceptable when intubation is successful in more than 90% of all cases and in more than 95% of the cases when the indication is screening in a healthy adult, given that a good colonic preparation was obtained. Hilsden et al.¹⁷ concluded that the rate of success in cecal intubation among endoscopists was associated with an increased rate of detecting lesions. Hence, achieving a higher rate of cecal intubation rate will lower the rate of PCCRC.

Adenoma Detection Rate

Adenoma detection rates (ADRs) of at least 25% in patients who are over the age of 50 years and are undergoing screening colonoscopy is recommended. In fact, Kaminski et al.¹⁸ found that the endoscopists who increased their ADR from the lowest to the highest quartile decreased their PCCRC rate from 25.3 cases/100,000 patients-year to 7.1 cases/100,000 patients-year. They showed that a benchmark of 24.6% was the threshold needed to reach a profound and statistically significant reduction in the risk of developing PCCRC.

Mean Withdrawal Time

The mean withdrawal time is ≥ 6 minutes in colonoscopies with normal results that are performed in patients with intact anatomy. In fact, the mean withdrawal time has been established as a key performance indicator. Although it has a well-established association with ADR, its power to predict missed lesions and consequent PCCRC is uncertain. Furthermore, Gellad et al.¹⁹ found no association between the withdrawal time and the risk of interval neoplasia. However, as the mean withdrawal time is considered a quality indicator for colonoscopy, further studies need to be conducted to establish a solid association with the incidence of PCCRC. Meanwhile, we suggest to keep documenting it during colonoscopies.

Surveillance Protocols

The adherence to surveillance protocols, either by the physicians or the patients is of utmost importance. In fact, Cheung et al.²⁰ studied the impact of physician adherence to surveillance guidelines on PCCRC, and concluded that the current surveillance guidelines may be inadequate to prevent most PCCRCs. Besides, Van Heijningen et al.²¹ documented poor adherence to surveillance guidelines by both patients and endoscopists, with appropriate surveillance intervals in less than 25% of the cases. They reported that delayed

surveillance was associated with an increased rate of advanced adenomas compared with appropriately-timed surveillance (8% versus 4%; $p < 0.01$), and an increased rate of CRCs (1.8% versus 0.4%; $p < 0.01$).²¹ Therefore, adherence to surveillance guidelines, be it by the patient or the physician, will aid in lowering the incidence of PCCRC.

Endoscopic Resection

Endoscopic resection (ER) is an alternative to the surgical resection of mucosal and submucosal neoplastic lesions and intramucosal cancers.²² It offers both diagnostic and therapeutic capability, and includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Studies^{23,24} have reported EMR for colonic neoplasms with complete en bloc removal rates between 86% and 97%. The factors associated with incomplete removal include size > 2 cm and a large sessile configuration. Furthermore, Oka et al.,²⁵ using data from a multicenter prospective cohort, showed that piecemeal resection is the most important risk factor for local recurrence after ER, irrespective of the method used. They report local recurrence rates of 0% to 17.9% for en bloc resection, and of 4.8% to 31.4% for piecemeal resection.²⁵ Moreover, Robertson et al.²⁶ showed that 26% of PCCRCs developed in the same anatomical area where the patient's previous polypectomy occurred. Chen et al.²⁷ also showed similar rates of PCCRC after incomplete polypectomy. In a study performed by Atkin et al.,²⁸ 31 out of 842 patients with tubulovillous adenomas, specifically of the rectosigmoid (which were most likely incompletely excised), ended up developing PCCRCs. Understanding the contribution of endoscopic incomplete ER to the development of PCCRC is of paramount importance, for it will lead to the birth of new programs; thus, achieving higher rates of complete ER, which will cause a decrease in the incidence of PCCRC, is the goal.

Colonoscopic Difficulties Related to a Medical Condition

The risk of developing PCCRC has also been associated with particular disease states and/or previous surgeries. Patients with a history of diverticular disease^{4,29} or pelvic/abdominal surgery,²⁹ for example, have been reported to be at higher risk of developing PCCRC. Conceptually, these conditions may hinder the ability of the colonoscopy to accurately survey the entire colon; therefore, the higher rates of PCCRC found may be due to false-negative results. In fact, as shown by Subramaniam et al.,³⁰ index colonoscopy prior to PCCRC was more likely to show diverticulosis.

Sessile Serrated Adenomas/Polyps

It is well known that one of the risk factors for the development of PCCRC is a precursor lesion that escapes detection, is difficult to resect (leading to incomplete resection), and has the ability to progress rapidly: sessile serrated polyps (SSPs), also known as sessile serrated adenomas (SSAs). They pose a dual challenge, one for the endoscopist, and one for the pathologists. Their prevalence at colonoscopy has always

been accepted to be in the range of 2%; however, a recent study suggests that these lesions may be more common than previously thought, specifically 4 to 6-fold higher.³¹ Furthermore, SSAs are more prevalent in the proximal colon. These polyps have a smooth surface, are often flat or sessile, and may be covered with mucus. Therefore, adequate serrated-polyp detection rates (SDRs) may reduce the incidence of PCCRC. In fact, Anderson et al.³² concluded that a clinically-significant SDR (CSSDR) of $\geq 7\%$ reduces the incidence of PCCRC. The management of SSPs is complete excision. Endoscopists often have difficulty in identifying SSAs without dysplasia due to their flat and indistinct nature. Endoscopically, SSAs with dysplasia (SSA-Ds) 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 non-dysplastic component behind.³³ Endoscopic snare resections of SSAs are often incomplete, with studies suggesting that, in 31% of the cases, residual SSAs are left behind; when compared with conventional adenomas, a residual rate of only 7.2% is observed.³³ Thus, their sessile nature and indistinct borders pose a challenge for complete endoscopic resection. On the other hand, the pathologists' challenge is manifested by the histology of SSPs, which contain significant architectural, proliferative, and maturation abnormalities, and may acquire morphologic evidence of dysplasia.³⁴ In one study³⁵ on 110 cases of SSPs, areas of dysplasia and foci of intramucosal carcinoma were found in 37% and 11% of the patients respectively. Furthermore, Bettington et al.³⁶ showed that in applying strict histologic criteria for the diagnosis of SSAs, a 14.7% rate of detection can be achieved, with a high rate of reproducibility among pathologists.

From another perspective, there is molecular and clinical evidence that these lesions, either because they have been missed, incompletely removed, or due to a more rapid progression from adenoma to cancer, contribute disproportionately to increase the rates of PCCRCs.¹⁵ In fact, SSAs commonly have activating mutations of the BRAF proto-oncogene, and develop hypermethylation of the CpG promoter regions of mismatch repair genes (such as MLH-1), which leads to MSI and is a well-recognized path to CRC.³³ Hence, as aforementioned, the predilection of PCCRC for the proximal colon, and being CIMP-high as well as MSI-positive, suggest a strong relationship between SSAs and PCCRCs. Thus, SSAs continue to be underdiagnosed and not optimally treated, leading to inadequate surveillance that will likely contribute to increase the rate of PCCRCs.

Inflammatory Bowel Disease

The risk of developing CRC is increased in patients IBD. In a population-based study³⁷ of over 96,000 patients with IBD, the overall risk of developing CRC was of 1.29 cases per 1,000 people-year. The association of ulcerative colitis (UC) and CRC depends mainly upon the duration, extent, and activity of the disease.³⁷⁻³⁹ On the other hand, there are much less data regarding Crohn disease and the risk of developing colon cancer; it appears that pancolitis due to Crohn disease is

associated with a relative risk of colon malignancy similar to that of extensive UC. The goal of surveillance for patients with IBD is to detect dysplasia, which is associated with a high risk of developing CRC, and to reduce mortality in those who develop colon cancer.⁴⁰⁻⁴² Colonoscopy remains the optimal surveillance tool for patients with IBD despite the lack of randomized controlled trials.⁴³⁻⁴⁶ The body of literature supporting the role of colonoscopy for surveillance in IBD patients is mainly derived from case series, case-control studies, and population-based cohort studies, which suggest that surveillance results in an earlier cancer stage at diagnosis and improved CRC-related survival.^{47,48} Furthermore, in IBD patients it is harder to detect colonic polyps, in contrast to the general population, whereby screening colonoscopy seeks to identify dysplastic or premalignant conditions, namely colonic polyps, which are typically easily visualized and resected.⁴⁹ Dysplasia in IBD is difficult to recognize on colonoscopy, as it is often observed to arise from flat, plaque-like, or occasionally raised polypoid lesions defined as dysplasia-associated lesions or masses (DALMs),⁴⁹ especially because this is usually associated with a background of acute and chronic inflammation. Strategies to improve the detection of dysplasia are warranted; hence, the importance of the role of chromoendoscopy, in which topical application of indigo carmine or methylene blue is used to enhance mucosal irregularities, facilitate targeted biopsies, and increase the detection rate of dysplasia. In fact, most society guidelines^{43,50-52} advocate for high-definition endoscopy with surface chromoendoscopy as the strategy that optimizes dysplasia detection. Applying the aforementioned strategies will decrease the incidence of PCCRC in IBD patients, which is believed to be higher than that of the general population. In fact, Wang et al.⁵³ investigated the rate of early/missed CRCs in IBD and non-IBD patients. Their findings showed that out of 3,589 early/missed lesions, 54 were observed in patients with Crohn disease, 103, in UC patients, and 3,432, in non-IBD patients. Patients without IBD showed a rate of early/missed CRCs after colonoscopy of $\sim 5.8\%$; however, the rate increased substantially in those patients with IBD, to 15.1% in cases of Crohn disease, and to 15.8% for UC patients.⁵³ Furthermore, in one study⁵⁴ on more than 1,200 patients with UC or Crohn disease enrolled in a surveillance colonoscopy program, 1.3% were diagnosed with CRC, and 30% of CRC cases were determined to be PCCRCs. Additionally, an analysis⁵⁵ of a prospectively-collected surveillance database demonstrated that more than 50% of the cancers among IBD patients were PCCRCs, which may again be explained by clinician-dependent factors such as: missed lesions, incomplete resection, or deviation from established surveillance protocols.⁵⁶ Therefore, it is of utmost importance for clinicians dealing with this pathology to educate the patients about the associated risk of developing CRC and the importance of strict adherence to surveillance protocols on one hand. On the other hand, the importance of utilizing the optimal screening and surveillance methods, in addition to training the endoscopists to detect dysplasia with a background of acute and chronic inflammation, will ultimately lead to a decrease the rate of PCCRC.

Lynch Syndrome and PCCRC

Lynch syndrome (LS) refers to individuals and families with a pathogenic germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) or the EPCAM gene, leading to an increased risk of developing colorectal cancer, as well as other cancers, such as endometrial, ovarian, gastric, small bowel, hepatobiliary system, renal pelvis, ureter, brain, and skin cancers. Individuals with LS should undergo CRC screening with an annual colonoscopy beginning at ~ age 20 to 25, or 2 to 5 years prior to the earliest age of CRC diagnosis in the family, whichever comes first. The recommendation for annual CRC surveillance is based on the observation of interval cancers or PCCRCs in some series of LS families, and rapid progression of the adenoma-carcinoma sequence.^{57,58} A prospective cohort study⁵⁹ that included 1,126 individuals from families with LS syndrome evaluated the efficacy of annual colonoscopies in detecting adenomas and CRCs. In this study, 99 CRCs were found in 90 individuals; 71 were diagnosed by surveillance colonoscopies. The median time between the CRCs detected through follow-up colonoscopy and the preceding colonoscopy was of 11.3 months, which opens a new debate: should surveillance in patients with LS be modified? Furthermore, adherence to the recommended surveillance protocols is among the factors contributing to the development of PCCRC in patients with LS is. Newton et al.⁶⁰ investigated compliance with large-bowel screening among carriers of the LS mutation in the United Kingdom, and found that the screening colonoscopy was only performed during the suggested screening interval in 62% of the cases. On the other hand, the causes for the development of PCCRC among patients with LS can also be found at the molecular level. In the study by Haanstra et al.,⁶¹ the authors found that most cases of PCCRC were proximally located, and, when considering all detected PCCRC, 65% were found within the right colon.⁶¹ 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 between 1 and 2 years after a colonoscopy.⁶¹ Furthermore, Richter et al.⁶² analyzed 42 PCCRCs, and showed that 41% of them exhibited DNA MSI, 54% of which exhibited somatic hypermethylation of the MLH1 promoter. They concluded that PCCRCs cannot be distinguished by the activation of the KRAS, NRAS, BRAF, or PIK3CA oncogenic pathways; however, defects on the MSI pathway represent a large proportion of PCCRCs, with an underlying LS possibly explaining half of these cases.⁶²

Future Directions

Although significant advances have been made in the definition and understanding of the circumstances involving PCCRC, more research is needed in order to prevent or at least further decrease the rate of PCCRC. The keys to reducing the incidence of PCCRC is identifying modifiable risk factors for its development and extrapolating from there, improving the quality of colonoscopy through better colonic preparation, more frequent cecal intubation, better visualization of the cecal folds, higher ADR, and developing better technolo-

gy. As for endoscopic resections, recognizing high-risk lesions and incomplete resections, and setting guidelines for endoscopists and pathologists regarding the margin of resection, is paramount. Furthermore, we suggest the modification or at least the adherence to the currently-recommended surveillance colonoscopy, and the development of a well-organized system to perform the follow-up of the patients, and we also suggest that, when colonoscopic views are not up to the expectations of the endoscopist, or when cecal intubation was not achieved, the colonoscopy should be repeated, taking into account the preferences and comorbidities of the patients, providing them with a reference document explaining the situation. Furthermore, we believe that deep sedation is associated with a lower rate of PCCRC. From another perspective, a recent study by Cheung et al.⁶³ showed that nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin before colonoscopy reduce the risk of developing PCCRC after a negative baseline colonoscopy; however, patients with IBD were excluded from the study. Considering the extremely important recommendations of the WEO consensus statements on postcolonoscopy colorectal cancer, published in 2018,⁶⁴ divisions and centers where colonoscopies are performed should follow a well-established guideline to identify and document all cases of PCCRC either prospectively or retrospectively. The identification of all cases of PCCRC, which is strongly recommended by the WEO consensus statements, opens the door toward studying each and every case to determine the most possible explanation for this disease. This will eventually lead to the implementation of changes to improve the performance of endoscopists and to monitor said performance. All of this combined will aid in decreasing the incidence of PCCRC, therefore decreasing the incidence of CRC.

Conclusion

The first step toward solving any problem is defining its presence, its scope, and the factors that lead to its existence. Over the last decade, our knowledge about PCCRC has increased dramatically. We believe that striving for perfection in colonoscopy, be it in technical or surveillance guidelines, is the key to decrease the rate of PCCRC. Developing the appropriate expertise, with advanced colonoscopic techniques and excellent follow-up programs, is critical to decrease the incidence of PCCRC, CRC, and its associated burden across the globe.

Conflict of Interests

The authors have no conflict of interests to declare.

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