My Gosh! Have I Missed it?

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Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in all industrialized countries and its prevention and early detection are a significant public health concern. Colonoscopy appears to be a highly effective modality for screening and affords the opportunity to view the entire colorectal mucosa and simultaneously remove premalignant adenomas before they become invasive cancer. While no large randomized controlled trials of screening colonoscopy have been reported, two recent case-control studies in the United States reported that having had a previous colonoscopy was associated with about a 60% reduction in CRC mortality and about a 70% reduction in the incidence of late-stage CRCs. In these studies, however, it is unclear how many of the cancers discovered at follow-up colonoscopy were actually lesions missed at the initial examination. It is hypothesized that most CRCs diagnosed within a few years (3-5 y) after an index colonoscopy are owing to missed lesions or new interval cancer development. In the literature, these tumors variously have been referred to as interval, missed, or postcolonoscopy CRC.

The aim of this paper is to describe and discuss the reasons for interval CRCs and what can be done to prevent interval CRCs.

Frequency and risk factors for interval colorectal cancer

Six population-based studies, 2 from Canada, 1 from Germany, 1 from the Netherlands, 1 from US, and an analysis of 3 chemoprevention polyp trials have described the development of CRC after colonoscopy with rates ranging between 2.9 and 7.9%. An additional study limited to a single Veterans Affairs medical cancer also reported an interval CRC rate of 5.1%. We reported an interval CRC rate of 6.2% at Kangbuk Samsung Hospital. Interval cancer group was younger and more frequent in the right colon than sporadic cancer group.

Etiology of internal colorectal cancers

According to the literature there are various reasons for such interval CRCs.
1. **Incomplete bowel preparation**

Non-polypoid colorectal neoplasms are a potential contributor to the pool of missed lesions because they can be easily missed as a result of inadequate colon preparation.

2. **Incomplete colonoscopy**

It is needless to say that an incomplete colonoscopy is together with an incomplete bowel preparation one of the main reasons for the non-detection of colonic lesion, especially in the right colon. Complete colonoscopy with intubation of the cecum enhances the detection rate of right-sided colonic neoplasia.

3. **Missed lesion**

Among expert endoscopists, the adenoma detection rate (ADR) varied almost 3-fold (range, 17-47%) and there was even higher variability in detection rates of serrated polyps (range, 1-18%). There is little doubt that missed lesions occur commonly and contribute meaningfully to interval CRC risk. The ADR depends on the withdrawal time. If the withdrawal time is > 6 min, the ADR is significantly higher compared to a withdrawal time < 6 min. (28.3% vs 11.8%). A withdrawal time of 9 min resulted in a statistically significant increase in adenoma and serrated polyp detection.

4. **Incomplete polypectomy**

The recurrence rate of adenoma after piecemeal resection is much higher compared to en-bloc resection. In a study by Robertson et al., 25% of interval CRCs occurred after previous polypectomy of a colorectal neoplasia in the area of the finally detected cancer.

5. **Rapid tumor progression**

The contribution of new rapidly growing lesions to the interval cancer rate is the most difficult to determine because the rates of missed and incompletely resected lesions may well be underestimates. Interval CRCs appear to have a different molecular profile than noninterval CRCs. They are 4 times more likely to have MSI, have the CpG island methylator phenotype, and have lower rates of KRAS mutations than noninterval CRCs. These molecular features are characteristic of the serrated pathway and support the concept that this pathway contributes disproportionately to interval CRCs.

**How to prevent interval colorectal cancers**

Although aggressive biology is not modifiable at this time, it may be possible to identify patients who are predisposed to the development of biologically aggressive neoplasia on the basis of their family history or perhaps by histologic and/or molecular analysis of their initial adenomas. For example, patients with a strong family history of CRC should have earlier and more frequent colonoscopic screening/surveillance.

It should be possible to decrease the proportion of missed and incompletely resected lesions by improving the quality of colonoscopy. Endoscopists with ADRs < 20% had more than a 10-fold higher rate of interval CRCs than those with higher ADRs. Some experts have argued that measuring ADR is not as robust as other measures such as adenomas per colonoscopy, advanced ADRs, right-sided ADRs, or serrated PDRs, whereas other
experts have argued that measuring ADRs is too cumbersome and proposed simpler measures such as polypectomy rates. Currently, ADR is the best evidence-based surrogate for quality of mucosal inspection during colonoscopy. The amount of time taken to visualize the mucosa also affects the quality of mucosal inspection. Colonoscopic withdrawal times traditionally have been used as a marker of time spent examining mucosa and withdrawal times have been shown to correlate with ADRs in some and not all studies. To maximize their effectiveness, endoscopists must be well trained to perform complete colonoscopy, to identify and completely removed colonic polyps of all types, and to actively look for flat lesions, especially in the right colon. It is reasonable to expect that endoscopy centers dedicate quality assurance resources to identify under-performing endoscopists who can be targeted for additional training.

In addition to specific training protocols, a variety of technologic advances have been developed to try to improve detection of difficult-to-find lesions. Cap-assisted colonoscopy, wide-angle colonoscopy, retrograde viewing devices, image enhanced endoscopy like narrow band imaging may improve lesion detection.

Incomplete polyp resection is in part predictable, and it varies substantially among endoscopists. There are some data supporting the use of high-magnification endoscopy to assess polypectomy completion and for coagulation at polyp edges of large polyps if complete resection is in doubt.

Collaboration with a good gastrointestinal pathologist is another important, but frequently neglected tool for the detection of incompletely resected polyp. Reporting of the completeness of polyp resection specifically is included as a quality measure for pathologists in the European guidelines.19

Conclusions

Although interval CRCs may be partially caused by aggressive biology, they are more likely caused by incomplete colonoscopy, missed lesions, and incomplete resection of adenomas. It is therefore necessary for the minimization of missed neoplasia to perform screening colonoscopy after an optimal bowel preparation. Furthermore, colonoscopy should be performed in an optimal setting with adequate withdrawal time and complete resection of all polypoid lesions by experienced examiners followed by an adequate histological work-up including the knowledge about sessile serrated adenomas. Clinicians must measure their colonoscopic quality and acknowledge that colonoscopy, even in the best of hands, does not prevent all interval CRCs. Despite its limitations, colonoscopy will remain a powerful tool in the fight against CRC both as a primary screening test and as the final pathway for other screening modalities.

References