Colonoscopy: What Are We Missing?

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KEYWORDS

• Colonoscopy • Adenoma • Miss rate • Detection

KEY POINTS

- Missed lesions during colonoscopy are a problem.
- Missed lesions contribute to interval cancers and impair assessment of the stability of the colorectal epithelium.
- Minimizing missed lesions will involve improving colonoscopy quality as defined by completion rates, technique, and accuracy of inspection.
- Improving inspection accuracy means an uncompromising approach to colon cleansing, development of pattern recognition for serrated polyps as well as adenomas, and taking an appropriate amount of time on scope withdrawal.

INTRODUCTION

Colonoscopy has three main roles in the area of colorectal neoplasia. The first is to screen for the disease, preventing it by the detection and removal of potentially premalignant lesions, or providing presymptomatic diagnosis of cancers at an early stage. The second is to diagnose the disease by the investigation of symptoms. The third is to prevent metachronous cancer by the surveillance of patients who already have had a colorectal neoplasm. The efficacy of colonoscopy in fulfilling these roles depends on an accurate examination of the entire colorectal mucosa. This is the rub. In an era of "pay for performance" and a time of increased demand for screening and surveillance colonoscopy, quality has become an important issue. Indices of quality of colonoscopy are now more pragmatic, focused more on what is found than how complete the examination or how satisfied the patient. In this article, the miss rates of colonoscopy are considered and the impact of miss rates on the incidence of colorectal cancer is examined.

BIOLOGY

Before discussing colonoscopy and its ability to detect colorectal neoplasia, it is important to consider the molecular mechanisms by which colorectal neoplasia

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develops. There are three main ones. Chromosomal instability is the most common, giving rise to 60% of colon cancers and 90% of rectal cancers.[1,2] The accumulation of genetic changes (mutations, hypomethylation, and loss of heterozygosity) is reflected in the mucosa by a progression from small adenomas to larger adenomas to severely dysplastic adenomas to cancer.[3] CpG island methylator phenotype (CIMP) is the second most common, a widespread methylation of CpG promoter islands that causes loss of expression of many genes. When combined with an initial BRAF mutation, such hypermethylation produces advanced serrated polyps (sessile serrated adenomas/polyps [SSA/Ps]) that become severely dysplastic and ultimately malignant.[4] Approximately 18% of colon cancers and 4% of rectal cancers are CIMP-high.[1,2] The third most common mechanism is loss of DNA mismatch repair. This causes mutations throughout the DNA due to single base or loop mismatches at DNA microsatellites, a phenotype known as microsatellite instability (MSI). High levels of MSI can lead to cancer by causing carcinogenic mutations in a variety of genes. Most mutator cancers arise from adenomas, but serrated polyps are also effects of the mechanism. Approximately 18% of colon and 3% of rectal cancers are mutator cancers.[1,2] The most common cause of MSI colon cancers is sporadic hypermethylation of *MLH1*, a DNA mismatch repair gene. Some MSI cancers, however, are due to a germline mutation in 1 of 4 DNA mismatch repair genes, known as Lynch syndrome. Colonoscopy intervenes in the mucosal manifestation of these mechanisms but does nothing to the underlying risk. Patients diagnosed with the hereditary versions of these mechanisms (chromosomal instability = familial adenomatous polyposis, CIMP+ = serrated polyposis, and mutator = Lynch syndrome) need specialized care that takes into account the instability of the colorectal epithelium with a subsequent high risk of colorectal cancer, the risk of extracolonic cancer, and the status of the family. This is best accomplished in the context of a registry.

AIMS OF COLONOSCOPY

The aims of colonoscopy, as far as colorectal cancer is concerned, are to prevent it or, if it is already there, at least to diagnose it early. The aim is not necessarily to remove all polyps regardless of size. The number and types of polyp in the colorectal mucosa are, however, a reflection of the mechanisms active at a molecular level.[5] This is why it is important to be able accurately to document the cumulative numbers of adenomas and serrated polyps. Just as every colorectal cancer has a unique molecular fingerprint, so every colon has a unique blend of molecular changes that either encourage or discourage neoplasia. Recognizing the degree of instability of the colorectal epithelium is a key to designing an appropriate endoscopic surveillance program. Therefore, the aim of colonoscopy is to find every polyp and to remove and biopsy most of the polyps—not because all polyps turn into a cancer (they do not) but because a risk status can then be assigned to the colon that determines the recommended surveillance interval.

COLONOSCOPY AND CANCER PREVENTION

The National Polyp Study caused a big stir in 1993 when it published its initial results showing a considerable reduction in the death rate from colorectal cancer in patients who had their adenomas removed. Compared to three different control groups, the reduction in colorectal cancer incidence rate was 76%, 88%, and 90%.[6] Recently, a longer follow-up of the patients confirmed a reduction in colorectal cancer mortality of 53%.[7] These data are not analyzed by site of the cancers, however. This was reported by Baxter and colleagues[8] in 2009, in a much different kind of study, looking at the integrated results of population-based colonoscopy; a sort of warts and all