

What must we do in a patient with multiple polyps through the large bowel?

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The question posed is intriguing. Isolated adenomas are extremely prevalent in the population. Screening colonoscopy has identified adenomas in 25-41% of the average risk persons aged 50 years and older in the United States. Autopsy studies suggest an even higher prevalence. Adenomas originate through the process of mutation. Sporadic adenomas begin most commonly with somatic mutations in both alleles of the adenomatous polyposis coli gene. Subsequent accumulation of additional mutations results in development of more severe histology. Most adenomas, however, do not develop sufficient mutations to transform into cancer.

Since 5 to 10 percent of these lesions undergo malignant transformation over the course of several years, the endoscopist may reduce the risk of cancer by removing them.

In the rare instances in which the colon contains multiple synchronous adenomas, the endoscopist's first reaction should be not to excise the lesions, but to count them. This is more than an arithmetic exercise: the number of polyps may play a key role in guiding the disease management.

Studies in humans and in mouse models have shown that the course of the disease can be directly related to the number of adenomas, because different ranges are frequently linked to specific genotypes. Thus, 50 to 80 percent of cases of adenomatous polyposis – a condition in which the patient presents 100 to 1000 adenomas (and, in severe cases, even more) – can be classified as familial

adenomatous polyposis (FAP), an autosomal dominant trait linked with germ-line mutations in the adenomatous polyposis coli gene (APC).¹⁻³ APC encodes a tumor – suppressor protein, that controls proliferation of the colonic epithelial cells. APC gene mutations are thus associated with overexpression of β -catenin, which in turn results in hyper-proliferation. The presence of more than 100 adenomatous polyps in the colon and rectum has been considered diagnostic of FAP. Ninety – five percent of patients have developed colorectal cancer by the age of 50. Patients with FAP should generally undergo colectomy, and the preferred operation is total proctocolectomy with ileoanal pouch anastomosis. Patients who are identified when they are children or teenagers may have surgery delayed until early adulthood if they are observed closely. In contrast to patients with adenomatous polyposis, patients with multiple colorectal adenomas have fewer than 100 adenomas and are older at the onset of disease. Five to 10 percent of these cases, classified as attenuated adenomatous polyposis coli, are also linked to the germline mutations in the APC gene, although these mutations tend to lie outside of the regions of mutational clusters.⁴ The position of the APC mutation appears to dictate not only the severity of the disease, but also the incidence of certain extracolonic manifestations, such as congenital hypertrophy of retinal pigment epithelium.⁵ But which of the remaining cases of adenomatous polyposis and multiple colorectal adenomas are not associated with APC mutations?

Recent evidence suggests that a substantial proportion of cases of multiple colorectal adenomas, perhaps as many as 30 percent of those with 15 to 100 polyps, might be associated with a novel type of DNA-repair defect. Hereditary nonpolyposis colorectal cancer (HNPCC) results from germline mutation of one of six mismatch repair genes, although two of the genes, hMLH1 and hMSH2, account for approximately 90% of

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cases. The term “HNPCC” is a misnomer, since patients with the syndrome do develop adenomatous polyps, and their cancers do arise in these adenomas. However, only one to a few adenomas are present, unlike FAP, and this distinction led to the term “HNPCC”. The syndrome is autosomal-dominant in inheritance, with 85% penetrance. Affected patients often develop cancer at a young age, although the mean age of development is older than in FAP. The distribution of cancers is shifted further to the right colon than the distribution of sporadic cancers, although left-sided and rectal cancers do occur in HNPCC. The most widely used criteria for definition of HNPCC kindreds are the modified Amstredam criteria. The Amsterdam criteria can be considered an indication to perform genetic testing.⁶ If genetic testing is not successful, is not feasible, or is refused by potentially affected individuals, then screening colonoscopy should be employed. Colonoscopy should begin at the age of 20-25, and be performed at 2-year intervals until the age of 40 and annually thereafter.

Genetic counseling and a formal risk assessment are in order for these patients, because the usual testing for FAP may not reveal AFAP due to the location of the mutation. After the thorough discussion with the patient and the understanding of the implications, genetic testing appears to be indicated to aid in establishing the exact diagnosis because issues of surveillance and the implications for other family members will need to be assessed. The issue of surgical resection is complex — if the genetic testing is informative, the answer is easy.

However, if the results of genetic testing are negative, or if the patient refuses testing, then an extended resection appears to be next in order. In any case, close surveillance of any residual mucosa will be needed. I do not believe that only colonoscopy with polypectomy is in this patient’s best interest, given the information provided, nor would a simple right-hemicolectomy be optimal.

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