Management of Colorectal Polyps

Arnold J. Markowitz, MD
Sidney J. Winawer, MD

Introduction
A colorectal polyp is defined as a visible protrusion above the surface of the surrounding normal large bowel mucosa. Polyps may be detected endoscopically by sigmoidoscopy or colonoscopy, or radiographically by barium enema.

Colorectal polyps are classified histologically as either neoplastic (adenomatous polyps) or non-neoplastic (Table). Although all adenomatous polyps have malignant potential, the majority are benign when detected. In contrast, hyperplastic, mucosal, inflammatory, and hamartomatous polyps are non-neoplastic and thus have no malignant potential. Lastly, submucosal polyps include lymphoid polyps, lipomas, and other less common histologic types.

Appropriate management of colorectal polyps requires an understanding of the typical clinical presentation, anatomic distribution, and associated clinical findings of these variable histologic types. Furthermore, although most colorectal polyps occur sporadically, some may be associated with a hereditary syndrome, such as familial adenomatous polyposis (FAP), juvenile polyposis, Peutz-Jeghers, or hereditary nonpolyposis colorectal cancer (HNPCC).

Adenomatous and hyperplastic polyps are the most commonly detected colorectal polyps and are the most likely to be found during screening sigmoidoscopy.

In this article we review the epidemiology, diagnosis, initial management, and follow-up surveillance of each polyp type. We discuss the indications for biopsy and removal of polyps found at sigmoidoscopy and colonoscopy and the need for further evaluation and follow-up. Additionally, we cover the diagnostic criteria, clinical manifestations, malignant potential, and recommendations for polyp management and surveillance in the associated hereditary syndromes.

Neoplastic Polyps
Adenomatous Polyps
Adenomatous polyps, or adenomas, are attached to the bowel wall by a stalk (pedunculated) or by a broad, flat base (sessile) (Fig. 1). The clinical significance of identifying an adenoma is that it has malignant potential and may develop into a cancer. It is generally accepted that all colorectal cancers originate from a precursor adenoma. The National Polyp Study has demonstrated that colonoscopic removal of adenomatous polyps significantly reduces the risk of developing colorectal cancer (Fig. 2).

Prevalence and Geographic Distribution
Colorectal adenomas are common in the general population. Autopsy studies from various regions of the world have reported prevalence rates ranging from 22 to 61 percent. Recent colonoscopy studies from the United States — including several screening studies of asymptomatic, average-risk individuals with no personal

Dr. Markowitz is a Clinical Assistant Physician in the Gastroenterology and Nutrition Service of the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York, New York.

Dr. Winawer is Chief of the Gastroenterology and Nutrition Service of the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York, New York.
or family history of polyps or cancer — have demonstrated rates ranging from 25 to 41 percent.\textsuperscript{12-16}

Worldwide, the prevalence rate of adenomatous polyps shows geographic variation and correlates with the regional incidence rates of colorectal cancer.\textsuperscript{17,18} Migration studies show that the prevalence rate of adenomas increases when people move from a low-risk country to one with a Westernized society.\textsuperscript{19} This suggests that environmental factors may exert some influence on the development of adenomas.

### Gender and Age

Adenomatous polyps occur more frequently in men than in women.\textsuperscript{6,10} Older patients have an increased risk of having an adenoma. Autopsy studies have reported adenoma rates of 17 percent in people younger than 50 years, 35 percent in those aged 50 to 59 years, 56 percent in those aged 60 to 69 years, and 63 percent in those aged 70 years or older.\textsuperscript{10} Screening colonoscopy studies in average-risk patients have demonstrated similar results, with rates ranging from 21 to 28 percent in those aged 50 to 59 years, 41 to 45 percent in those aged 60 to 69 years, and 53 to 58 percent in those aged 70 years or older.\textsuperscript{14,15}

### Size, Number, and Anatomic Distribution

Although adenomas vary greatly in size, most are small, measuring less than 1.0 cm in diameter. In the National Polyp Study, of the 3,371 colonoscopically removed adenomas, 38 percent were only 0.5 cm or less, 36 percent were 0.6 to 1.0 cm, and 26 percent were larger than 1.0 cm.\textsuperscript{20} In those found to have adenomatous polyps at colonoscopy, about 60 percent have a single adenoma and 40 percent have multiple adenomas.\textsuperscript{12} Increased age is associated with an increased rate of multiple adenomas.\textsuperscript{10} Adenomatous polyps exhibit the same predominantly left-sided colonic distribution that is found with colorectal cancers. Several clinical studies have reported that more than 60 percent

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| Neoplastic (Adenomatous) Polyps | Non-Neoplastic Polyps | Submucosal Polyps |
|---------------------------------|-----------------------|-------------------|
| Benign                          | Hyperplastic          | Lymphoid          |
| Mild dysplasia                  | Mucosal               | Lipoma            |
| Moderate dysplasia              | Inflammatory          | Other             |
| High-grade dysplasia            | Hamartomatous         |                   |
| Severe dysplasia                | Juvenile              |                   |
| Carcinoma in situ              | Peutz-Jeghers         |                   |
| Malignant                      |                       |                   |
| Invasive carcinoma             |                       |                   |

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Fig. 1. (A) Pedunculated polyp. (B) Small sessile polyp.
of colonoscopically removed adenomas are located distal to the splenic flexure.\textsuperscript{20-22} Some autopsy studies of patients who had died of other causes, however, have shown that coincidentally found adenomas are more common in the proximal colon.\textsuperscript{8,10}

**Pathology**

Adenomatous polyps are classified histologically as tubular, tubulovillous, or villous. Tubular adenomas are most common. The St. Mark’s Hospital data and National Polyp Study data have shown that 75 to 87 percent of adenomas are tubular, 8 to 15 percent are tubulovillous, and 5 to 10 percent are villous.\textsuperscript{1,20}

In tubular adenomas, the adenomatous epithelium proliferates and forms straight or branched tubules that are separated by normal lamina propria (Fig. 3A). Grossly, tubular adenomas are more commonly pedunculated and have a smooth, lobulated surface. In villous adenomas, the epithelial proliferation results in adjacent elongated crypts that give an overall appearance of thin, villus-like projections of normal lamina propria surrounded by adenomatous epithelium, extending out perpendicularly from the muscularis mucosa (Fig. 3B). Classification as a villous adenoma requires that more than 75 percent of the polyp show villous architecture. Grossly, villous adenomas are more typically sessile and have a “shaggy” surface. Tubulovillous adenomas show a mixture of both tubular and villous architecture, demonstrating between 25 and 75 percent of villous features.
The size of an adenoma correlates with its underlying histology. The St. Mark’s Hospital data showed that of their tubular adenomas, 76 percent were smaller than 1.0 cm, 20 percent were between 1.0 and 2.0 cm, and 4 percent were larger than 2.0 cm; of their tubulovillous adenomas, 25 percent were smaller than 1.0 cm, 47 percent were between 1.0 and 2.0 cm, and 28 percent were larger than 2.0 cm; and of their villous adenomas, 14 percent were smaller than 1.0 cm, 26 percent were between 1.0 and 2.0 cm, and 60 percent were larger than 2.0 cm. Thus, larger adenomas are more likely to demonstrate villous features.

Because adenomatous epithelium is by definition neoplastic, every adenoma exhibits some degree of dysplasia. Dysplasia is classified histologically as mild, moderate, or severe (high grade). The grade of dysplasia is determined by the degree of cytologic epithelial atypia and glandular architectural distortion.

Carcinoma in situ and intramucosal carcinoma are terms used for adenomas with severe dysplasia contained within their mucosa and refer to dysplastic cells either being limited to the mucosal glands or extending out into the lamina propria, respectively. Because the severely dysplastic cells have not yet invaded through the muscularis mucosae, these adenomas pose no risk of lymph node metastases. Therefore, it is preferable to avoid using the terms carcinoma in situ and intramucosal carcinoma because they often produce unwarranted anxiety for both patient and physician and may lead to excessive surveillance and even unnecessary surgical resection.

The National Polyp Study demonstrated that about 86 percent of adenomas show mild, 8 percent moderate, and 6 percent high-grade (severe or carcinoma in situ) dysplasia. Larger polyp size, greater villous architecture, and increased patient age are all associated with a higher risk of high-grade dysplasia in adenomas (Fig. 4).

Adenoma-Carcinoma Sequence

The concept of the adenoma-to-carcinoma sequence is well accepted and describes a stepwise progression from normal colorectal epithelium to adenoma to carcinoma, in association with an accumulation of multiple genetic alterations within the epithelial cells. Many lines of evidence support this concept. Prevalence rates of adenomas correlate with colorectal cancer incidence rates in different worldwide geographic regions, and prevalence rates increase after migration to a high-risk area for colorectal cancer. The risk of adenoma and the risk of cancer both increase with patient age. Cancer risk increases with increased adenoma size. In clinical studies, adenomas and cancers show a predomi-
nantly left-sided anatomic distribution. Synchronous adenomas are common in patients with cancer, and residual adenomatous tissue may often be found in the cancer. In familial adenomatous polyposis, colorectal cancer occurs several years after the development of hundreds to thousands of adenomas. Lastly, the National Polyp Study demonstrated that colorectal cancer incidence is decreased after colonoscopic removal of adenomas.2

At the molecular level, several well characterized genetic changes have been associated with the progression of normal colonic epithelium to invasive cancer. The earliest alteration appears to be a mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q, which inactivates the gene and leads to epithelial cell proliferation and the development of an early adenoma. Additional major genetic alterations include oncogene activation, as a result of a mutation in the Ki-ras gene, and loss of tumor suppressor genes, caused by deletion of the deleted in colorectal cancer (DCC) gene on chromosome 18q and mutation of the p53 gene on chromosome 17p.

Although the actual time course of the adenoma-to-carcinoma sequence is not certain, it appears to be a slow process occurring over many years. Data from both the National Polyp Study24 and the St. Mark’s Hospital study, which described the long-term observation of unresected colorectal adenomas, support an average time course of at least 5 to 10 years for progression from an adenoma to a carcinoma. An exception, however, may be seen in the hereditary nonpolyposis colorectal cancer syndrome. A report from the Netherlands showed an unexpectedly high incidence of advanced colorectal cancers detected within 3.5 years after a negative screening examination.
(colonoscopy or barium enema) in a large number of HNPCC patients participating in a national screening program. These findings suggest that HNPPC patients may have a shorter time interval to develop colorectal cancer and thus an accelerated adenoma-to-carcinoma sequence.

Dietary and Hereditary Factors
Dietary factors such as high fat and low fiber have been associated with an increased risk of both colorectal adenomas and cancer. Some evidence exists that modification of certain dietary factors may have an effect on the adenoma-to-carcinoma sequence. A study of calcium supplementation in patients with a family history of colorectal cancer showed a decrease in colonic epithelial cell proliferation. Modification of dietary fat intake has been reported to alter epithelial cell proliferation in humans. These results suggest that these and other dietary components found in fruits, vegetables, and other food sources may be able to regulate colon cancer carcinogenesis at a relatively early stage in the adenoma-to-carcinoma sequence.

An inherited predisposition to common, sporadic colorectal adenomas and cancer appears to exist. An individual's risk of having a colorectal adenoma is increased if he or she has a first-degree relative who had colorectal cancer. The National Polyp Study demonstrated that an individual's risk of developing colorectal cancer is increased if he or she has a sibling or a child who had an adenomatous polyp, particularly if the adenoma was diagnosed before 60 years of age. An individual's risk of colorectal cancer is also significantly increased if he or she has a first-degree relative who had colorectal cancer, particularly if the cancer was diagnosed before 55 years of age, and this risk is even greater if two first-degree relatives were affected with cancer.

One can speculate that environmental factors such as dietary substances and toxic carcinogens may perhaps interact with underlying genetic factors in patients with an inherited predisposition to allow initiation of, and progression along, the adenoma-to-carcinoma sequence.

Pathologic Features of Polyps Associated with Cancer
Given that the prevalence of adenomatous polyps far exceeds that of colorectal cancer, it is clear that only a small proportion of adenomas go on to develop into cancer. Although it is not yet possible to determine which adenomas will progress, certain pathologic features of adenomas have been found to correlate with the risk of finding cancer in those polyps.

Increased polyp size, villous histology, and severe dysplasia are all associated with an increased risk of malignancy in an adenoma. The St. Mark's Hospital study demonstrated that (1) 1.3 percent of adenomas smaller than 1 cm, 9.5 percent between 1 and 2 cm, and 46 percent larger than 2 cm were malignant; (2) 4.8 percent of tubular, 22.5 percent of tubulovillous, and 40.7 percent of villous adenomas were malignant; and (3) 5.7 percent of mild, 18 percent of moderate, and 34.5 percent of adenomas with severe dysplasia were malignant.

A patient's future risk of colorectal cancer may also be associated with characteristic features of his or her adenomas. A pre-colonoscopy long-term follow-up study from St. Mark’s Hospital of a large cohort of patients who had sigmoidoscopy and removal of rectosigmoid adenomas, but did not have colonoscopy, showed that distal villous, tubulovillous, or large (1 cm or more) adenomas increased their risk for the subsequent development of colon cancer, and that this risk was even greater for those who had multiple polyps. Presumably, this increased risk was caused by additional adenomatous polyps located more proximally in the colon that were not removed.
Management

Detection

Although colorectal adenomatous polyps may account for small amounts of stool blood loss, they are predominantly asymptomatic. Because of their high prevalence in our general population, however, adenomas are often found during screening examinations for colorectal cancer in asymptomatic individuals and during evaluations of symptomatic patients with gastrointestinal complaints. Adenomas may be detected either endoscopically (by sigmoidoscopy or colonoscopy) or radiographically (by barium enema). Patients with colorectal polyps detected radiographically are referred for colonoscopic polypectomy.

If a small (less than 1 cm) polyp is found at sigmoidoscopy, it undergoes biopsy and further management is based on its underlying pathology. If a large (1 cm or more) polyp is detected, a biopsy is generally not necessary and the patient may be directly referred for colonoscopic polypectomy. If a polyp detected at sigmoidoscopy is found to be an adenoma after the biopsy, colonoscopy is recommended.

At colonoscopy, the adenoma found during sigmoidoscopy is removed and the more proximal colon is examined for potential synchronous adenomas and other neoplastic lesions. Several colonoscopy studies support the increased risk of finding a proximal synchronous lesion in patients with a distal adenoma. In a recent prospective study of asymptomatic individuals at average risk for colorectal cancer, 31 percent of those who were found to have a benign distal adenoma at screening flexible sigmoidoscopy had proximal synchronous neoplasms, including eight percent with advanced adenomas (larger than 1 cm, villous, moderate to severe dysplasia) and invasive cancers. A second study of screening colonoscopy in asymptomatic average-risk men showed that 42 percent of those with distal adenomas found during the initial evaluation of their distal 60 cm of colon, before the examination was completed to the cecum, had proximal synchronous adenomas.

Some investigators, however, question the need for colonoscopy in patients found to have a small (less than 1 cm) adenoma at sigmoidoscopy. In a study of asymptomatic and symptomatic patients who had colonoscopy after adenomas were found at sigmoidoscopy, the occurrence of a proximal advanced (larger than 1 cm, villous, or severe dysplasia) synchronous adenoma in those who had only one or more small (1 cm or less) tubular adenomas at sigmoidoscopy was less than one percent. Another study found that asymptomatic patients whose worst index lesion was a single small (less than 1 cm) tubular adenoma and who had no first-degree relatives with colorectal cancer had only a three percent prevalence of a proximal advanced synchronous adenoma or invasive cancer at colonoscopy, which was no greater than that expected in the general population. In comparison, a recent prospective study of asymptomatic, average-risk individuals showed a seven percent prevalence of synchronous proximal advanced adenomas and invasive cancers in those whose index lesion at screening flexible sigmoidoscopy was a small (1 cm or smaller) adenoma, including two proximal adenomas with severe dysplasia and two early (stage I) invasive cancers in four patients whose index adenoma was only 0.5 cm or less. In the St. Mark’s Hospital’s long-term follow-up study of patients who had removal of rectosigmoid adenomas without colonoscopic follow-up, patients who were initially found to have one or more small (less than 1 cm) tubular adenomas with only mild to moderate dysplasia had a low risk for subsequent development of colorectal cancer that was no greater than that in the general population.
Thus, the need for colonoscopy and further follow-up surveillance in patients found to have a small distal tubular adenoma at sigmoidoscopy is controversial. Currently we recommend colonoscopy initially and post-polypectomy surveillance in these individuals. Longer surveillance intervals (perhaps every five years) may be reasonable in this group of patients.

We consider colonoscopy to be superior to barium enema for the follow-up management of colorectal polyps. Although barium enema is less costly and has a low risk, colonoscopy offers a more sensitive examination and provides the opportunity for colonoscopic polypectomy in addition to diagnostic biopsies of suspicious mass lesions.

Colonoscopic Polypectomy
At colonoscopy all polyps are completely removed. However, there are circumstances such as serious co-morbid medical conditions or a significantly reduced life expectancy that would preclude the removal of coincidentally found colorectal polyps detected during a diagnostic colonoscopy performed for evaluation of gastrointestinal symptoms in such patients.

When a polyp is detected at colonoscopy, a polypectomy is performed and all tissue is retrieved and sent for pathologic evaluation. The most commonly used techniques for colonoscopic polypectomy include snare polypectomy, polyp fulguration using the hot biopsy forceps, and excisional biopsy without fulguration.

Snare polypectomy is typically performed on pedunculated polyps and involves the placement of a wire snare around the polyp and subsequent application of electrocautery to transect the stalk. The excised polyp is then retrieved and sent to pathology. Small sessile polyps in the distal colon are commonly removed with the hot biopsy forceps. With this technique, the polyp is gently pulled upwards from the bowel wall and thermal energy is then delivered to fulgurate the lesion. The polyp tissue left inside the hot biopsy forceps is insulated from thermal damage and is sent for pathologic examination. Small sessile polyps may also be removed by excisional biopsy without fulguration. This is especially useful for small polyps in the proximal colon where biopsy fulguration has been associated with a higher frequency of post-polypectomy bleeding.

Large sessile polyps with a broad base present more of a challenge to the endoscopist. In certain situations these large polyps may be removed with several applications of the snare cautery. Currently a new technique known as saline-assisted polypectomy may also be used for large sessile polyps. With this method, saline is first injected below the mucosa to lift the polyp up and off of the colonic wall before snare polypectomy. The saline injection provides a protective cushion that decreases the potential risk of post-polypectomy perforation. Large sessile polyps that cannot be removed safely or completely by endoscopy may be referred for surgical resection.

Colonoscopic polypectomy is a safe technique with an acceptably low complication rate. Post-polypectomy perforation or major bleeding occurs in approximately 0.1 to 0.2 percent of cases.

Post-polypectomy Surveillance
Follow-up colonoscopy is usually recommended after removal of one or more adenomatous polyps to decrease the patient’s risk of developing colorectal cancer. The National Polyp Study recently demonstrated that surveillance colonoscopy can be safely deferred for three years after the complete colonoscopic removal of all colorectal adenomas. In that study 1,418 patients were randomly assigned after colonoscopic clearance of all adenomas to follow-up surveillance colonoscopy either at one and three years
or at three years only. There was no difference (3.3 percent in both groups) in those found to have adenomas with advanced pathology (larger than 1 cm, severe dysplasia, or invasive cancer).

After complete colonoscopic resection of an adenoma containing severe or high-grade dysplasia (carcinoma in situ) a three-year surveillance interval is recommended. Since pathologic studies of adenomatous polyps have shown that the lymphatic channels do not penetrate above the level of the muscularis mucosa, polyps with severely dysplastic cells limited to the mucosa are not at risk for lymph node metastases. Follow-up of patients after colonoscopic resection of these polyps has revealed no adverse outcome.

In individual cases of patients who have had colonoscopic polypectomy of adenomas, earlier follow-up may be recommended after an incomplete polypectomy, removal of a very large sessile polyp, excision of multiple adenomas, or a suboptimal examination resulting from poor bowel preparation.

**Malignant Polyps**

A malignant colorectal polyp is an adenoma that contains invasive cancer, defined as malignant cells that have invaded down through the muscularis mucosa into the submucosa. Prior studies have reported that approximately five percent of endoscopically resected adenomas are malignant; however, recent data from the National Polyp Study have found this figure to be only two percent (Zauber, A: The National Polyp Study data, personal communication).

Malignant polyps may be pedunculated or sessile. Although their gross appearance is generally not distinguishable from that of other benign polyps, colonoscopic findings that may suggest malignancy include irregularity of the polyp surface, ulceration, firmness when pushed with the biopsy forceps, a broad or deformed stalk, or excessive friability.

In contrast to an adenoma with high-grade dysplasia, cancer cells in a malignant polyp are no longer limited to the mucosa; therefore, they do have the potential to metastasize. For this reason, after colonoscopic removal of a malignant polyp one must consider the need for surgical referral. This decision includes consideration of the risks of possibly leaving behind residual malignant disease at the polypectomy site and of lymph node metastases versus the surgical risks of laparotomy and bowel resection.

Several important risk factors are used to guide the decision for surgical resection after colonoscopic removal of a malignant polyp. Favorable criteria include a well or moderately well differentiated adenocarcinoma, no venous or lymphatic invasion, a polyp resection margin that is clear of malignant cells, and colonoscopic assessment of a complete resection. Unfavorable criteria include a poorly differentiated adenocarcinoma, venous or lymphatic invasion (or both), malignant cells close to the resection margin, and colonoscopic assessment of an incomplete or questionably complete resection. The most common unfavorable finding is detection of cancer cells at or close to the margin of resection.

A review of colonoscopically resected malignant polyps from the Cleveland Clinic by Cranley and colleagues, combined with their review of the literature, showed that the risk of residual cancer or lymph node metastases in polyps with favorable criteria was 0.3 percent for pedunculated polyps and 1.5 percent for sessile polyps. The mortality of elective colorectal surgery is approximately one to two percent; however, operative risk may be lower for young patients and higher for the elderly with significant comorbid medical conditions.

After colonoscopic removal of a pedunculated malignant polyp with favorable risk criteria, because the risk of surgery is greater than that of having residual cancer or lymph node metastases...
tases, surgical resection is generally not indicated. In the case of a young otherwise healthy individual, however, surgery may be considered because operative risk is minimal and the patient may not accept even the most remote chance of residual disease or lymphatic spread. In contrast, after colonoscopic removal of a pedunculated malignant polyp demonstrating unfavorable risk criteria, patients are considered for surgical resection, unless they are poor surgical candidates.

Controversy exists in the management of the sessile malignant polyp. In contrast to the pedunculated polyp, in which the submucosa extends out into the polyp stalk and head, in the sessile polyp the invasive cancer cells, by definition, invade into the submucosa of the colonic wall. Some physicians recommend surgery for all sessile malignant polyps, even if they demonstrate favorable risk characteristics, because they believe that the sessile morphology in and of itself increases the patient’s risk of having residual disease. Others believe that there is not enough evidence to support sessile morphology as an absolute indication for surgical resection in all cases. One group’s review of the literature concluded that malignant polyps with favorable risk factors, whether pedunculated or sessile, did not differ in their risk of residual disease or lymph node metastases, and therefore suggested that small sessile polyps with favorable risk characteristics that did not have extensive malignant invasion and did not require piecemeal resection do not require surgical resection.

Our approach to the management of the sessile malignant polyp with favorable risk criteria is that colonoscopic polypectomy alone is adequate treatment for most patients; however, the decision must be individualized for each patient. For the sessile malignant polyp with unfavorable risk characteristics our approach is the same as that for the pedunculated malignant polyp.

At colonoscopy, when a polyp is found that is suggestive of malignancy, the endoscopist first assesses whether or not it is endoscopically resectable. Pedunculated and small sessile polyps may be completely resected, whereas very large sessile lesions undergo biopsy. When a polyp is removed, all tissue is retrieved and sent for pathologic evaluation. Polyp location is always carefully documented because if the polyp is found to be malignant and shows unfavorable risk characteristics, surgical resection may be necessary. At colonoscopy, India ink may be injected into the bowel wall at the polypectomy site to create a permanent localization marker for possible subsequent surgical resection.

After colonoscopic removal of a malignant polyp with favorable risk criteria, a follow-up colonoscopy is generally performed in about three to six months to assess the polypectomy site for completeness of removal, particularly if the polyp was sessile. If residual cancer is found, the individual is referred for surgical resection, provided that the patient is a good surgical candidate. If there is no residual cancer, a one-year follow-up colonoscopy may be performed; if this examination has negative findings, it may be repeated again in three years. Additional clinical follow-up with radiographic imaging and other tests may be appropriate in select patients.

Non-neoplastic Polyps

Hyperplastic Polyps

Hyperplastic polyps account for the majority of non-neoplastic colorectal polyps. They are entirely benign and have no malignant potential. Autopsy and screening colonoscopy studies report prevalence rates of 20 to 34 percent. Hyperplastic polyps, predominantly located in the distal colon and rectum, are commonly found at sigmoidoscopy. A report of screening flexible sigmoidoscopy in...
400 patients showed a prevalence rate of 30 percent. 46

Hyperplastic polyps generally appear as small (0.5 cm or less), sessile, flat or convex lesions that are relatively pale or the same color as the surrounding normal colorectal mucosa. Although most hyperplastic polyps are small, not every small polyp is hyperplastic. In a study of 1,048 colonoscopically removed small (0.1 to 0.6 cm) polyps only 20 percent were hyperplastic, compared with 61 percent neoplastic adenomas.47 Histologically, hyperplastic polyps demonstrate a characteristic extensive papillary infolding of their epithelial cells that results in elongated crypts and, at low power, a distinctive serrated or saw-tooth appearance to the polyp surface.

Distal colorectal hyperplastic polyps do not increase a patient’s risk of harboring proximal synchronous adenomas.14,48 Thus, when a patient is found to have a hyperplastic polyp at sigmoidoscopy, it is not necessary to recommend further evaluation with colonoscopy and special follow-up surveillance.

**MUCOSAL POLYPS**

Mucosal polyps appear as small (0.5 cm or less) outgrowths of tissue from the large bowel mucosa. They are non-neoplastic lesions and can be found anywhere in the colon or rectum. Histologically they show normal colonic mucosa that has been elevated by the underlying submucosa. These polyps may account for 18 percent of endoscopically resected small polyps.47 Mucosal polyps have no clinical significance and do not need follow-up surveillance.

**INFLAMMATORY POLYPS**

Inflammatory colorectal polyps are associated with severe inflammatory conditions of the large bowel. These non-neoplastic polyps develop as a result of severe ulceration and regenerative repair of the epithelium and may occur in any segment of the colon and rectum. Inflammatory pseudopolyps represent residual islands of intact colonic mucosa that appear to project into the bowel lumen because of ulceration and undermining of the surrounding areas of adjacent mucosa. They are most commonly associated with chronic idiopathic ulcerative colitis or Crohn’s colitis.

Another type of inflammatory polyp consists of regenerating mucosa and granulation tissue. Some individuals may present with single or several large inflammatory polyps that, on rare occasions, may cause abdominal pain or obstruction.49,50 Inflammatory polyps may be associated with any inflammatory condition and have been reported in amebic colitis, ischemic colitis, schistosomiasis, and bacterial dysentery; at surgical anastomotic sites; and adjacent to ulcers or ureterosigmoidostomies. They can also occur without any underlying inflammatory condition in the colon.

**HAMARTOMATOUS POLYPS**

**Juvenile Polyps**

Juvenile polyps most commonly present as solitary rectal polyps in children before 20 years of age and occasionally in young adults.51 Patients may, however, present with more than one polyp, and the polyps may be located more proximally in the large bowel.52 Most juvenile polyps are pedunculated red polyps with smooth surfaces that are friable and bleed easily. More than 90 percent of patients present with rectal bleeding; some also develop crampy abdominal pain, prolapse of the polyp from the rectum, and rectal prolapse.52 Patients may even present with passage of the polyp in their stool as a result of autoamputation.53

Histologically, the juvenile polyp surface is lined with a single layer of columnar epithelial cells. These hamartomas are also known as retention polyps.
because they contain characteristically dilated cystic glands filled with mucus, separated by abundant edematous lamina propria that has been expanded by inflammatory cells and a rich vasculature.

Solitary juvenile polyps are benign lesions and have no malignant potential. Very rare case reports exist, however, of solitary juvenile polyps containing adenomatous and malignant changes. Since most children are symptomatic at presentation, complete removal of all juvenile polyps is generally recommended.

**Peutz-Jeghers Polyps**

Peutz-Jeghers polyps are non-neoplastic hamartomatous polyps that may occur anywhere in the gastrointestinal tract, from the stomach to the rectum. Although these polyps are most commonly associated with a hereditary polyposis syndrome, sporadic cases of solitary Peutz-Jeghers–type polyps of the stomach, small bowel, and colon have been reported.

Peutz-Jeghers polyps may be pedunculated or sessile and usually measure up to 3 cm but may grow as large as 5 cm. Histologically, they are composed of elongated, branching, tortuous glands lined by the normal epithelial cells typically found in the segment of the gastrointestinal tract in which they developed. Their characteristic histologic feature is a branching or arborizing proliferation of smooth muscle that originates from the muscularis mucosa and extends up into the lamina propria, surrounding the glands.

**Submucosal Polyps**

Submucosal colorectal lesions may protrude into the bowel lumen and produce a polypoid appearance. Colonoscopic biopsies of these lesions are usually non-diagnostic because the biopsies are too superficial and sample only the normal overlying mucosa. Multiple sequential biopsies at a single location may obtain a piece of the underlying submucosal tissue and provide a definitive diagnosis.

**Lymphoid Polyps**

Benign lymphoid polyps may occur as a result of hyperplasia of the normal underlying lymphoid tissue found in the intestinal mucosa and submucosa. These polyps result from an expansion of the lamina propria caused by a lymphocytic infiltration. They are usually single and most commonly occur in the rectum. Lymphoid polyps are typically small and sessile but on occasion may grow as large as 3 cm. These polyps may present at any age but usually are found between the second and fifth decades of life. Although they are commonly asymptomatic, rarely a large lymphoid polyp may cause anorectal discomfort, prolapse from the rectum, or rectal bleeding.

**Lipomas**

Lipomas are usually found in the proximal colon, on or close to the ileocecal valve. They are usually single, asymptomatic, and found incidentally at colonoscopy. They appear yellowish and soft and are easily deformed when probed with the biopsy forceps (“pillow sign”). Asymptomatic colonic lipomas do not need to be removed and require no follow-up.

**Other Submucosal Polyps**

Rectosigmoid carcinoid tumors and metastatic cancer, particularly melanoma, may present as a submucosal mass lesion. Other rare causes of submucosal colorectal lesions include leiomyomas, fibromas, neurofibromas, hemangiomas, endometriosis, and Kaposi’s sarcoma.

**Inherited Syndromes**

**Familial Adenomatous Polyposis**

Familial adenomatous polyposis is an autosomal dominant disorder characterized by the progressive development of hun-
dreds to thousands of colorectal adenomas. FAP accounts for about one percent of all cases of colorectal cancer. Affected patients have a germline mutation in the APC gene on the long arm of chromosome 5. Adenomas typically begin to present early in the second decade of life. In untreated patients, colorectal cancer inevitably occurs by the fourth to fifth decade of life.

Gardner’s syndrome, a variant of FAP, is characterized by colorectal adenomas and extraintestinal manifestations, including osteomas (particularly of the mandible and skull), soft tissue tumors (such as lipomas, fibromas, and epidermoid and sebaceous cysts), supernumerary teeth, desmoid tumors, mesenteric fibromatosis, and congenital hypertrophy of the pigmented retinal epithelium (CHPRE). Thyroid cancers and adrenal adenomas and cancers have also been associated with this syndrome. Turcot’s syndrome, another variant of FAP, is characterized by colorectal adenomas and brain tumors.

Upper gastrointestinal polyps are also common in FAP and Gardner’s syndrome. Gastric polyps, mainly small hyperplastic fundic gland polyps, may be found in up to 50 percent of patients. These hyperplastic polyps are benign and have no clinical significance. In contrast, duodenal adenomas occur in about 80 percent of patients and have malignant potential. The duodenal adenomas are usually multiple, are sessile, range in size from 0.5 cm to 1 cm, and commonly involve the periampullary region. FAP and Gardner’s patients have a significantly increased risk of duodenal and ampullary cancer. Small intestinal polyps distal to the duodenum may also occur, but the development of cancer in these areas is much less common.

Genetic testing for an abnormal APC gene is available for members of FAP families. Individuals at risk for FAP begin annual screening sigmoidoscopy at about 12 years of age. The frequency of screening can decrease to every three years after age 40. If polyps are found and biopsies show adenomas, the patient may be referred for surgical consultation. The timing of surgery is somewhat controversial. In patients with perhaps ten or fewer adenomas, some physicians may recommend total endoscopic removal of all polyps and if no evidence of severe dysplasia or early cancer is found, close follow-up surveillance. If at initial diagnosis or during follow-up the number or size of the polyps is found to be unmanageable, immediate surgery is indicated. Surgical options include total proctocolectomy with ileostomy, subtotal or total abdominal colectomy with ileorectal anastomosis (which requires close annual surveillance of the remaining at-risk rectal mucosa) and total colectomy, mucosal proctectomy, and ileoanal anastomosis.

After diagnosis of FAP, a baseline upper endoscopy is performed to screen for gastric and duodenal polyps and to establish their underlying histologic characteristics. If either no polyps or only small benign hyperplastic gastric fundic gland polyps are found, a follow-up upper endoscopy may be performed in three years. If, however, duodenal adenomas are present, the patient requires close surveillance for the development of severe dysplasia and malignancy in these polyps. These duodenal adenomas can be difficult to manage because of their multiplicity and typical confluent, sessile nature. Endoscopic control of duodenal adenomas may become unmanageable and surgery may be required. The surveillance of FAP patients is further compounded by their increased risk of developing adenomatous changes and malignancy of the major papilla (ampulla of Vater). Thus, at the time of each endoscopy it is essential to also use the side-viewing endoscope to assess and biopsy the major papilla, even if it appears to be grossly normal. If biopsies of the papilla reveal adenoma with severe dysplasia or invasive cancer, the patient
is referred for surgical consultation. For FAP patients with duodenal adenomas the follow-up surveillance interval for upper endoscopy is every one to three years.

Sulindac (Clinoril), a nonsteroidal antiinflammatory drug that inhibits prostaglandin synthesis, has been reported to cause regression of colorectal adenomas in FAP patients. In one prospective, randomized, double-blind, placebo-controlled trial of 22 patients with FAP, sulindac decreased the number and size of colorectal adenomas; however, none had total regression, and three months after treatment stopped the number and size of polyps increased. An even smaller randomized, placebo-controlled, double-blind crossover study of sulindac in nine post-colectomy FAP patients with ileorectal anastomoses also showed some efficacy in regression of rectal adenomas (six of nine had complete regression); however, after the drug was stopped, recurrence was again rapid. Such interesting findings suggest that although sulindac cannot prevent the need for surgical resection in FAP, perhaps it may have some protective role in postoperative patients with retained rectal mucosa.

**JUVENILE POLYPOSIS SYNDROME**

Juvenile polyposis syndrome is characterized by multiple gastrointestinal juvenile polyps. It is familial in 25 percent of affected families. Familial cases may have multiple juvenile polyps limited to the stomach (familial juvenile polyposis of the stomach) or the colon (familial juvenile polyposis coli) or extensive involvement from the stomach to the rectum (generalized juvenile gastrointestinal polyposis). Affected families probably have an autosomal dominant mode of inheritance. The number of polyps may range from 25 to 40 or more. Extraintestinal congenital abnormalities may also occur. Patients commonly present during childhood with anemia caused by chronic gastrointestinal blood loss, crampy abdominal pain, recurrent intussusceptions, or rectal bleeding.

Patients with juvenile polyposis syndrome have an increased risk of colorectal cancer. Although affected patients are found to have typical histologically benign juvenile polyps, their increased risk of cancer appears to be the result of the occasional occurrence of polyps with mixed juvenile and adenomatous features or synchronous adenomas (or both). These patients may also be at risk for upper gastrointestinal malignancy.

In patients with juvenile polyposis syndrome, surveillance colonoscopy with endoscopic removal of all polyps is recommended. Asymptomatic individuals from these families begin screening during their second decade of life. After diagnosis, these patients also have a baseline upper endoscopy and either small bowel enteroscopy or a barium study to screen the upper gastrointestinal tract for gastric and small bowel polyps. Lifelong surveillance is performed.

**PEUTZ-JEGHERS SYNDROME**

Peutz-Jeghers syndrome is characterized by multiple gastrointestinal hamartomatous polyps and mucocutaneous melanin pigmentation. The syndrome has an autosomal dominant mode of inheritance. Although Peutz-Jeghers polyps may occur throughout the gastrointestinal tract, they most commonly involve the small intestine. The total number of polyps is usually less than 100. The pigmented macules are usually found on the face (around the mouth, nose, lips, and buccal mucosa) but may also involve the hands, feet, and perianal and genital areas.

Patients typically become symptomatic between their second and third decades of life. They most commonly present with intestinal obstruction caused by mechanical blockage or intussusception from their small intestinal polyps. Some present with iron deficiency anemia re-
sulting from chronic gastrointestinal blood loss or hematochezia from rectal polyps. Nasal, bronchial, and bladder polyps have also been reported in some patients.

Peutz-Jeghers patients have an increased risk of gastrointestinal cancers and other associated extraintestinal malignancies.\textsuperscript{71-77} Reported rates of gastrointestinal cancer range from 2 to 13 percent.\textsuperscript{74} These patients may develop adenomas, carcinomas, and hamartomas containing both adenomatous and malignant changes of the stomach, small intestine, and colon.\textsuperscript{71-77} Carcinoma arising in residual adenomatous tissue has also been reported.\textsuperscript{72-78} Extraintestinal tumors are also associated with Peutz-Jeghers syndrome and include ovarian sex cord tumors,\textsuperscript{79-81} testicular Sertoli cell tumors,\textsuperscript{82-84} adenoma malignum (a rare type of cervical cancer),\textsuperscript{72,81,85} breast cancer,\textsuperscript{71,86,87} and pancreatic cancer.\textsuperscript{71-73,88,89} A review of the Johns Hopkins Polyposis Registry showed that the relative risk of a Peutz-Jeghers patient developing a cancer was 18 times greater than that expected in the general population.\textsuperscript{71} A review of the St. Mark’s Polyposis Registry found that 22 percent developed cancer and that the relative risk of death from gastrointestinal cancer was 13 and that from all cancers was nine.\textsuperscript{73}

As a result of the growing evidence of adenomatous and malignant changes in Peutz-Jeghers hamartomas and reports of synchronous adenomas, upper endoscopic and colonoscopic surveillance with endoscopic removal of all polyps is performed. Small bowel enteroscopy or barium study can search for jejunal polyps beyond the reach of the upper endoscope. Since these polyps may at times be broad based or large, surgical enterotomy may be necessary for their removal. If a patient does require laparotomy, this is a good opportunity to clear the entire gastrointestinal tract of all polyps through a combination of preoperative or intraoperative (or both) endoscopic and surgical excisions. Lifelong surveillance and special screening for extraintestinal malignancies are also recommended.

**HEREDITARY NONPOLYPOSIS COLORECTAL CANCER**

Hereditary nonpolyposis colorectal cancer, commonly referred to as \textit{Lynch Syndrome I} and \textit{II}, is a disorder in which affected patients develop small numbers of colorectal adenomas and are at increased risk for colorectal cancer. HNPCC accounts for about five percent of all cases of colorectal cancer. In some families there is also an increased risk of extracolonic malignancies. HNPCC shows an autosomal dominant mode of inheritance.

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\textit{It is preferable to avoid using the terms carcinoma in situ and intramucosal carcinoma.}

Because affected patients do not express an obvious phenotype, such as the diffuse colonic polyposis seen in FAP, the diagnosis of HNPCC has been primarily based on family history. The Amsterdam criteria define HNPCC as a syndrome in which three or more close relatives (one being a first-degree relative of another two) from at least two generations are affected with colorectal cancer, with at least one diagnosed before age 50, in the absence of gastrointestinal polyposis.\textsuperscript{90} Germline mutations in four DNA mismatch repair genes have now been identified in HNPCC patients. The four HNPCC genes include \textit{hMSH2} on chromosome 2, \textit{hMLH1} on chromosome 3, \textit{hPMS1} on chromosome 2, and \textit{hPMS2} on chromosome 7. Mutations in
these genes result in genomic instability in these patients. Genetic testing for mutations in these HNPCC genes is currently available.

HNPCC patients are at increased risk for early onset of colorectal cancer, at an average age of diagnosis of 40 to 45 years. The colon cancers are predominantly right sided, with 60 to 70 percent proximal to the splenic flexure. They often present with multiple primary colon cancers and are at increased risk for metachronous lesions. HNPCC is also associated with extracolonic cancers of the endometrium, ovary, stomach, small intestine, renal pelvis and ureter (transitional cell cancer), and the pancreaticobiliary system.

Adenomatous polyps in HNPCC patients are also predominantly located in the proximal colon and, likewise, show a high rate of synchronous and metachronous lesions. It has been reported that these adenomas attain a larger size and are more likely to have an underlying villous histology; however, others have not supported these findings. There are also reports of “flat adenomas” in HNPCC patients.

Screening in HNPCC patients and their family members must be done by colonoscopy because of the increased incidence of proximal adenomas and cancers. A long-term follow-up study from Finland of 251 at-risk individuals from 22 HNPCC families showed a significant reduction in incidence (P = 0.03) and a reduction in mortality (P = 0.08) of colorectal cancer in a subgroup who had screening examinations (colonoscopy or flexible sigmoidoscopy and barium enema) every three years compared with a control subgroup who had no screening. The reduction in the risk of colon cancer is probably the result of the colonoscopic removal of adenomas. Preliminary data from Memorial Sloan-Kettering Cancer Center in New York on long-term follow-up of a smaller group of patients at high risk for HNPCC showed that screening colonoscopy reduced the incidence of colorectal cancer to a rate close to that of the unscreened general population.

Because HNPCC adenomas may progress more rapidly through the adenoma-to-carcinoma sequence than do typical sporadic adenomas, and given the evidence that screening clearly decreases the risk of colorectal cancer in these individuals, screening colonoscopy is generally recommended every one to two years for patients and their relatives at risk for HNPCC. We currently recommend colonoscopy every one to two years beginning at age 21. Additionally, special screening for extracolonic malignancies is recommended.

Guidelines for Polyp Management

1. If a small (less than 1 cm) polyp is found at sigmoidoscopy, it is biopsied, and if it is an adenoma colonoscopy is recommended to remove the polyp and to examine the proximal colon for synchronous neoplastic lesions. We continue to recommend colonoscopy even if only a small tubular adenoma is found at sigmoidoscopy. In these cases conservative follow-up recommendations may be reasonable.

2. If a large (1 cm or more) polyp is found at sigmoidoscopy, a biopsy is not necessary; colonoscopic polypectomy is done and the proximal colon is examined for synchronous neoplastic lesions.

3. If a non-neoplastic polyp (such as a hyperplastic, mucosal, or inflammatory polyp) is found at sigmoidoscopy, no further evaluation or special follow-up is necessary.

4. If a polyp is identified by barium enema, the patient is referred for colonoscopic polypectomy to remove the polyp and to examine the rest of the colon for synchronous neoplastic lesions.

5. After complete colonoscopic removal of all polyps, a follow-up surveillance colonoscopy is performed in three
years. In selected cases follow-up surveillance may be done earlier for incomplete polyp resection, excision of a very large sessile adenoma, removal of numerous adenomas, or a suboptimal examination resulting from poor bowel preparation. If no new adenomas are found at the three-year follow-up colonoscopy, subsequent surveillance intervals may be increased to five years.

6. Very large sessile polyps that cannot be safely or completely removed colonoscopically require surgery.

7. After complete colonoscopic resection of an adenomatous polyp with severe or high-grade dysplasia (carcinoma in situ), further evaluation or treatment is not necessary. A follow-up surveillance colonoscopy may be performed in three years, and if no new adenomas are found, the subsequent surveillance interval may then be increased to five years.

8. After colonoscopic removal of a malignant adenomatous polyp (an adenoma containing invasive cancer) further management is based on polyp risk criteria. If the endoscopist’s impression was that the polyp was completely removed and, pathologically, it contained a well or moderately well differentiated adenocarcinoma, there was no venous or lymphatic invasion, and the resection margin was clear of malignant cells, then colonoscopic resection is generally adequate treatment. If, however, the polyp was not believed to be completely removed colonoscopically or, pathologically, it contained a poorly differentiated adenocarcinoma, venous or lymphatic invasion (or both), or malignant cells close to the resection margin, the patient is referred for surgical resection because of the increased risk of residual cancer at the resection site or lymph node metastases. In selected cases, the decision to undergo surgical resection after colonoscopic removal of a malignant polyp is also influenced by the presence of comorbid medical conditions.

9. Special screening and surveillance recommendations are necessary for the management of colorectal polyps in patients and family members of patients with inherited syndromes, such as familial adenomatous polyposis, juvenile polyposis, Peutz-Jeghers, and hereditary nonpolyposis colorectal cancer.

**Future Considerations**

A national multi-institutional screening colonoscopy trial is currently being organized to investigate whether a single lifetime screening colonoscopy will decrease the incidence and mortality of colorectal cancer in the general population.

A new and innovative radiographic examination of the colon and rectum (computed tomographic colography or “virtual colonoscopy”) is currently being developed.98 This technique is noninvasive; if it is found to be sensitive and cost-effective, it may be used in the future for general population screening for colorectal polyps and cancers.

Noninvasive stool screening for specific genetic alterations, such as ras mutations,99 and biochemical abnormalities, such as elevations in decay-accelerating factor,100 may offer another potential approach for the detection of colorectal adenomas and cancers in the general population.

Genetic testing studies in families with HNPCC will help in the development of optimal screening and surveillance strategies for these individuals.
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