ANNALS OF GASTROENTEROLOGY 2003, 16(3):219-229

Colorectal cancer screening and surveillance: Past, present and future

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SUMMARY

In this communication, the available colon cancer screening methods are reviewed and the recommendations for both average a high risk groups are discussed. But before we proceed with the specifics of both screening and surveillance, it is imperative that we give the definition of these terms that will prove instrumental in the throrough understanding of this paper. Screening involves the use of a simple test to identify average-risk persons who have a high probability of the disease. Surveillance, on the other hand, is the periodic use of a definitive diagnostic test in persons with special risk factors for the disease.

INTRODUCTION

Colorectal cancer is one of the most prevalent cancers in the US, affecting 1 in 20 people, ranking second overall only to lung cancer as a cause of cancer death.[1] Adenocarcinoma of the colon is also one of the leading causes of cancer death in Europe,[2] albeit mortality rates differ dramatically from one country to another (Table 1). Ninety percent of colon cancer deaths occur in patients over 50 years old. It has been estimated that among western populations, 5% of men and 6% of women will eventually develop colorectal cancer.[3] But what is most disturbing is that, according to several authorities, more than 75% of all cancers could be prevented.[4] Today, there is strong evidence that, unlike most other types of cancer (i.e. lung, pancreas), colorectal cancer usualy exists in a detectable and easily curable preclinical phase for a long time.[1] Thus, the greatest rewards regarding morbidity and mortality are likely to be realized in the fields of prevention and early diagnosis by the vigorous application of various screening and surveillance strategies.

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A. RISK FACTORS FOR COLORECTAL CANCER

The main risk factrors for colorectal cancer are as shown in table 2.

Age: The incidence of colon cancer increases significantly after the 40th-45th year of age and continues to increase until it reaches a peak at age 75. The risk for men and women is approximately the same. Although the incidence of colon cancer below age 40 is relatively low, it does occur at young ages, particularly among those who have familial risk factors or associated diseases, such as ulcerative colitis.

Polyps: Patients with either current or previous adenomatous polyps should be considered at higher risk for colon cancer. According to the hypothesis of adenoma-carcinoma sequence, most colon cancers arise from preexisting polypoid lesions while the de novo development of colon cancer is considered extremely rare. Although not all adenomatous colon polypys become malignant, patients with polyps have a 20-fold increase above average risk. The probability that a polyp is malignant is related to the cell-type (tubular vs villous), the total number of polyps and, especially the size of the polyp. Polyps which are smaller than 0.5 cm are rarely malignant, whereas almost half the polyps which are larger than 2.5 cm in diameter contain malignancy at the time of detection.

Table 1. Colorectal cancer cases by registry, period of diagnosis, sex, age and site EUROCARE high resolution study on colorectal cancer (69)

Country	Registry	Total cases	Period of study	Males (%)	Age 75+(%)	Colon (%)
Italy	Varese	445	90	53	37	62
	Modena	306	91	5232	65	
France	Calvados	262	90	47	40	52
	Somme	228	90	60	38	64
	Cote d'Or	237	90	54	46	66
Netherlands	Rotterdam	202	90	54	40	63
	Einthoven	256	91	52	33	68
Spain	Granada	173	90	51	31	54
UK	Mercey	207	90	48	47	58
	Thames	176	90	47	43	55
Poland	Cracow	22	88	42	21	52
Total	All registries	2,720	88-91	51	37	60

Table 2. Risk factors for colorectal cancer

- Age over 50
- Family history of colorectal cancer or adenomatous polyps
- Personal history of colorectal cancer or adenomatous polyps
- Long-standing ulcerative colitis or Crohn's colitis
- Personal history of female genital cancer (?)

Prior colorectal cancer: At diagnosis of colon cancer, there is a 2-5% risk of having a synchronous cancer, and a 50% chance of an adenomatous polyp. There is a 5-10% risk for a subsequent (metachronous) colorectal cancer. Experimental data support the concept that a field abnormality continues to exist in the colon of patients after resection of a cancer, which predisposes to subsequent neoplasia.[5]

Genetic predisposition: Well-defined genetic syndromes associated with a high incidence of colorectal cancer are listed in Table 4. These account for about 2.5-3% of the total of new cases of colorectal cancer. Most follow an autosomal dominant form of inheritance. Several reports have indicated that these syndromes may

Table 4. Hereditary syndromes associated with high risk for colorectal cancer

Syndrome	Lifetime risk for CRC	Responsible gene(s)
Polyposis syndromes		
FAP Gene Carrier	Near 100%	APC
Familial Adenomatous Polyposis (FAP)		
Gardner's syndrome		
Attenuated Adenomatous Polyposis (AAP)		
Turcot syndrome		
Juvenile polyposis	As high as 50%	SMAD4/DPC4
Cowden's syndrome	Negligible	PTEN
Cronkite-Canada syndrome		
Peutz-Jeghers syndrome	2-13%	STK11
Non-polyposis syndromes (HNPCC)	MMRT	
Lynch I syndrome		
Lynch II syndrome		
Muir-Torre syndrome		
Ashkenazi mutation	Two-fold increase	"Mild APC"

represent only the tip of the iceberg of the genetic factors involved in predisposition to colon cancer. A threefold excess of colon cancer and a high frequency of adenomas have been found in the first degree relatives (parents, siblings, children) of patients with colon cancer, although one small study did not confirm these findings.[6-8] Other recent work has suggested that a dominant mode of inheritance with low penetrance is operative in most cases of apparently sporadic cancer.[9]

Inflammatory Bowel Disease: Patients with ulcerative colitis have been known to be at greater than average risk of developing colon cancer, ever since the description of the first case of adenocarcinoma complicating ulcerative colitis by Crohn and Rosenberg in 1925.[10] However, the extent of the risk has been difficult to quantify because a) it has varied considerably in different areas of the world and, b) all studies of the extent of risk suffer from a variety of biases and methodologic errors. For example, it is not clear if the risk is low, as reported from the former republic of Czechoslovakia, Denmark and Israel, moderate, as reported from analysis of a large private practice in the U.S., or high, as reported from Sweden, Britain and referral centers in the U.S. The risk clearly is greatest in total colitis and increases with time, being negligible in the first 8-10 years of disease, with a sharp increase after 20 years, and is as high as 20-30% in some series. The most realistic estimate of colon cancer risk, after the first 10 years of ulcerative colitis, is an annual colon cancer incidence of 0.5-1% per year.[11] Some studies report that onset of colitis at a young age is a risk factor for subsequent colorectal cancer, but the bulk of evidence suggests that childhood onset of colitis does not confer an added risk independent of total disease duration and anatomic extent.[12,13] In addition, neither the severity of the colitis nor the intensity of the first attack appears to be a cancer risk factor. In the subset of ulcerative colitis patients with primary sclerosing cholangitis (PSC), the frequency of colon cancer is approximately 4-10%, and the risk of colon dysplasia is 22%.[14,15] Conversely, when ulcerative colitis patients with and without colonic dysplasia/carcinoma were studied, PSC was found only in the dysplasia/carcinoma group.[16] Whether the liver disease promotes the development of colonic neoplasia is not clear, since colon cancer has developed even after liver transplantation for PSC in patients with ulcerative colitis.[17] Although these suggestions are not conclusive, link between PSC and colonic neoplasia should heighten clinical awareness of PSC as a potential cancer risk factor.

Crohn's disease: These appears to be a lesser risk in Crohn's disease, although this notion has been debated extensively in the literature.[18-20] Risk factors for developing colorectal cancer in Crohn's disease are a history of colonic (or ileocolonic) involvement and long disease duration.[21,22] While these risk factors are similar to those of ulcerative colitis, a peculiar double-standard is often practiced. It is commonly believed that the risk for developing colorectal cancer is much lower in Crohn's disease than in ulcerative colitis even though there are data showing that the colon cancer risk may be equivalent in the two inflammatory bowel diseases.[21,22] In addition, the long-term survival rate for colon cancer associated with Crohn's disease is similar to that for ulcerative colitis.[23]

Colon cancer developing in inflammatory bowel disease is an exception to the rule that the adenoma precursor is present in the vast majority of cases. In ulcerative colitis, the situation is similar to other areas of the GI tract, where the best marker available for premalignancy is the presence of dysplasia in flat mucosa. High grade dysplasia appears to be a good indicator that cancer is iminent or present in the colon, or at the biopsy site in the case of a lesion or mass.[24]

B. TESTS, TECHNIQUES AND METHODS FOR COLON CANCER SCREENING AND SURVEILLANCE

Digital Rectal Examination (DRE): There has been a tendency in the past decade for a more proximal distribution of colon cancer, with fewer rectal and more cecal cancers. In the 1960s, it was said that 25% of colon cancers could be detected by DRE and about 50% by (rigid) proctosigmoidoscopy. By contrast, more recent statistics indicate that 20% of cases occur in the rectum, but less than 10% are detectable by DRE, which reaches only 7-8 cm of the 11-13 cm rectum.[25] It should be emphasized, however, that the ease and low expense of the examination mandate its use as part of the standard physical examination.

Fetal Occult Blood Test (FOBT): The rationale for the development of the FOBT has been the hypothesis that most colon cancers bleed at one time or another. The impregnated guaiac slide (Hemoccult), which is prepared with good quality control of the guiaiac-impregnated paper slide, and stabilized, reagent appears relatively reliable and has prevailed over most of its competitors to become the FOBT of preference of most investigators and clinicians. In four independent large controlled trials (Table 3) involving 117,000 average risk patients in Sweden, England, New York and Minnesota, the Hemoccult test obtained in spontaneously voided stools after a period of dietary modification were consis-

Table 3. Randomized controlled trials of FOBT

Location	Screening interval (y)	Follow-up (y)	MR (%)	IR (%)
Minnesota	1	18	33	20
	2	18	20	17
Denmark	2	10	18	NM
England	2	10	15	NM

*MR=mortality reduction

**IR=incidence reduction

***NM=no measurement available

tent with regard to frequency of positive tests (1.7-2.4%), positive predictive value for neoplasia (22-40%) and a prdominance of Duke's stage A and B cancer detected, versus Dukes' C in controls.[25] As expected, the greatest yield was in older patients. Compliance with the test ranges from 75% in motivated patients seeking health care to about 25% in community outreach programs and this may have had a significant impact on the final data. The test is far from being perfect, with 30% of cancers and 75% of adenomas escaping detection. In the study from New York, an overall survival benefit of the screening group versus the control group was demonstrated, but the critical mortality reduction data is still pending from all studies. The clinically important message reiterated in several studies is that results of fecal blood tests are often normal in both symptomatic and asymptomatic patients with proved colorectal cancer. Thus, it is imperative that health care providers who offer this modality for colorectal cancer screening warn their patients that roughly 1/3 of cancers and 3/4 of adenomatous polyps can escape detection by FOBT. A recent review paper with clinical guidelines for FOBT techniques and interpretation was published by the American College of Physicians[26] and further analyzed by Ransohof and Lang.[27]

Sigmoidoscopy: The development of flexible fiberoptic endoscopic instruments has led to widespread application of sigmoidoscopy for screening for colon cancer. The old rigid 25 cm proctosigmoidoscope was usually not inserted beyond 15 cm and was associated with unacceptable patient discomfort. For this reasons, current recommendations limit the indications of rigid proctosigmoidoscopy to the examination of the rectum only, i.e. the lower straight segment of the colon. Flexible instruments, essentially short colonoscopes, in sizes from 35-60 cm, examine more of the lower colon with far greater acceptability. It is estimated that approximately 50% of the colorectal neoplasms can be detected by the flexible sigmoidoscope and several uncontrolled and controlled studies have showed mortality reduction in patients screened by flexible sigmoidoscopy.[28-30] Its role as a screening tool was critically reviewed, more than a decade ago, by Neugat and Pita[31] who found shortcomings in those studies. Since all patients with polyps detected by flexible sigmoidoscopy subsequently undergo pancolonoscopy, it is estimated that only 25-30% of colon polyps and cancers will escape detection in only flexible sigmoidoscopy screening programs.[29] However, there is an increasing consensus that this "left side" colonoscopy is inadequate for cancer screening because of the number of solitary proximal lesions that will be missed.

Carcinoembryonic Antigen (CEA): The emergence of the radioimmunoassay for the detection of CEA in the blood in the mid-1960s inspired a widespread optimism among clinicians for the early detection of colorectal cancer. Unfortunately, the initial promising results did not live up to the expectations because elevated serum CEA levels were confirmed in cancers of other organs, in chronic benign diseases, or even among healthy smokers. Thus, CEA currently has no role in screening for primary colon cancer.[32] It remains of some value as an early biochemical marker of recurrence in patients who have undergone "curative" resection of colon cancer.

Air Contrast Barium Enema (ACBE): There is a widespread acceptance of double contrast barium enema for the detection of small colon neoplasms. The ACBE is usually successful in examining the entire colon but in most studies is less sensitive than colonoscopy. In an early study at the Strang Clinic in New York, ACBE missed 25% of the lesions found through colonoscopy; similar results we recently reported in a retrospective multicenter clinical study in USA among 2193 patients.[33] Some clinicians still believe that the combination of ACBE with flexible sigmoidoscopy provides sufficient sensitivity and is comparable to colonoscopy. Single contrast barium enema is very insensitive and inappropriate for diagnosis of polyps.

Colonoscopy: There is an increasing trend toward use of colonoscopy as a first line diagnostic test in colon cancer screening and surveillance.[34-36] Advantages over barium enema include the improved detection of small lesions. Colonoscopy also is imperfect and very small adenomas are readily missed even with meticulous colonoscopy.[37] However, colonoscopy is clearly far superior to any other diagnostic modality for detecting colorectal polyps and cancer. Clear advantages of colonoscopy include: permits complete and thorough examination of the entire colon, few false positives because, unlike barium enema, colonoscopy can easily distinguish between tumours and

adherent stool; permits diagnostic biopsy both of suspicioius lesions and of uninvolved colon (for example to screen for dysplasia in ulcerative colitis); finally and most importantly, colonoscopy may prevent colon cancer by detecting and removing adenomatous polyps.

In recent years, improved instruments and techniques allow safe and complete examination to the cecum in more than 90% of patients, with the barium enema reserved only for those with incomplete examinations. This, in conjuction with the findings of two recent studies, make a strong case for screening colonoscopy,[38,39] although it seems that there is still much to learn about all determinants of colorectal cancer screening. First of all, screening policy is not decided by effectiveness alone. Often, factors such as cost, feasibility, convenience, availability of expertise, complications patient acceptance and compliance will have to be seriously taken into account. In a recent editorial, Fletcher epitomizes the challenges of the future with regard to the acceptance of screening colonoscopy into three major issues: cost, safety and the emergence of new screening tests.[40]

Virtual colonoscopy, also known as CT or MR colonography, is the most recent imaging technique used for the visualization of the colon.[41] At this stage, it has not had consistently adequate sensitivity to be considered a reliable colorectal cancer screening test. Likewise, specificity has been reported to be insufficient to rely upon for either screening or surveillance of colorectal cancer. In addition to the issues of sensitivity and specificity, the role of virtual colonoscopy will also be determined by several other factors, such as intervals of application, cost of the test, etc.

Chromoendoscopy and magnification endoscopy of the colon. This is a technique in which tissue stains are applied to the gastrointestinal mucosa at endoscopy to better characterize, delineate, or highlight specific gastrointestinal findings.[42] Some preliminry data suggest that chromoendoscopy can be used primarily in two clinical situations: a) in the differentiation of neoplastic from non-neoplastic polyps, and b) in the assessment of neoplastic changes (dysplasia) of the colonic mucosa in diseases such as ulcerative colitis.

Tissue markers of cancer risk. As mentioned above, the ability to visualize the colonic mucosa, to obtain samples of both benign and malignant tissue and, particularly to remove polyps at the time of colonoscopy, has revolutionized our understanding of colonic carcinogenesis and our approach to the prevention, diagnosis and treatment of colorectal cancer.[43] The endoscopic and histologic features of the adenoma-carcinoma sequence were mainly characterized in the 1970s and 1980s. The genetic and biochemical events that drive the process and their biologic consequences are being uncovered in the 1990s. Several genetic tests such as the APC gene, the DCC gene, the p53 gene, and various DNA repair genes (MSH-2, MLH-1 PMS-1/PMS-2 and GTBP) and the resultant microsatellite instability (MSI) are done routinely in research laboratories, and some of them are already available commercially. There are high hopes that this continuing revolution in our understanding of the genetic basis of colorectal carcinogenesis will be translated into better preventive and therapeutic approaches to this disease.

C. AVERAGE-RISK COLON CANCER SCREENING

Despite the fact that colon cancer screening has been recommended by professional groups for more than 3 decades, the evidence in favour of such screening has been at best tentative. As recently as 10 years ago, two independent comprehensive reviews concluded that there was insufficient evidence to advise for or against colon cancer screening for the average-risk population.[44,45] During the last decade, however, the emergence of data from several ongoing studies has drastically changed this view. Thus, today the concept of colon cancer screening among average-risk populations has been established in the minds of both public and private organizations and has resulted in dramatic policy changes. Moreover, it has increased public awareness and has moved this topic from a medical issue of dubious validity to the forefront of national attention.[46]

Following an extensive review of the new prospective mortality data, three policy-making organizations have made recommendations for colon cancer screening in the average-risk population (Table 5). Thee guidelines differ dramatically from those that had been recommended previously and considered to be more realistic and scientifically sound.

D. HIGH-RISK COLON CANCER SCREENING

Familial risk of colon cancer. Colon cancer is perhaps the most familial of all cancers and known inherited syndromes account for approximately 1-5% of all colon cancer cases. More importantly, even when these syndromes are not considered, familiial clustering of cases is common and seems to constitute a single, independent risk (Table 6). For example, first-degree relatives of individuals

Table 5. Recommendations for average-risk screening for colorectal cancer* (70)

American College of Gastroenterology:

- Preferred strategy: colonoscopy every 10 years
- Alternative strategy: flexible sigmoidoscopy every 5 years plus annual FOBT

Agency for Health Care Policy and Research (AHQR):

- Annual FOBT or
- Flexible sigmoidoscopy every 5 years or
- Annual FOBT plus flexible sigmoidoscopy every 5 years or
- Colonoscoy every 10 years or
- Double contrast barium enema (DCBE) every 5-10 years

American Cancer Society:

- Same as ADHR except that DCBE option now recommended every 5 years

*All recommendations imply beginning screening at age 50

with colorectal cancer have consistently been found to have a 2-3 fold increased risk of colon cancer compared with control or population incidence. In a prospective study, the colon cancer risk in persons with an affected first-degree relative was approximately the same at age 40 years as the general population at 50 years.[47] It is interesting to note that similar patterns are also observed for the risk of developing adenomatous polyps. Furthermore, colon cancer risk appears to be increased even among second- and third-degree relatives of affected persons but only 50% above the risk of the general population.[48]

All screening recommendations for persons with familial risk should be considered empiric due to the fact that no prospective controlled studies with mortality endpoints have been performed in this setting. The American Cancer Society recommends full colon examination if colorectal cancer or adenomatous polyps were diagnosed in a first-degree relative younger than 60 years, or if 2 or more first-degree relatives were diagnosed with colon cancer at any age. The screening should begin at age 40 years or 10 years before the youngest age in family, whichever is earlier, and should be repeated every 5 years.[49]

E. COLON CANCER SURVEILLANCE IN HIGH-RISK GROUPS

Familial adenomatous polyposis (FAP): This inherited group of polypoid syndromes results from the germline mutation of the adenomatous polyposis coli gene (APC) on chromosome 5, and in addition to FAP, includes the variants of Gardner's syndrome. Affected individuals develop hundreds to thousands of colorectal adenomatous polyps and colon cancer invariably develops before the age of 45 years if the large bowel is not surgically removed.

All persons with the clinical features of FAP and all offspring in affected families should be offered genetic counseling and commercially available genetic testing beginning at the age of 12-14 years. Those with positive results of genetic tests are then observed with annual or biannual flexible sigmoidoscopy until adenomas appear, indicating the need for prophylactic colectomy. Uncontrolled series from several medical centers strongly indicate that with the proper implementation of these guidelines the mortality from colorectal cancer can be largely prevented.

Hereditary nonpolyposis colorectal cancer (HNPCC): HNPCC results from inherited derangements of one of

Table 6. Familial risk of colorectal cancer (CRC)

Familial setting	Life time risk of CRC
General population risk	6%
One first-degree relative with CRC	1-3 fold increased
Two first-degree relatives with CRC	3-4 fold increased
First-degree relative with CRC before age of 50 y	3-4 fold increased
One second or third-degree relative with CRC	1.5 fold increased
Two second-degree relatives with CRC	2-3 fold increased
One first-degree relative with an adenomatous polyp	2 fold increased

* First-degree relatives: parents, siblings and children

** Second-degree relatives: grandparents, uncles and aunts

*** Third-degree relatives: great-grandparents and cousins

Modified from Burt and Ahnen[71]

four different mismatch repair genes, two on chromosome 2 and one each on chromosomes 3 and 7. This genetic defect leads to genomic instability, making cells more prone to other acquired genetic changes that promote rapid neoplastic development. In HPNCC, colonic cancers develop rapidly, are preceded by only a few polyps, tend to be multiple, occur at an early stage, and often are located in the proximal colon. In some kindreds, extraintestinal cancers are common, especially endometrial cancer, and less often breast, ovarian, pancreatic, urinary tract and gastric cancer.[50]

This syndrome should be considered whenever two or three relatives in a family have colorectal cancer, if any of these cancers is proximal or if the cancer is diagnosed at an early age. Families that satisfy the Amsterdam criteria (Table 7) for HNPCC should be offered genetic counseling and genetic testing. Those with positive results need colonoscopic surveillance at least every 2 years beginning at the age of 25 years or 5 years younger than the youngest person with cancer in the family. The choice of colonoscopy as the diagnostic tool is mandatory as most of these cancers have proximal colon location. In a Scandinavian study (Table 8) families who accepted total colon screening every 3 years had fewer colorectal cancers than those who declined this surveillance.[51]

MSI genetic testing has recently been recommended for patients with HNPCC, for those who meet the Amsterdam criteria as well as some other less homogenous groups (Table 9).

Postpolypectomy surveillance: Patients with previous colonoscopic removal of adenomatous polyps are at increased risk for subsequent development not only of adenomas but, more importantly, of colorectal cancer. Thus, continued surveillance can be expected to benefit this group of patients. There may be exceptions as two studies, from the Mayo Clinic and St Mark's Hospital, London, have shown that a single small tubular adenoma found at proctosigmoidoscopy, carries no significant risk for colorectal cancer.[52,53] What seems to be important is that at the initial polypectomy, the entire colon should be cleared of all synchronous neoplasia.[54] After resection of large (>1 cm), multiple, or villous-containing adenomas, the first surveillance colonoscopy should usually be performed 3 years later.[55] Following normal results of one 3-year colonoscopic examination, subsequent surveillance intervals can safely be increased to 5 years (Table 10). However, it should be emphasized that surveillance must be individualized according to the age and comorbidity of each patient and discontinued when it is no longer likely to be of benefit.

In the National Polyp Study patients whose adenomas were initially removed and who underwent follow-up colonoscopy at 3-year intervals were found to have a subsequent incidence of metachronous cancer that was only 10% to 25% of that predicted from three reference populations.[56] Likewise, several cohort and case-control studies have demonstrated a 50% to 80% reduction in mortality rate from colorectal cancer as the result of prior colonoscopy and polypectomy.[30,57]

Following resection of colorectal cancer: The goals

Table 7. Amsterdam criteria for detection of HNPCC (modified)

- Three or more family members with colorectal cancer (one is a first-degree relative of another affected person)
- Two generations are affected
- One person is diagnosed with colon cancer before the age of 50 years
- One relative with a first-degree relative of the other two
- The following cancers may be substituted for colon cancer: endometrial, small bowel, ureter, renal pelvis

Table 8. Norwegian guidelines for postpolypectomy surveillance (72)

1. After malignant polyp resection
   Recommendations: examination of resection site at least once within 12 months and thereafter as for ordinary adenomas
2. For persons with resected adenomas having at last 1 of the following features:
   A. High-grade dysplasia or villous components and age <75 y
   B. Size >10 mm and age <75 y
   Recommendations: colonoscopy in 10 y
3. For persons with adenomas having the following features:
   A. >Three adenomas of any size and age <75 y
   B. Biopsy verified adenomas 1-4 mm in diameter left in situ
   C. Features in category 2 plus history of previous gynecologic cancer
   Recommendations: colonoscopy in 5 years
4. For persons with adenomas having the following features:
   A. 1 or 2 tubular adenomas <10 mm in diameter
   B. Resected hyperplastic polyps±small solitary adenoma
   C. Age >75 y at initial polypectomy
   D. No remaining adenomas, adenoma remnants, or remaining polyps of unknown histology
   Recommendations: NO follow-up colonoscopy

Table 9. Bethesda criteria for consideration of MSI testing

- Individuals with cancer in families that meet Amsterdam criteria
- Individuals with 2 HNPCC-related cancers, including synchronous and metachronous CRCs or associated extracolonic cancers*
- Individuals with CRC and a first-degree relative with CRC and/or a HNPCC-related extracolonic cancer and/or a colorectal adenoma: 1 of the cancers diagnosed before age 45 and the adenoma diagnosed before age 40.
- Individuals with colorectal or endometrial cancer daignosed before age 45.
- Individuals with right-sided CRC with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed before age 45.**
- Individuals with signete-ring cell type CRC diagnosed before age 45.***
- Individuals with adenomas diagnosed before age 40.

* Endometrial, ovarian, gastric, hepatobiliary or small bowel adenocarcinoma or transitional cell carcinoma of the renal pelvis or ureter.

** Solid/cribriform pattern defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells containing small glandlike spaces; medullary carcinoma.

*** Composed of >50% signet-ring cells.

of surveillance after curative resection of colorectal cancer are to detect treatable recurrences, missed synchronous cancers or adenomas, as well as new (metachronous) benign and malignant neoplasia. Surveillance policies vary widely between institutions and are mainly empiric, inconsistent and irrational. Curative therapy for recurrent colorectal cancer is rarely possible and palliation for unresectable colorectal cancer is relatively ineffective. Finally, most recurrences are outside the intestine; anastomotic recurrences are extremely rare after resection of colon cancer, particularly beyond the first year postoperatively. Based on these considerations, it is now recommended that colonoscopy should be performed during the perioperative period to clear the colon all neoplasms. Ideally this should be done before surgical intervention so that all synchronous large polyps and cancers will be included in the resected specimens (58). Postoperative follow up is scheduled as clinically needed. Repeat colonoscopy is performed at three years and then every 3 to 5 years thereafter to detect metachronous neoplasia. During the first two years following curative resection surveillance should include a chest x-ray every 6 months and CEA levels at least every 3 months. Routine surveillance with computed tomography has not yet proved cost-effective, and liver chemistry is not sensitive enough to be of much clinical value.

Table 10. Incidence of advanced adenoma at 3 and 6 years in the National Polyp Study according to findings at Index Colonoscopy

	Advanced adenoma (%)	
Index Colonoscopy Finding	**3 y**	**6 y**
>3 adenomas or age >60y and parent with CRC	10	20
2 adenomas or age >60 y with negative family history	3	4
1 adenoma and age <60 y	<1	<1

Inflammatory bowel disease. As mentioned above, patients with extensive, long-standing chronic ulcerative colitis (CUC) have an increased incidence of cancer estimated to be 0.5% per year after 8-10 years from the onset of the disease.[59] In CUC, cancer does not usually arise from a preexisting adenomatous polyp but it appears to originate in epithelium that has undergone neoplastic, dysplastic changes. Consequently, the distribution of cancers in CUC is universal throughtou the colon rather than following the typical distribution of polyp-associated cancers with a strong left side preponderance. The dysplastic changes may precede or be associated with cancer, and its discovery at biopsy constitutes the cornerstone of colonoscopic surveillance to ascertain which patients need prophylactic colectomy to prevent fatal cancer.[60]

Most guidelines recommend that colonoscopy surveillance begin 7 to 10 years after the onset of pancolitis and 12-15 years after the onset of left-sided colitis.[28] Biopsy specimens should be obtained randomly every 10 cm from all 4 quadrants and from any lesion, such as stricture, raised or polypoid mucosa. Early in surveillance, follow-up colonoscopy should be performed every 2-3 years but when the cancer risk increases appreciably (i.e. >20 years of CUC), colonoscopic surveillance should be performed annually (Table 11). Surveillance in Crohn's disease is still controversial and there are no clear recommendations. However, most experts have recently started to recommend periodic colonoscopic surveillance after 10 years of disease for patients with extensive Crohn's colitis. It should be noted that even with regular screening colonoscopy, cancer in ulcerative colitis may escape early detection; in high risk patients with UC, total colectomy should be considered.

Table 11. Management of ulcerative colitis in patients undergoing colonoscopic surveillance

Mucosa biopsy	Management
Normal	Repeat surveillance every two years
Indefinite	Repeat colonoscopy in 6 months
Low-grade dysplasia, flat mucosa	Repeat in 1-2 months; if still present colectomy
Low-grade dysplasia, mass lesion	Colectomy, if performed by experienced path
High-grade dysplasia	Colectomy, if confirmed by experienced path

F. COST-BENEFIT OF COLON CANCER SCREENING AND SURVEILLANCE

Over the last two decaces, colorectal cancer screening has been an issue of open debate within the scientific community. Its supporters maintain that in the absence of reliable measures of primary prevention, the best approach consists of screening and early detection. Its opponents dispute this contention, mainly due to the absence of scientific evidence that screening really reduces mortality for the disease, and maintain that the cost of screening is too high when compared to the benefit that derives from these programs.[61-63] Several mathematical models have been developed by various investigators for the cost-benefit analysis of colorectal cancer screening with conflicting results. The main reason for these discrepant results has been twofold: a) methodological deficiencies and inconsistences and b) most of the major cost-benefit analyses on colon cancer screening were done before recent controlled data were available.[64]

In the future, however, the evaluation of the cost-effectiveness issue for colon cancer screening can and should be reexamined in the light of the newly published controlled studies that have shown that colorectal cancer screening does reduce colorectal cancer mortality.[65-67] Thus, policy-makers and professional organizations will only have to deal with specific issues such as strategies for various subpopulations (i.e. single adenoma post-polypectomy), choice of diagnostic techniques (i.e. colonoscopy vs barium enema, vs flexible sigmoidoscopy) as well as frequency of both screening and surveillance for colorectal cancer.[68] It is ironic that it has taken us more than two decades to accept and re-endorse the recommendations for colorectal cancer screening of the American Cancer Society.

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