Diagnosing Colorectal Carcinoma: Clinical and Molecular Approaches

J. Milburn Jessup, MD
Herman R. Menck, MBA
A. Fremgen, PhD
D.P. Winchester, MD

Introduction

Colorectal carcinoma is the fourth most prevalent carcinoma and second most frequent cause of death from cancer in the United States, with an estimated 131,200 new cases and 54,900 deaths in 1997.[1] Although the death rate from large bowel cancer may be decreasing slightly, it still remains a health risk that consumes national resources and creates considerable personal suffering. Dietary modification may decrease the neoplastic transformation potential of bowel mucosa,[2] but the widespread adoption of low fat, high fiber diets will not eliminate totally the risk of large bowel cancer. The consumption of aspirin[3,4] or other nonsteroidal anti-inflammatory drugs[5] may also reduce the risk of developing the adenomatous polyps that precede large bowel cancers. However, not all patients benefit from these chemoprevention strategies and some may have deleterious side effects. Recently, fecal occult blood testing (FOBT) and large bowel endoscopy have been found to detect cancers at an earlier stage and decrease the formation of colorectal carcinomas. Also, the recent identification of specific genetic mutations that cause two different types of inherited colorectal carcinoma suggests that in the near future early diagnosis will be possible through blood or stool tests. As a result, considerable enthusiasm now exists that both the rate of earlier diagnosis and the outcome of colorectal carcinoma will be improved.

This review first assesses the common patterns of presentation of colorectal carcinoma, then summarizes the current status of clinical diagnostic methodology, and finally outlines the future potential of molecular diagnostic tests. Critical to the successful application of molecular diagnostic tests is an appropriate understanding of the clinical background within which the tests will be used. Initially, this review focuses on the clinical presentation of colorectal carcinoma, then considers the genetic and biologic causes of colorectal carcinoma. Any molecular approach to diagnosis must explain the range of clinical and pathologic features involved in the manifestations of the disease at presentation. Currently, more patients are diagnosed because they develop signs or symptoms of colorectal cancer than are identified in an asymptomatic state. A major goal is to increase the proportion of patients who are diag-

Dr. Jessup is an Associate Professor of Surgery in the Department of Surgery at New England Deaconess Hospital and Harvard Medical School, Boston, Massachusetts.

Mr. Menck is the Manager of Clinical Information Systems for the Commission on Cancer of the American College of Surgeons in Chicago, Illinois.

Dr. Fremgen is the Associate Manager of Clinical Information Systems for the Commission on Cancer of the American College of Surgeons in Chicago, Illinois.

Dr. Winchester is Professor of Surgery at Northwestern University Medical School, Director of the Cancer Department at the American College of Surgeons in Chicago, and Chief of Surgery at Evanston Hospital in Evanston, Illinois.

This work funded in part by grant PO1 CA44704 from the National Cancer Institute, National Institutes of Health, Bethesda, MD, and grant CCG #252E from the American Cancer Society, Atlanta, Georgia.

Table 1
Conditions Associated with Colorectal Carcinoma

Clinical
Rectal bleeding (occult or clinical)
Abdominal, pelvic, or back pain
Obstruction or perforation
Inflammatory bowel disease
Pelvic radiation
Genetic
History of colorectal carcinoma
History of adenomatous polyps
History of two or more first-degree relatives with bowel cancer
Familial adenomatous polyposis, hereditary nonpolyposis colon cancer, or variant syndromes
History of breast, ovarian, or endometrial carcinoma

nosed while they are asymptomatic because these patients present at an earlier stage that is more amenable to cure.[6]

Common Patterns of Clinical Diagnosis

The clinical and genetic conditions associated with the development of colorectal carcinoma (Table 1) represent the situations in which the clinician should consider the diagnosis of colorectal carcinoma. Although it is difficult to identify the fraction of patients who are symptomatic at diagnosis, analysis of a large number of patients who are diagnosed in hospitals across the country is informative because it demonstrates the distribution of stage at diagnosis. The National Cancer Data Base (NCDB), a national cancer management and outcomes data base that is a joint effort of the American Cancer Society and the American College of Surgeons,[7] currently captures more than 50 percent of the estimated new cases of cancer in the United States and is an excellent starting point for an analysis of the patterns of care and outcome for patients with cancer. Data on the interaction of age, ethnicity, site of primary carcinoma, and stage at presentation are presented in Table 2. As reported earlier in a study of colon cancer,[8] patients over the age of 70 years are more likely to present with stage I or II disease than are younger patients. This trend is also present in rectal cancer, in which 62 percent of patients over 80 years of age have stage I or II disease compared with 50 percent for those patients who are less than 50 years old and 53 percent for those who are between 50 and 60 years old (Table 2). Ethnicity is another significant factor because African Americans are less likely to present with stage I or II colon or rectal cancer than are non-Hispanic whites (Table 2). Hispanics are also slightly less likely to be diagnosed with stage I or II colorectal carcinoma than are non-Hispanic whites (Table 2). However, Asians have a pattern of stage at diagnosis similar to that of non-Hispanic whites (data not shown),

Table 2
Distribution of Adenocarcinoma of the Colon and Rectum by AJCC Stage, Age at Diagnosis, and Ethnicity of Patients Diagnosed in 1993 at Hospitals Participating in the National Cancer Data Base

Site and Category	% Distribution by Stage I-II	III	IV	Total %	Number of Cases
Age					
Colon					
< 50	44	27	29	100	2,503
50–59	47	27	26	100	4,130
60–69	53	26	21	100	9,112
70–79	57	25	19	100	12,871
≥80	59	25	16	100	8,661
Subtotal					37,277
Rectum					
< 50	50	33	17	100	1,338
50–59	53	30	17	100	2,406
60–69	58	27	15	100	4,273
70–79	59	26	15	100	4,579
≥80	62	22	16	100	2,238
Subtotal					14,834
Ethnicity					
Colon					
Non-Hispanic white	55	25	20	100	32,463
Hispanic	51	29	20	100	680
African American	48	27	25	100	3,087
Subtotal					36,230
Rectum					
Non-Hispanic white	58	27	15	100	11,731
Hispanic	53	27	20	100	372
African American	54	25	21	100	950
Subtotal					13,053

AJCC = American Joint Committee on Cancer.

and the sample of Native Americans is too small to draw any conclusions about their stage at presentation. The data in the NCDB do not reveal any significant effects of median income, region of the country, or type of hospital on the stage of disease at diagnosis (data not shown). As a result, these data from the NCDB suggest that age and ethnicity are important factors to consider in the diagnosis of colorectal carcinoma.

Importance of Age

Age has two contrasting effects on the diagnosis of colorectal carcinoma. Young (less than 40 years old) patients have a worse outcome than middle-aged patients, whereas older (more than 70 years old) patients present with earlier stage of disease. Bacon[9] first reported that colorectal carcinoma is diagnosed before age 40 in 2 to 6 percent of all colorectal carcinoma patients. The delay in attributing symptoms to a possible colorectal cancer may contribute to the worse outcome.[10,11] Although several series indicate that there is a worse outlook for patients who develop colorectal carcinoma before the age of 40,[12-17] two series[18,19] suggest that younger patients have the same survival as older patients, possibly because the distribution of patients with stage III and IV disease was similar to that of the older patients in their series.

The outcome of younger patients may be worse because they present with more advanced disease or disease with a poorer histologic grade of differentiation. Several authors[10,12-16] have found that younger patients present with more nodal or visceral metastases than do older patients, as is the case with the current data from the NCDB (Table 2). However, the data of others[13,14,17,20] suggest that the outcome of younger patients is worse than that of older patients, even when matched by stage.

The frequency of more advanced disease in younger patients may result from longer delays in diagnosis compared with older patients; however, the frequency of rectal bleeding or abdominal pain in these young patients is similar to that in older patients. Further, Adkins et al[16] observed that eight of the 45 patients were found incidentally during evaluation for other problems, which suggests that the potential delay in detecting a cancer from the onset of symptoms was less than three months. Similarly, in other studies[18,20] there was no significant difference in symptom duration between young and old patients. In summary, there is a consensus that the disease presents at a more advanced state in younger patients. Therefore, patients who develop colorectal cancer before age 40 in the absence of a defined genetic syndrome, such as familial adenomatous polyposis or hereditary nonpolyposis colonic cancer, may still have an accelerated rate of mutations that may provide clues to the analysis of the genetic mechanisms that cause sporadic colorectal carcinoma.

Older patients with colorectal cancer are defined as older than 75 or 80 years at the time of diagnosis. Comorbid disease and type of presentation may produce a worse outcome. The series of Payne et al,[21] Wise et al,[22] and Hobler[23] suggest that sepsis and complications of surgery may occur more frequently in the elderly population. However, Arnaud et al[24] showed that the postoperative five-year survival rate of older patients was similar to that of younger patients. In addition, the three-year[23] and five-year[21] cancer-specific survivals of patients over the age of 75 were the same as that of younger patients. Interestingly, several authors suggested that more right-sided cancers arise in the elderly than in the slightly younger population.[18,21] The elderly seem to have a slightly increased frequency of emergency operations, since 7.4 percent of older patients required emergency surgery, compared with four percent for patients younger than 75 years.[21] Thus, the biologic behavior of cancers is not likely to be

more aggressive in older patients than in patients between 40 and 70 years old.

Ethnicity as a Diagnostic Factor

Ethnicity may be associated with an increased frequency of advanced cancer at diagnosis in African Americans. Thomas et al[25] suggest that inner-city blacks are diagnosed with colorectal carcinoma at an earlier age than white patients, and that this trend is significantly greater in black males than in white males. Boring et al[26] have reported that there has been a significant increase in cancer-specific death rates in both black men and women for colorectal cancer compared with white men and women over the last 30 years. In fact, the cancer-specific death rate declined in white men and women, whereas it increased in black men and women by 47 and 16 percent, respectively.[26] Interestingly, when incidence rates are stratified by educational level and socioeconomic status, the incidence of cancer of the colon and rectum is higher for whites than for blacks for each stratification.[26] As in the current NCDB data, Boring et al[26] observed a trend in which the frequency of localized cancer at diagnosis is lower in blacks (30 percent) than in whites (36 percent). Thus, the poorer outcome may be attributable to more limited access to care. Weaver et al,[27] reporting their experience over a 10-year period at Meharry Medical College, found that their black patients tended to present with more advanced disease than did those observed by Boring et al.[26] Their experience may also reflect limited access to health care systems. A major challenge for improving early diagnosis is to increase the proportion of stage I and II colorectal cancers diagnosed in African Americans.

Presenting Symptoms and Signs

The symptoms and signs of carcinoma of the colon and rectum are rectal bleeding (either gross blood in the stool or a guaiac-positive reaction on digital rectal examination), abdominal pain, change in bowel habits, nausea, vomiting, abdominal distention, weight loss, fatigue, and anemia. Rectal bleeding may be associated with an improved outcome, possibly because it prompts earlier diagnosis. Various authors[28-31] have observed that rectal bleeding as a presenting symptom was associated with a better overall survival in univariate analyses, but when rectal bleeding was analyzed in multivariate analysis in which it was corrected for stage and site, it either had no effect[29,31] or became less important as an independent prognostic variable.[28] Similarly, Wiggers et al[32] found that only 19 percent of patients who presented with rectal bleeding died of disease compared with 33 percent of patients who did not present with rectal bleeding (P=0.017). Cappell and Goldberg[33] observed that rectal bleeding was 2.8 times more prevalent at the time of diagnosis in early stage I lesions than in stage IV cancers. Also, Graffner and Olsson[34] reported that rectal bleeding was more frequently associated with rectal (50 percent) than colon (14 percent) cancer. Thus, rectal bleeding may be associated with early stage lesions (perhaps because early lesions are more vascularized than more advanced lesions) and, as a result, may carry a better prognosis. Thus, blood on the stool on digital rectal examination, on guaiac test, or by history must be further evaluated and not dismissed as caused by hemorrhoids.

Abdominal pain is another symptom that may lead to the diagnosis of large bowel cancer. Two types of abdominal pain are caused by cancer of the colon or rectum. The first is cramping or colicky pain associated with complete or partial bowel obstruction. Although uncommon in rectal cancer, it may be a presenting symptom in colonic cancer. This symptom may be best considered as representing the clinical syndromes of obstruction or perfora-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.