

attributed to these “significant lesions” found in the distal colon. Although seemingly minor, nonacute rectal bleeding is never actually defined in the study. It would have been useful to know the spectrum of clinical bleeding per rectum to interpret the results with respect to previous studies. Finally, although the authors define the terms proximal colon and distal colon, the results of the study are presented in terms of the left or right colon. This difference is more than just semantic because the study addresses the issue of choosing between colonoscopy and sigmoidoscopy. The “left colon” and that part of the colon accessible by flexible sigmoidoscopy may not be synonymous.

Can the history provided by the patient help select those who are at increased risk for significant pathology in the proximal colon? The literature is conflicting in this regard. Based on the pattern of bleeding, Church prospectively categorized 269 patients presenting with hematochezia into those with outlet bleeding, suspicious bleeding, hemorrhage, and occult bleeding. All patients underwent colonoscopy. Thirty-five adenomas and 5 cancers were found in the group categorized as outlet bleeding. All lesions except 1 adenoma were confined to the left colon and would have been found at sigmoidoscopy (*Dis Colon Rectum* 1991;34:391–395). In contrast, Segal et al. found that physicians’ assessment was not reliable in separating patients with a perianal source of bleeding from those with more substantial proximal pathology (*Am J Gastroenterol* 1998;93:179–182). Guillem et al. came to similar conclusions when they retrospectively analyzed 372 consecutive patients undergoing colonoscopy for rectal bleeding. Patients were categorized into 3 groups based on their bleeding pattern. The authors found that bleeding patterns were not predictive of the “severity” of findings on colonoscopy. A third of all neoplasms in this study were found in the proximal colon (*Ann Surg* 1987;206:606–611). Given the perhaps limited use of clinical characterization of bleeding per rectum, the absence of a definition in the study by Mulcahy et al. may not be a significant limitation.

What is the optimal way to evaluate a young, otherwise healthy patient who presents with hematochezia? For this demographic group, there are limited data and few specific recommendations from professional gastroenterology societies. For persons under the age of 40, the average annual age-adjusted incidence of adenocarcinoma of the colon is 9.5 per million persons (*Gastroenterology* 1991;100:1033–1040). Although rare from a population standpoint, we do not know the rate of colorectal cancer in younger patients who present with hematochezia. Although younger patients are included in several large series evaluating hematochezia, the results are often not reported by age. Acosta et al. reviewed the results of 280 colonoscopies performed on patients younger than 40 years. Minimal passage of blood per rectum was the indication for colonoscopy in 83% of patients, and occult blood in stool accounted for the remainder. Neoplastic polyps were found in 4.2% of patients and colitis in 8.6%. One colon cancer was also found, but its location in the colon was not reported (*Am Surg* 1994;60:885–861). Fine et al. reported on 312 consecutive patients presenting with hematochezia. Of these, 58 patients were less than 40 years of age. Inflammatory bowel disease, polyps, cancer, benign ulceration, and ischemic colitis were found in 21, 6, 5, 2, and 2 patients, respectively. Three of the 5 cancerous lesions were found in the proximal colon and would have been beyond the reach of a flexible sigmoidoscope (*Am J Gastroenterol* 1999;94:3202–3210).

Ultimately, the study by Mulcahy et al. does not definitively answer the question of the optimal workup for young patients with nonacute rectal bleeding, and the conclusions drawn from the study will reflect the bias of the reader. One could conclude that despite a

highly selected patient population, colonoscopy offers little incremental benefit over flexible sigmoidoscopy in patients under age 40 years with regard to colorectal neoplasia. Alternatively, one could justify colonoscopy on the basis of finding isolated right-sided “significant lesions” in 7% of these patients, although a formal cost-effectiveness analysis would be needed. We agree with authors’ conclusions that age should not be the only criteria used to determine colonoscopy use. We do not know the yield of colonoscopy in unselected young patients presenting with nonacute rectal bleeding. History provided by the patient does not reliably predict the source or site of bleeding. The search for the most cost-effective strategy to evaluate these patients continues.

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A MARKER FOR PREDICTIONS OF HCC RECURRENCE POSTRESECTION?

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The prognostic value of alpha-feto protein (AFP) messenger RNA (mRNA) was assessed in patients undergoing curative hepatic resection for hepatocellular carcinoma (HCC). Peripheral blood samples were taken pre- and postoperatively, during a median follow-up period of 28 months for measurement of AFP mRNA. Preoperative AFP mRNA positivity was of no predictive value. Patients with consistently positive postoperative AFP mRNA showed the highest recurrence rate of HCC of 85%, and, in general, patients with postoperative AFP mRNA positivity had shorter disease-free intervals than AFP mRNA–negative patients. Cox’s proportional-hazards model identified the postoperative positivity of AFP mRNA as an independent prognostic factor for HCC recurrence.

Comment. HCC is the fifth most common cancer in the world today (*CA Cancer J Clin* 1999;49:33–64), and its incidence is rising. This is due to the worldwide rise in the incidence of viral hepatitis B and C, resulting in chronic viral hepatitis and cirrhosis, the precursor of the majority of cases of HCC (*Eur J Gastroenterol Hepatol* 1996;8:845–849). For example, in the United States, the incidence of histologically proven HCC has risen from 1.4/100,00/year population in 1975, to 2.4/100,000/year population between the years 1991 to 1995, together with a decrease in the median age of onset (*N Engl J Med* 1999;340:745–750).

Twenty years ago the prognosis for patients with HCC was dismal, with the median survival of a patient presenting with HCC of about 8 months (*Cancer* 1985;56:918–928). However, at the same time, it was clear that patients presenting earlier with small tumors, <5 cm in diameter, were potentially curable. With that in mind, screening/

surveillance programs were started, in high-risk patient populations, such as patients with hepatitis B, in an effort to diagnose HCC earlier (Hepatology 2000;32:1006–1008). Although such programs did reveal patients with small, resectable, potentially curable tumors, it is still not clear whether the apparently improved outcomes are not simply due to lead time bias (Hepatology 1998;27:273–278). Most screening/surveillance programs use some form of combination of serum AFP estimations and abdominal ultrasonography examinations with intervals of about 6 months, based on the doubling time of HCCs (Gastroenterology 1985;89:259–266). For serum AFP, using cut off levels in the region of 16–20 ng/mL, the sensitivity is not better than 65%, the specificity ranges from 75% to 90%, and the positive predictive value ranges from 10% to 30% (J Hepatol 2001;34:570–575). Some of the reasons for the relatively poor performance of serum AFP as a screening test are that not all tumors form AFP, and that levels may rise nonspecifically in hepatic inflammation (J Hepatol 2001;34:603–605).

The management of a small HCC after diagnosis will depend to some extent on the preference of the local institution, as to whether to treat the patient surgically, by resection, or nonsurgically. At this time, although a number of new modes of therapy are now available, the most frequently used nonsurgical therapy is percutaneous ethanol injection (PEI). Ablation of small tumors, <5 cm, by PEI have been reported to lead to 5-year survival rates of 47% in Italian patients (Cancer 1998;83:48–57) and 52% in Japanese patients (Cancer 1991;68:1524–1530). In contrast, 5-year survival rates after surgical resection have been reported to vary from 30% (Surgery 1996;120:34–39) to 70% in the most favorable circumstances in Japan (Arch Surg 1996;131:71–76). Although as yet there are no reported randomized controlled trials, a comparison of the 2 therapies in the same institution revealed identical outcomes with 5-year survivals of 59% and 61.5% for PEI and resection, respectively (Hepatology 2001;34:707–713). However, during the same follow-up period, the rate of tumor recurrence was 85% and 71%, respectively.

Apart from the state of the underlying liver disease, including the degree of portal hypertension (Gastroenterology 1996;111:1018–1022) and the age of the patient, recurrence of HCC is the most important factor influencing survival after resection (Gastroenterology 1994;106:720–727). Surprisingly, the cancer-free margin of the resection is not a significant factor. With this in mind, investigators started searching for markers for recurrence after resection. Using a nested reverse-transcription polymerase chain reaction assay targeting AFP mRNA in *in vitro* experiments, Matsumura et al. showed that a single liver cancer cell was detectable in 5 mL of blood (Biochem Biophys Res Commun 1995;207:813–818). At the same time, these investigators showed that although AFP mRNA was undetectable in normal healthy controls, it was detectable in patients following resection for HCC (Hepatology 1994;20:1418–1425). Furthermore, there was now general agreement that evidence of portal vein invasion by tumor at the time of surgery was the strongest predictor of local intrahepatic recurrence (Cancer 1994;74:2772–2780, Gastroenterology 1995;108:768–775). These and other investigators then suggested that the appearance of circulating AFP mRNA after resection might well predict the likelihood of recurrence of HCC (J Hepatol

1999;31:332–339, J Gastroenterol Hepatol 2001;16:445–451). The present study goes some way to confirming this. Importantly, the investigators avoided sampling for AFP mRNA during the first week because it has previously been shown that hepatic surgery results in the simultaneous release of non-neoplastic hepatocytes (Hepatology 1999;29:879–882), together with AFP mRNA into the circulation (Ann Surg 1997;226:43–50). However, the present study was relatively short and only deals with early recurrence over the first 1 and 2 years. The evidence is that over time the majority of patients, between 70% and 90%, will have intrahepatic or widespread recurrence following hepatic resection for asymptomatic, small HCC (Br J Surg 1996;83:330–333, Br J Surg 1996;83:758–761).

The problem of postresection recurrence of HCC is now exercising a large number of groups in this field. However, there is unlikely to be a single solution to this problem. For example, in 58 of the 87 patients, or 66%, in this series from Japan, the predisposing factor to chronic liver disease and HCC was hepatitis C virus (HCV). There is now increasing evidence that alpha interferon therapy for patients with chronic hepatitis C reduces the incidence of HCC, especially in responders (Dig Dis Sci 2002;47:170–176). Therefore, initial studies have shown that interferon treatment of patients with HCV-associated HCC after resection, or after ablation, may lead to a delay in intrahepatic recurrence of HCC (Hepatology 2000;32:228–232). Monitoring such patients with circulating AFP mRNA might enable a more rational use of such therapy.

In the present study, Ijichi et al. have provided more evidence supporting the concept of the value of postresection circulating AFP mRNA in predicting predominantly intrahepatic recurrence of HCC. Further questions remain as to whether this technique can be used in predicting recurrence in other forms of therapy, such as PEI. For example, AFP mRNA has been detected in the peripheral blood of patients with HCC undergoing radiotherapy and chemotherapy (Cancer Lett 2001;167:183–191). There is no doubt that the best chance of cure for HCC is liver transplantation. This is especially the case if strict criteria, a single tumor <5 cm, or no more than 3 tumors, all <3 cm, govern the use of this scarce resource (N Engl J Med 1996;334:693–699). Fulfillment of the use of strict criteria for liver transplantation resulted in 83% recurrence-free survival at 4 years. In addition, histologic evidence of vascular invasion by the tumor and poorly differentiated tumors that predispose to vascular invasion were additional predictive factors for recurrence (Hepatology 2001;33:1080–1086). Therefore it would be of considerable interest to study the role of circulating AFP mRNA as a predictor of recurrence in the setting of hepatic transplantation. The detection of earlier tumors from screening/surveillance programs for HCC now has to be converted into therapeutic benefit and improved survival. The ability to predict which patients are more liable to early recurrence, and the implementation of preventive measures in such patients, might help to convert earlier detection of HCC into improved survival in the future.

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