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Postoperative Screening of Patients with Carcinoma of the Colon*

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A prospective evaluation of 149 patients with Dukes' B_2 or C colorectal carcinoma, including periodic history, physical examination, chest radiograph, liver function tests, complete blood count, carcinoembryonic antigen (CEA) radioimmunoassay, barium enema, and endoscopic studies, has been underway since 1976. Thirty-four patients have had recurrence. This study suggests that the history and CEA are the most sensitive noninvasive methods with which to detect recurrent tumors but are unlikely to indicate recurrence at a therapeutically advantageous stage. [Key words: Carcinoembryonic antigen; Colonic cancer, follow-up studies, recurrence; Neoplasm recurrence]

OUR WISDOM in the use of new diagnostic and therapeutic tools often lags behind their development. This discrepancy is particularly evident when we consider the plethora of diagnostic tests available in the postoperative screening of patients with colorectal cancer. It is currently recommended that such patients be assessed postoperatively by any one or a combination of tests that include history; physical examination; complete blood count; examination for occult stool blood; proctoscopy; flexible sigmoidoscopy; colonoscopy; measurement of levels of serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, lactic dehydrogenase, and bilirubin; carcinoembryonic antigen (CEA) radioimmunoassay; and radiologic examinations such as barium enema studies, liver scan, chest roentgenogram, bone scan, computed tomographic scan, and intravenous pyelogram. There is no prospective information in the literature that allows one to assess the relative values of each of these tests or to determine at what point postoperatively they are most likely to be of value.

To determine the relative value and appropriate frequency of some of these tests, we performed a standardized series of diagnostic tests at fixed intervals postoperatively in a group of patients who had resection of a colon or rectal carcinoma without known residual disease. The results of this experience are the basis for this report.

Methods

Follow-up study was begun in 1976; the clinical course in 149 patients who had resection of Dukes' B_2 or C colorectal carcinoma was followed from the time of operation until the time of tumor recurrence or writing of this report. The follow-up period ranged from one to three years. Some patients received adjuvant therapy such as pelvic radiotherapy, chemotherapy, and immunotherapy, and others had no adjuvant therapy. All patients were seen at least every 15 weeks. At each interview, a complete history was taken, and physical examination was carried out. A chest roentgenogram was obtained, and laboratory determinations included complete blood count, alkaline phosphatase, SGOT, SGPT, and CEA. The test for lactic dehydrogenase and proctoscopic examinations were done every six months. A barium-enema

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x-ray study and liver scanning were done annually. Additional studies including computed tomography, laparoscopy, liver biopsy, and abdominal exploration were ordered as indicated by the history, physical examination, or positive laboratory results. All recurrent tumors were documented histologically.

Results

Thirty-four of the 149 patients who had follow-up for as long as three years have had histologically documented tumor recurrences. In spite of being seen at least every 15 weeks, 29 patients had symptoms before or at the time a recurrent tumor was detected by physical, biochemical, or radiologic abnormalities. Symptoms included coughing, abdominal or pelvic pain, change in bowel habits, rectal bleeding, and malaise.

Besides the history, CEA assay appeared to be the most sensitive means of detecting tumor recurrence. In 25 of the 34 patients, an elevation (greater than 5 ng/ml) was noted at the time of recurrence; 20 patients had both symptoms and an elevated CEA, five patients had an elevated CEA without symptoms, and nine patients had symptoms without an elevation in the CEA. In other words, all patients had either elevation of the CEA or symptoms to suggest the recurrence.

In addition to either symptoms or elevation of CEA, 16 patients had some abnormal physical finding at the time of recurrence, and 13 of 14 patients with liver metastases in whom liver scanning was performed had confirmation of recurrence on the scan. Six patients had an abnormal chest roentgenogram. Two of 12 patients with recurrence of pelvic disease had abnormal findings on proctoscopic examination; all had symptoms suggesting disease recurrence.

Computed tomographic scans were ordered on six occasions, and results were positive in each case. No false-negative results were noted. This test was generally ordered when there was a question of recurrence of pelvic disease, and computed tomography appears to be particularly sensitive for recurrence in this location.

Liver function was abnormal in 12 of 15 cases of hepatic recurrence. The alkaline phosphatase seemed to be the most sensitive liver function test, and its elevation was usually associated with liver metastasis. Of 15 patients who had documented liver recurrence, 12 had elevated alkaline phosphatase, and all had elevated CEA.

In only one case of proven tumor recurrence was there an abnormality in liver function that was not reflected in elevation of the CEA, and in that case, subsequent follow-up has not demonstrated liver metastasis to date. Two patients had persistent elevation of the CEA in the postoperative period, and recurrence of the colorectal carcinoma occurred within three months of operation.

Eighteen of 115 tumor-free patients had transient elevations in CEA. The abnormalities persisted for two to six months. In 16 of these patients, the CEA returned to normal, and the patients have had follow-up for as long as 33 months without clinical evidence of recurrent carcinoma. Two patients currently have elevation of CEA without detectable evidence of recurrence.

If one considers the likelihood that CEA will be elevated in relation to the site of primary tumor, it appears that the CEA test is least sensitive for recurrent rectal carcinoma. This would support the previously published work of Moertel and associates.[1] In six of 11 patients with recurrent rectal carcinoma, the CEA was elevated. For lesions of the left colon, CEA was elevated in six of seven; for lesions of the transverse colon, two of three; for lesions of the right colon, ten of 12; and for multiple primary lesions, one of one. When the analysis was performed according to the distribution of recurrent cancer, only one of six patients with pelvic or perineal recurrence had an elevated CEA, whereas 22 of 26 patients with distant metastasis had an elevated CEA at or before the time recurrence was detected clinically.

Discussion

In 1979 it is estimated that 52,000 persons died of cancer of the colon.[2] Although much attention has been given to long-term therapy of resected and recurrent colonic cancer, little information is available about the best way to detect a tumor recurrence. Many maintain that there is no effective treatment for recurrent colonic cancer, and therefore there is no reason to look for it. Such therapeutic nihilism is difficult to accept but appropriately reflects our present limitations in managing established recurrent colonic cancer. Nevertheless, it is important to know which tests will indicate evidence of recurrence at the earliest possible point. To ignore this consideration would suggest that early treatment may never be effective for recurrent disease.

Having decided that it is important to know how to follow the clinical course of patients in the postoperative period, we raise three important questions: How often should patients be examined? What tests are necessary and valuable for evaluation? What should be done if a recurrence is detected?

Polk and Spratt[3] calculated that if one accepts an interval recurrence rate of 2 per cent as sufficient to justify examination then follow-up examinations

should be performed about every two months in the first postoperative year, every three months in the second year, every six months in the third and fourth years, and annually thereafter. In spite of seeing patients every ten to 15 weeks, we were disappointed to find that symptoms usually preceded biochemical or radiographic evidence of recurrence.

The rate of recurrence varies with the stage and grade of tumor.[4,5] Our experience supports those studies that suggest an early recurrence for patients with persistently elevated CEA in the postoperative period[6] in that we had two patients with a persistently elevated CEA who both had a recurrence within three months.

Alkaline phosphatase is probably the most sensitive biochemical liver function test for indicating liver metastasis. The CEA test has also been reported to be sensitive for identifying recurrence of liver disease.[7,8] In our group, all 15 patients with documented liver metastasis also had an elevated CEA, whereas three of the patients had normal alkaline phosphatase levels;[7,8] thus, the CEA test appears to be more sensitive than the other biochemical tests we performed.

The accuracy of liver scanning varies with the volume of tumor present in the liver. If tumors are greater than 2 cm or replace more than 50 per cent of the liver volume, the accuracy is good. Obviously, one would hope to be able to identify recurrence before involvement reaches this level, so liver scanning seems relegated to the status of a confirmatory test rather than to that of a first-line screening test.[9,10]

Occult stool blood detection has been suggested as being valuable for identifying recurrent tumor. Only two of our 34 patients had mucosal disruption caused by recurrence. Welch and Donaldson[11] reported that 12 per cent of patients had gastrointestinal bleeding related to recurrence. Even in their experience, this was a low-yield test and would not appear to be of great value in the search for recurrent cancer.

Computed tomography was used sporadically in our experience, but when employed, it was highly accurate. Both hepatic and pelvic lesions can be delineated well. Because of its expense, however, like that of radionuclide liver scanning, computed tomography should be used as a confirmatory test.

Endoscopy was of surprisingly limited value. Since mucosal recurrence of colonic cancer is rare, one would expect that colonoscopy would be of limited value, particularly if adequate barium studies are available. Only two of 12 pelvic recurrences could be detected by proctoscopy. Thus, although important because a locally resectable recurrent tumor may be identified, routine proctoscopic evaluation appears to be of low yield. Endoscopy and barium studies would appear to have their greatest function in identifying synchronous and metachronous lesions rather than recurrence.

Physical examination was a frequent indicator of disease, but it was not as sensitive as the presence of symptoms. All patients with abnormal physical findings had either symptoms or an elevated CEA. Physical examination remains an important means of localizing otherwise nonspecific complaints.

Carcinoembryonic antigen assay was a sensitive means of identifying recurrent disease in this series. Unfortunately, it did not appear to identify tumors at a resectable stage. When we examine this group of patients according to site of primary tumor, we find that CEA is less sensitive for recurrent rectal carcinoma. There is nothing to suggest that these tumors are biologically different from other colonic tumors, but it may be that symptoms occur early in the course of recurrence and that the lesser incidence of elevated CEA reflects the small volume of the tumor at recurrence. Also, the recurrence is generally localized, and CEA is clearly more sensitive for disseminated disease. Pelvic recurrence is a notoriously difficult situation, and it is disappointing that CEA is not more helpful.

No patients in this study had a resectable local tumor at recurrence. Although the definition of "resectable" may not be precise, none of the patients had isolated recurrence in the liver or any other unifocal sites in the pelvis. Because symptoms had occurred in all patients with pelvic recurrence, the tumors were unlikely to be resectable, and radiation therapy was our primary form of treatment.

A review of the literature supports a low, but real, level of resectable tumor recurrence. Excluding the early report of Minton and associates,[6] a "resectable recurrence" rate of 5 to 7 per cent of patients would be expected, of whom 30 to 50 per cent will survive five years if resection is accomplished.[11-14] This small though real hope is probably the strongest motivation to look for recurrence in asymptomatic patients because we have no other curative therapy to offer, with the exception of a 5 to ten per cent cure rate with the use of radiation therapy for locally unresectable rectal cancer. Our experience, however, does not suggest that any of the techniques currently available can identify recurrent tumor at a more resectable point in its development.

From a clinical standpoint, our study does not demonstrate any significant value for postoperative follow-up as described in this report because all tumors were unresectable. A pertinent medical history and careful physical examination, coupled with periodic assessment of the anastomosis by proctos-

copy and barium-enema study, remain the most effective means of identifying recurrence and metachronous tumors. The CEA test is the most sensitive noninvasive laboratory test with which to detect recurrent tumor, but it is unlikely to indicate the recurrence at a therapeutically advantageous stage. The CEA determination is helpful in conjunction with computed tomography and other diagnostic tests for patients with unexplained symptoms that could be caused by recurrent carcinoma.

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