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Postsurgical Surveillance of Colon Cancer

Preliminary Cost Analysis of Physician Examination, Carcinoembryonic Antigen Testing, Chest X-Ray, and Colonoscopy

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Objective
This study is the first to examine the relative and absolute costs of physician examination, carcinoembryonic antigen (CEA) assessment, chest x-ray, and colonoscopy in detecting recurrent disease in patients who have undergone surgical resection for primary colon carcinoma.

Methods
Of the 1356 Eastern Cooperative Oncology Group patients in Intergroup Protocol 0089 who underwent surgical resection for Dukes' B2 and C colon carcinoma, 421 patients who developed recurrent disease were reviewed. Follow-up testing was performed according to protocol guidelines, with the cost of each test equal to 1995 Medicare reimbursement. Follow-up was defined as the time to recurrence for the 421 patients in whom disease recurred (mean 18.6 months) or up to 5 years for the additional 930 patients in whom disease did not recur (mean 38.6 months). Patients were divided into three categories: nonrecurrent, recurrent but not resectable, and recurrent but resectable with curative intent. The estimated mean cost of each test in detecting group 3 (recurrent but resectable) patients was calculated.

Results
Of the 421 patients who developed recurrent disease, 96 underwent surgical resection of their disease with curative intent (group 3). For group 3 patients, the first indication of recurrent disease was CEA testing (30), chest x-ray (12), colonoscopy (14), and other (40). Of the 40 "other" patients, 24 presented with symptoms. Routine physician examination, however, failed to identify a single resectable recurrence, and the total cost for physician examination was $418,615. The detection rate for CEA testing was 2.2%, the total cost was $170,880, and the cost per recurrence was $5,696. The detection rate for chest x-ray was 0.9%, the total cost was $120,934, and the cost per recurrence was $10,078. The detection rate of colonoscopy was 1%, the total cost was $641,344, and the cost per recurrence was $45,810.

Conclusions
CEA measurement was the most cost-effective test in detecting potentially curable recurrent disease. Physician visits were useful only in the evaluation of symptoms; a routine physician examination had no added benefit.

Monitoring patients after surgery for colon carcinoma is predicated on two basic goals: to increase lead time in the detection of recurrent disease, thereby improving results with either curative or palliative therapy, and to identify metachronous disease early in its natural history. Different follow-up strategies have been recommended, ranging from patient education with instructions to call if symptoms appear[1,2] to periodic physician visits with frequent laboratory tests and x-rays.[3,4] The sensitivity and specificity of these various tests are well established.[5] Little information exists, however, about the actual cost of identifying either recurrent or metachronous disease.

The cost of oncologic follow-up can be divided into two categories: the cost of each test to monitor patients for recurrent disease and the cost to evaluate and treat the patients whose test results are positive. Because the evaluation and treatment schedules vary widely with the site and extent of recurrent disease, costs are difficult to estimate for this component of follow-up care. This paper, therefore,

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focuses on the costs of four common tests used to monitor patients for recurrent disease—routine physician examination, carcinoembryonic antigen (CEA) measurement, chest x-ray, and colonoscopy—and estimated the cost of each test to detect recurrent disease after curative surgery and adjuvant chemotherapy for either Dukes' B2 or C colon carcinoma.[6]

METHODS

Of the 1356 patients (mean follow-up 43.6 months) enrolled by the Eastern Cooperative Oncology Group (ECOG) in Intergroup Protocol 0089, we reviewed all 421 patients who developed recurrent disease. This represents 80% of the expected recurrences based on recurrence patterns in previous ECOG studies. All patients had either a Dukes' B2 or C colon carcinoma, underwent surgical resection of their primary disease, and were randomized to one of four adjuvant treatment arms: 5-fluorouracil (5-FU) plus low-dose leucovorin (6 months); 5-FU plus high-dose leucovorin (6 months); 5-FU plus levamisole (12 months); or 5-FU plus levamisole plus low-dose leucovorin. Patients were followed according to protocol guidelines: in year 1, a physician examination every 3 months, CEA measurement every 3 months (optional), chest x-ray every 3 to 6 months, and colonoscopy every 6 months; in years 2 through 5, a physician examination every 6 months, CEA measurement every 6 months (optional), chest x-ray every 6 to 12 months, and colonoscopy every 1 to 2 years. (Colonoscopy or a proctoscopic examination with barium enema were both allowable by protocol guidelines. Colonoscopy was preferentially used [almost 100%] as the procedure of choice.)

The charts of all 421 patients were reviewed to determine the time to recurrence from initial surgery, the presence or absence of symptoms when recurrent disease was first detected, the test that first suggested recurrent disease in asymptomatic patients, and whether the recurrent disease was inoperable or still amenable to a potentially curative surgical resection.

To determine compliance with testing guidelines, 200 charts (100 patients with recurrent disease and 100 patients without evidence of disease) were then randomly chosen for separate review. The date of each test was recorded, and the number of tests ordered was compared with the number of tests recommended by protocol guidelines to calculate compliance. When a range of follow-up testing was allowable (*e.g.*, chest x-ray every 6 to 12 months), the longer interval (12 months) was used to determine the number of recommended tests. For example, if three chest x-rays were performed after 3 years of follow-up (recommended number of chest x-rays = 4), compliance was 75%.

The cost of each test was estimated using 1995 Medicare reimbursement guidelines: physician examination (CPT 99214), $65; CEA testing, $28; chest x-ray, film $33 and physician interpretation $13, colonoscopy, 1 hour facility fee $89 and physician fee $320.

Table 1. SITES OF RECURRENT DISEASE

Site	Group 2 (%) n = 325 (Not Resectable)	Group 3 (%) n = 96 (Resectable)	Total (%) n = 421
Liver	108 (33.2)	22 (22.9)	130 (30.9)
Lung	22 (6.8)	17 (17.7)	39 (9.3)
Colon	16 (4.9)	12 (12.5)	28 (6.7)
Abdominal	80 (24.6)	32 (33.3)	112 (26.6)
Mixed	86 (26.5)	9 (9.4)	95 (22.6)
Other	13 (4.0)	4 (4.2)	17 (4.0)

Follow-up was defined as the time to recurrence for the 421 patients in whom disease recurred (mean 18.6 months) and up to 5 years for the additional 930 patients who did not recur (mean 38.6 months). Follow-up data were incomplete on five patients, and they were therefore not included in the analysis.

Patients were divided into three groups based on outcome: group 1, nonrecurrent; group 2, recurrent but not resectable; and group 3, recurrent but resectable with curative intent. The estimated mean cost of each test to detect recurrent disease was calculated as follows:

$$\frac{(\text{Number of tests done at mean month} \times 1356 \text{ patients} \times \text{cost/test})}{\text{Number of patients in a given group detected by specific test}}$$

These calculations were done based on the actual number of tests performed and were done separately for all patients with recurrent disease (groups 2 and 3) and for group 3 patients only, specifically those who underwent surgical resection of their recurrent disease with curative intent.

RESULTS

Of the 421 patients who developed recurrent disease, 325 were found to have unresectable disease (group 2) and 96 underwent surgical resection of their disease with curative intent (group 3). The mean time to recurrence was 18.6 months (range 2 to 63 months), with no difference observed between groups 2 and 3. For the 930 patients in whom disease did not recur, mean follow-up was 38.6 months (range 7 to 60 months). The sites of recurrent disease are listed in Table 1.

The first indicators of recurrent disease are listed in Table 2. Despite the intensive follow-up schedule, only 53% of recurrences were identified solely by physician examination, CEA measurement, chest x-ray, or colonoscopy. Routine physician examination, in the absence of patient symptoms, identified only 1% of patients with recurrent disease, and none of those patients was amenable to potentially curative surgery.

For patients who developed recurrent disease, compliance with protocol guidelines was 64.9% for physician

Table 2. FIRST INDICATORS OF RECURRENT DISEASE

	Group 2 (%) n = 325 (Not Resectable)	Group 3 (%) n = 96 (Resectable)	Total (%) n = 421
Physician exam	5 (1.5)	0 (0)	5 (1.2)
CEA	131 (40.3)	30 (31.2)	161 (38.2)
Chest x-ray	16 (4.9)	12 (12.5)	28 (6.7)
Colonscopy	15 (4.6)	14 (14.6)	29 (6.9)
Patient symptoms	106 (32.6)	24 (25.0)	130 (30.9)
Multiple/Other	52 (16.0)	16 (16.7)	68 (16.2)

examination, 52.4% for chest x-ray, and 41.3% for colonoscopy. The compliance rates for the 100 randomly chosen patients who did not have recurrent disease were 58.7% for physician examination, 63.3% for chest x-ray, and 71.9% for colonoscopy. CEA measurement (an optional test) was obtained in 61.5% of patients with recurrent disease and 51.7% of patients without recurrent disease, respectively.

Cost estimates, using actual compliance for patients with recurrent disease and projected compliance based on the sample of 100 charts reviewed for patients without recurrent disease, were then calculated for each test used to monitor patients for recurrent disease (Table 3). Because the major goal of follow-up care was to cure patients who developed recurrent disease, the costs of detection were calculated separately for groups 2 and 3. CEA measurement was the most cost-effective test used; routine physician examination was the least cost-effective test and was of no benefit in identifying patients with potentially curable recurrent disease. (However, information was not available on the number of false-positive tests and the resulting costs of additional evaluation.)

DISCUSSION

Given the current trends in health care reform, it is essential to analyze the cost effectiveness of surveillance procedures for patients after treatment for primary colon carcinoma. In this study, we attempted to determine the mean cost of four tests (physician examination, CEA measurement, chest x-ray, and colonoscopy) commonly used to identify recurrent disease in the asymptomatic patient. These calculations were at best a crude estimate, but they do represent actual costs rather than theoretical costs generated by a mathematical model. We also did not stratify for B2 *versus* C colon carcinomas. The recurrence rate is known to be higher for more advanced stages of disease, and it is presumed that the costs of detection will decrease with higher rates of recurrence.

Our cost estimates understate the total costs generated by a careful surveillance policy. Because >80% of recurrences occur within the first 3 years of follow-up,[7] additional surveillance of the 930 ECOG patients who have not had recurrent disease (mean follow-up 38.6 months) would add significant expense with little added benefit in the detection of recurrent disease. However, the additional 20% of patients expected to have future recurrences may benefit most from prompt detection. Several studies have shown that survival after resection of recurrent disease increases with a longer disease-free interval between detection of the primary and recurrent disease.[8–10]

Additional costs include those of evaluating and treating patients with recurrent disease, as well as the cost of evaluating patients whose surveillance test results are falsely positive. This latter expense can be substantial, with some series demonstrating a higher false-positive than true-positive rate for certain tests.[11,12] The false-positive rates for the ECOG patients were not known and were therefore not included in this analysis.

Finally, there are the psychological and medical burdens associated with a positive test result, the fears of early detection of an incurable recurrence, and the morbidity and mortality rates related to surgery done as a result of either true-positive or false-positive test results.[5] Each of these potential costs is hard to quantify.

The role of each test in monitoring asymptomatic patients remains controversial. Several authors promote the idea of a routine history and physician examination,[13–15] although Beart and O'Connell[11] are the only authors who have separately analyzed the utility of the patient history and the physician examination. In following 48 patients who developed recurrent disease, they found that 85% of recurrences were suspected based on patient symptoms; none was found on physician examination alone. In a series of 406 patients

Table 3. ESTIMATED MEAN COST TO DETECT RECURRENT DISEASE

	Detection Rate (n = 1356)			Cost per Recurrence in $	
	Group 2 (Not Resectable)	Group 3 (Resectable)	Total Cost in $	Group 2 (Not Resectable)	Group 3 (Resectable)
Physician exam	0.4%	0%	418,615	83,723	–
CEA	9.7%	2.2%	170,880	1304	5696
Chest x-ray	1.2%	0.9%	120,934	7558	10,078
Colonscopy	1.1%	1.0%	641,344	42,756	45,810

followed at the Middlesex Hospital, only 1 patient was found to have recurrent disease on physician examination alone.[1] Our identification of five patients, none of whom had disease that was operable for cure, supports the idea that physician examination alone, in the absence of patient symptoms, is of little or no benefit.

CEA measurement was the most cost-effective test in identifying recurrent disease, although our detection rate of 38% (161/421) was lower than that in the literature. This may reflect a relatively long interval between tests (every 3 months for year 1, every 6 months for years 2 through 5) and the fact that CEA testing was optional. It may also reflect the value at which CEA is considered abnormal. Wanebo et al.,[12] who followed 226 patients after resection of colon carcinoma, measured the CEA level on a monthly basis, used a low cut-off value of 3.0 ng/ml, and found that CEA was the first indicator of recurrent disease in 89% of patients. Minton et al.,[16] using a longer interval of 8 weeks and a similar cut-off value for CEA (>2.5 ng/ml on two consecutive tests), found that CEA was the first indicator of recurrent disease in 81% of patients. As these studies suggest, more frequent testing with lower cut-off values would be likely to increase the detection rate but would also add greatly to the overall cost of a surveillance program.

Strict colonoscopic surveillance has been used to identify both recurrent and metachronous disease. In a series of 290 patients followed by the same ECOG colonoscopic guidelines, 12 patients (4.1%) were identified with an asymptomatic anastomotic recurrence, and 9 underwent a potentially curative resection.[17] A similar surveillance program of 132 patients with Dukes' B or C colon carcinoma found 6 patients (4.5%) with an anastomotic recurrence and no extracolonic spread.[18] In our series of 1356 patients, only 14 patients (1%) were identified who were both asymptomatic and amenable to a potentially curative resection. This low detection rate may reflect the low rate of compliance in our series (41.9%). Compliance in the earlier series was mandatory and close to 100%.

The role of a surveillance chest x-ray has not been established. Beart and O'Connell,[11] in following 168 patients with primary colon carcinoma, identified 5 (3%) with an abnormal chest x-ray. All of those patients were symptomatic; none had potentially curable disease.

In a large review series, Pommier and Woltering[19] concluded that chest x-rays have an extremely low yield and should be used only to localize or stage disease. Safi et al.,[20] in following 1045 patients after surgery for colon carcinoma, identified 7 patients (0.7%) who underwent curative resection of isolated pulmonary metastases. This closely resembles our experience, in which 12 of 1356 patients (0.9%) were identified with potentially curable disease.

Several key issues require emphasis. First, this was a contemporary study representing multiple institutions and therefore should resemble practice in the real world. Surveillance guidelines were similar to those identified in a survey of fellows of the American Society of Colorectal Surgeons.[3] Despite participation in a protocol, however, physician compliance with testing recommendations was relatively poor, especially for colonoscopy. This may reflect the results from the National Polyp Study, which compared 1- and 3-year follow-up programs for patients with adenomatous polyps (not cancer) and concluded that colonoscopy every 3 years was adequate.[21] These low compliance rates must be factored into any cost estimate of a surveillance program.

Second, the median time to recurrence for our patients was no different from other historical series,[20] despite the more advanced tumors in our patients (Dukes' stage B2 and C); more advanced tumors are known to predispose patients to earlier recurrences.[22] This "relative" delay in recurrent disease may have resulted from the routine use of adjuvant chemotherapy. In any case, it does validate the concept that surveillance testing should be concentrated in the first 5 years, even in patients receiving adjuvant chemotherapy.

Third, this paper establishes the following rank order of cost effectiveness for our follow-up tests: CEA testing > chest x-ray > colonoscopy > physician examination. Moreover, 96 of 1356 patients (7.1%) were identified with potentially curable disease. At least 20% of these patients should be ultimately cured,[5] although one series reported a 5-year cancer-related survival rate as high as 47%.[23] In addition, the potential benefits of early detection of unresectable disease and of identifying metachronous disease are not included in these estimates. We hope this paper will help form a basis for future cost calculations as we attempt to determine the cost/benefit relation of our surveillance policies.

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