# CEA-Directed Second-look Surgery in the Asymptomatic Patient after Primary Resection of Colorectal Carcinoma

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**Since 1971, serial carcinoembryonic antigen (CEA) levels have been measured to monitor patients after primary resection of colorectal cancer. Based solely on a rise in CEA level above the baseline established after primary resection, 146 patients were readmitted to the hospital. Chest films, liver-spleen scan, colonoscopy, bone scan, abdominal and pelvic CAT scan, and hepatic arteriograms were performed, and elevated CEA levels were confirmed before reexploration was undertaken. In the 146 patients, 139 (95%) had recurrences, and 81 (58%) of these were resectable for potential cure. Two of the first 22 patients reexplored between 1971 and 1975 are still living 11 and 14 years after second look; of 45 patients reoperated upon from 1976 through 1979 and followed for at least 5 years, 14 (31%) are still living. A rise in CEA above the baseline established after primary resection proved to be a sensitive indicator of recurrence and prompted reexploration before symptoms developed. Early alternative therapy was begun in patients with unresectable recurrences.**

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TWENTY YEARS HAVE PASSED since the nonspecific tumor marker carcinoembryonic antigen (CEA) was described by Gold and Freedman.[1] Much has been learned about this tumor-associated antigen since 1965, both in the laboratory and in clinical experience. The time required to determine the serum level of CEA, formerly 48 hours, has been shortened to 4 hours. Polyclonal antibodies and the radioimmunoassay (RIA) used in the early work have been replaced by a faster and easier enzyme immunoassay (EIA) method. As experience accumulated in the laboratory and clinical experience grew, clinicians began to use the accumulating information to improve the treatment of patients with colorectal carcinoma.

The prevalence of colorectal cancer continues to escalate. The American Cancer Society estimates that 138,000 new cases will be found in 1985, and 59,000 people will die of the disease, including 51,600 from colon cancer and 8,300 from cancer of the rectum.[2] Little improvement in this dismal outcome has taken place over the past 30 years, and the 5-year survival remains below 50%.[3] Earlier detection of primary tumor by improved screening procedures and dietary intervention constitute first-line efforts to improve the outcome, but a major challenge lies in better detection of recurrent tumor and improved therapy after the surgical removal of recurrences.

Early efforts at The Ohio State University to improve the outcome in this disease were based on second-look operations undertaken in asymptomatic patients whose CEA levels were rising after a primary resection. Second-look surgery was first described in the early 1950s by Wangensteen et al.,[4] who reoperated at an arbitrary interval after the primary procedure. We chose to follow patients with CEA determinations and to perform second-look operations in asymptomatic patients when the postoperative CEA level rose.[5-7] Although the number of patients was small, the results warranted a prospective study that has extended from 1976 to the present. The assessment of the value of an increase in serum CEA as an indicator for early reoperation depends on how many patients are cured of their recurrent tumor by reoperation.

## Materials and Methods

### *Retrospective Study*

From 1971 to 1976, 300 patients were followed after primary resection of colorectal carcinoma by serial serum CEA determinations. Twenty-two (7.3%) asymptomatic patients underwent second-look operations solely because of a rise in CEA. The time of reexploration varied widely, owing to variations in the degree of cooperation secured from patients and referring physicians in the absence of a formal protocol. As a result, the interval between CEA assays varied from 3 to 6 months, and the interval between

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TABLE 1. *CEA Second-Look Prospective Study*

| Year | Number Patients | Alive |
|---|---|---|
| 1976 | 10 | 3 |
| 1977 | 13 | 5 |
| 1978 | 11 | 3 |
| 1979 | 11 | 3 |
| Five Years | 45 | 14 (31%) |
| 1980 | 10 | 5 |
| 1981 | 12 | 8 |
| 1982 | 10 | 6 |
| 1983 | 23 | 19 |
| 1984 | 24 | 21 |
| Eight years | 79 | 59 (74.6%) |
| Total | 124 | 73 (58.8%) |

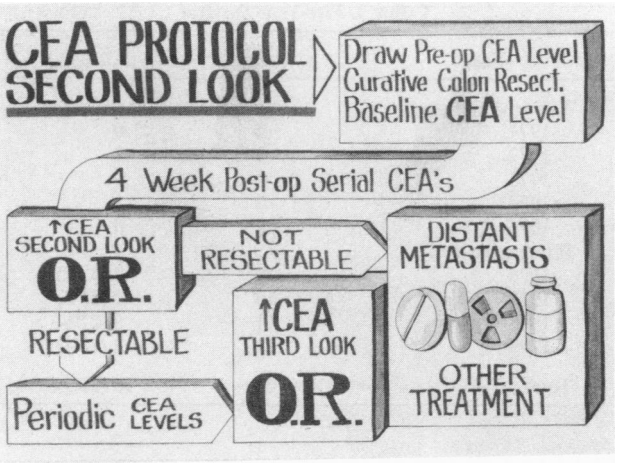


FIG. 1. Graphic representation of the protocol followed in the serial determination of CEA levels in patients who have undergone a primary resection of colorectal carcinoma. A rise in CEA signals reoperation.

the elevation in CEA level and second-look operation was 4.1 months. These 22 patients are termed "retrospective".[8]

*Prospective Study*

In January 1976, a protocol was designed for the serial determination of CEA levels in the postoperative follow-up of patients with colorectal cancer who had undergone a presumptively curative resection.[9] During the intervening years (1976–1984), 124 asymptomatic patients have undergone second-look operations solely because of a rise in postoperative serial CEA levels. These patients are termed "prospective" (Table 1).

All patients had preoperative CEA assay and presumptively curative resection of proved primary colorectal cancer. Preoperative CEA levels and operative and pathology reports were recorded. Following the primary procedure, a postoperative baseline CEA level was established. Subsequent serial CEA assays were performed every 4 to 6 weeks for the first 2 years, and every 8 to 10 weeks for the next 3 years (Fig. 1). If a CEA level exceeded the limit of confidence established by the CEA nomogram, the assay was immediately repeated.[9] If the repeated level remained elevated, the patient was thoroughly evaluated as an outpatient by stool blood test, colonoscopy, chest roentgenogram, intravenous pyelogram, liver function tests, tomograms, liver-spleen scan, bone scan, axial tomography, and CEA radioimmunodetection scan. If these procedures did not reveal tumor spread outside the abdomen, a second-look operation was performed. The interval between assays averaged 1.8 months, and the interval between a confirmed rise in CEA and the second-look operation, 2.5 months.

*Radioimmunoassay Methods*

Between 1971 and 1974, assays were performed in a research laboratory using a dialysis step that required 48 hours. In 1974, the hospital clinical immunology laboratory began to perform the assay using the Hansen Z-Gel method, which required 12 to 18 hours.[10] During this period, the use of an Amicon® filter was introduced. In 1982, the use of the Abbott Enzyme Immunoassay (EIA), which uses a polyclonal antibody, was adopted and the time required to perform the assay was reduced to 6 hours, or one hospital shift. Since September 1984, the Abbott EIA monoclonal antibody technique has been used. Comparative studies have shown that the accuracy of the assay remains at the same high level (Table 2).

*Radioimmunoassay Evaluation*

Calculating intraassay and interassay error, values were plotted on linear graph paper with equal axes to fashion a CEA nomogram, which establishes a 95% confidence limit for any given assay result.[9] Levels above 7.5 ng/ml were considered to indicate tumor recurrence. A second method of evaluating levels is the use of slope analysis, described by Staab et al., in which the increase in CEA

TABLE 2. *CEA Assay Methods*

| Method | Antibody | Years | Assay Time | Cost ($) |
|---|---|---|---|---|
| Reseach | Poly/pooled 1° | 1971–1974 | 48 hours | |
| Roche Dialysis | Poly/pooled 1° | 1974–1976 | 18 hours | 25 |
| Roche Amicon Filter | Poly/Hepatic Met 2° | 1976–1981 | 10 hours | 29 |
| Abbott EIA | Poly/Hepatic Met 2° | 1982–1984 | 6 hours | 39 |
| Abbott EIA | Mono/Hepatic Met 2° | 1984–1985 | 4 hours | 48 |

1° = primary tumor; 2° = metastatic tumor.

TABLE 3. *Five-Year Survival*

| Year | Number | Alive (%) |
|---|---|---|
| Retrospective study | | |
| 1971 | 4 | 0 |
| 1972 | 2 | 1 |
| 1973 | 4 | 0 |
| 1974 | 6 | 1 |
| 1975 | 6 | 0 |
| Prospective study | | |
| 1976 | 10 | 3 (33%) |
| 1977 | 13 | 5 (38%) |
| 1978 | 11 | 3 (27%) |
| 1979 | 11 | 3 (27%) |
| Total | 67 | 16 (23.9%) |

(ng/ml) is plotted for 10 days.[11] The degree of the slope is established by at least two or three consecutively performed CEA assays. The use of several serial levels differentiates transient elevations due to heavy smoking, inflammatory conditions of the gastrointestinal tract, pulmonary conditions, or other causes. A rising slope indicates tumor recurrence.

*Second-look Procedure*

The second-look procedure included careful examination of the incision area and biopsy of all suspicious tissues. A standard staging exploration was carried out. All resectable recurrent tumor was surgically removed. Major decisions concerning the liver were often required. Hepatic recurrences were resected, either by lobectomy or, when possible, wedge resection. When additional tumor could not be identified outside the liver but hepatic involvement was too extensive for hepatic resection, catheters were placed during surgery to direct subsequent chemotherapy directly to the liver. Recurrences were not considered surgically resectable if the CEA level failed to return to baseline after the second-look procedure.

*Postoperative Care*

If resection of recurrent tumor took place at reoperation and extraabdominal tumor was not demonstrated, the patient returned to the study group to undergo a new series of CEA assays for continuing evaluation. If diffuse tumor was evident, other therapeutic regimens were begun.

TABLE 4. *Recurrence at Second-Look Sixteen Five-year Survivors*

| Location | Number | Per cent |
|---|---|---|
| Liver | 10 | 62.5 |
| Abdominal wall | 2 | 12.5 |
| Mesentery | 2 | 12.5 |
| Anastomosis | 1 | 6.25 |
| Periaortic node | 1 | 6.25 |

## Results

Of the 146 asymptomatic patients reexplored between 1971 and 1984 because of a rise in CEA after a presumptively curative resection, 81 (55%) had a resectable recurrence and 58 (40%) had unresectable tumor. No recurrence was found in seven patients (5%), but six of the seven have subsequently had recurrent tumor demonstrated. Of the 139 positive second-look patients, 75 (54%) remain alive and 64 (46%) have no evidence of disease. Of the 81 patients with a resectable recurrence, 57 (60%) remain alive at the present.

Of the 22 patients reexplored from 1971 through 1975, two are still living 11 and 13 years after the second look. Fourteen (31%) of the 45 patients reoperated upon from 1976 through 1979 are five-year survivors (Table 3).

The location of the tumor is of major importance. Liver invasion and diffuse tumor involvement were the two most common findings, followed by anastomotic recurrence and mesenteric involvement. Table 4 shows 5-year survival according to the location of recurrent tumor.

The median CEA value at the time of the second-look procedure in the 81 patients with resectable recurrences was 10.2 ng/ml with a range from 0.8 to 300 ng/ml. The time interval between a significant elevation in CEA value and reexploration was 4.5 months in the retrospective group (resectability rate 27%) and 2.5 months in the prospective group (resectability rate 60.5%).

## Discussion

Second-look surgery for colon cancer is not a new concept. In 1951, Wangensteen[4] proposed the second-look procedure in an effort to detect occult disease amenable to surgical treatment in asymptomatic patients. Wangensteen arbitrarily chose first 6-month intervals and then 9-month intervals between explorations.[12] While the concept was sound, only a few patients could be considered to be potentially cured, and most were unnecessarily subjected to the risks of a second operation. The use of rising CEA levels following the establishment of a baseline to indicate reoperation may now better serve asymptomatic patients.

At The Ohio State University, serial CEA levels are now performed as part of the usual follow-up program in patients who have undergone presumptively curative resection for adenocarcinoma of the colon and rectum. All the patients in this study were asymptomatic but underwent a second-look procedure because of an elevated CEA. Following a rise in CEA judged significant by the use of the nomogram, all were aggressively evaluated in an attempt to identify recurrent tumor. Chest films, liver-spleen

scan, colonoscopy, bone scan, and abdominal and pelvic CAT scan were performed as outpatient procedures. The patient was then admitted for an hepatic arteriogram prior to surgical exploration. In addition, in the past 2 years, radioimmunoscan has been performed. Physical examination, thorough history, abdominal computed axial tomography scan, and endoscopy have been the most useful preoperative procedures. Before reexploration, the CEA values are always rechecked.

The CEA assay has undergone five major changes in methods during the 13-year period of the study. Each time a major change in methods was made, samples from each patient were compared to establish new baselines for the new assay in that patient. During the period 1971 to 1974, the CEA determinations were performed in the research laboratory, required 48 hours to perform because of a lengthy dialysis step, and few samples could be processed at one time. During 1974, the assay was performed in the hospital clinical immunology laboratory using the Hansen Z-Gel method which required 12 hours and continued to include a dialysis step. From 1978 to 1982, the method was again improved and the time required cut to 8 hours. In addition, in 1978, the use of an Amicon® filter was instituted. In 1982, the hospital laboratory converted to the EIA system, using a polyclonal antibody, and the time required was shortened to 6 hours. Beginning in September 1984, another major development in the EIA method occurred, namely, the use of a monoclonal antibody. Comparative studies confirm the fact that the monoclonal antibody identifies the same tumor population as the polyclonal antibody.

A persistent rise in CEA levels has played an important role in making therapeutic decisions. Currently, we send two reports to the primary physician, one showing the result of the most recent sample and the other a computer print-out with the date and the results of the previous six determinations. This report shows variation in CEA levels and also informs the physician as to the frequency of the CEA determinations (Fig. 2). The use of the CEA nomogram enables the physician to establish, within 95% confidence limits, values that are significantly different. The accuracy and reproducibility of the CEA assay were determined each time we changed assay methods in order to determine the sources of error not only within an assay, but also between assays. Data were plotted on linear graph paper with equal axes to demonstrate the standard deviation of the assay in this laboratory, or the 95% confidence limit for any result.[9]

An alternate method of evaluating rising CEA levels is slope analysis. Patients showing CEA slope increases greater than 5 ng per liter of serum per 10 days have shown a poorer chance for a successful second resection than patients with less steep slopes. Both methods, nomogram or slope analysis, help to indicate that recurrence

*CLINICAL LABORATORY REPORT*

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Report Date: 041285

**CARCINOEMBRYONIC ANTIGEN TESTING**

Kefgen, Penelope
900237133

Location 410E
Dr. Edward Martin

| DATE | RESULT (NG/ML) |
|---|---|
| 041185 | 2.1 |
| 032785 | 2.0 |
| 021085 | 1.7 |
| 010285 | 0.8 |
| 121284 | 0.7 |
| 111984 | 0.8 |
| 102484 | 0.2 |
| 091784 | 0.5 |

TEST DONE BY ABBOTT (EIA) METHODOLOGY

OSU ESTABLISHED NORMAL RANGES:
NON-SMOKERS: 0 - 4.4 NG/ML
SMOKERS: 0 - 5.5 NG/ML

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FIG. 2. Computer print-out showing results of serial determinations of CEA levels.

is present in patients who are still asymptomatic. It appears that the best frequency of CEA determinations is every 4 to 6 weeks for the first 2 years to ensure the early detection of tumor recurrence, and that second operations should be performed when the CEA level is 10 ng/ml or less for the best possibility of resection at the second procedure.

Others performing second-look operations have reported varied results. Staab[12] stated that 12% of all patients who underwent second-look procedures were curable on reoperation. He reported that seven of nine patients with resectable recurrences showed rates of increase in CEA of less than 2.1 ng/ml/30 days by slope analysis. Four of 14 patients found to have tumor at second-look operation were resected for cure, and one of these patients remained alive. Five patients whose recurrences could not be completely resected had partial tumor resection, regional infusion of chemotherapy, systemic chemotherapy, or external beam radiotherapy, and four of these were alive at least 10 months later. Six patients found to have widespread regional or distant tumor recurrence were not treated at all and were dead 6 months after reexploration. Persistently increasing CEA levels appeared to be linked with progression of recurrent disease.

Wanebo and colleagues[13] reported four of 16 patients to be disease-free after second-look operations. Mavligit[14] supported the usefulness of CEA to detect liver metastases, but pointed out its lack of capability to consistently detect pelvic recurrences. He suggested that many pelvic recurrences can be identified by thorough physical examination. Beart et al.[15] have shown that the patient's history and

the CEA level are the most sensitive noninvasive methods with which to detect recurrent tumors. In his experience, if only CEA values above 7.5 ng/ml are considered pathologic, many false-negative results are avoided, and elevated CEA concentration then predicts recurrence correctly in 83%. These authors believe that CEA will detect recurrence without the use of more complicated and expensive examinations.

Others have compared CEA-directed second-look procedures in asymptomatic patients with those in symptomatic patients. Tornqvist et al.[16] reported 69 patients undergoing second-look surgery, 38 of whom (55%) were symptomatic and 31 (45%) asymptomatic. Reoperation was curative in three of the 38 symptomatic patients, whereas 12 of 31 asymptomatic patients had curative resection. Blumgart et al.[17] supported the use of sequential CEA determinations, stating that while the detection of recurrent tumor remains difficult in asymptomatic patients, slope analysis to define the CEA pattern may be helpful both in diagnosis and in distinguishing between local recurrence and metastases.

Finally, in a combined report by the members of the Society of Surgical Oncology,[18] 43 patients underwent second-look surgery solely because of an elevated CEA level, and recurrent tumor was confirmed in 92%, with 30% remaining disease-free 5 years later. Resectability was highest when the CEA was 11 ng/ml or less.

As experience with CEA assay accumulates, more appropriate use will be made of this biologic marker. Armitage et al.[19] have addressed ways of improving the ability to select patients who will benefit the most. They suggested that the major contributing factors are preoperative elevation of CEA level, pathologic tissue grading indicating a well-differentiated tumor, and dark peroxidase staining for the presence of CEA. Better understanding of the CEA assay will also lead to improved use of the results. Transient rises in CEA are not infrequently encountered and can be ascribed to hepatic dysfunction, heavy smoking, or transfuion of CEA-rich blood.[20]

On the other hand, recently developed immunodetection methods using CEA have demonstrated metastatic deposits unsuspected by the conventional clinical tests.[21-23] Goldenberg,[24] Mach,[25] and others used radiolabeled CEA antibody and total body scan to disclose occult tumor not detected by other methods. Using double and triple antibody CEA analysis, Staab[26] believes the extent of primary and secondary tumor can be identified before the first operation. Our study also suggests that the current CEA assay identifies secondary tumor, but not primary tumor. This may occur because the assay kit has an antibody made from secondary tumor. An assay with antibodies to the antigen of primary CEA might possibly result in more specific detection of the primary tumor. Patients with elevated preoperative CEA levels are definitely at high risk to have secondary tumor and a more thorough intraoperative search for metastases is required.

The concept of a second-look procedure was introduced in 1951 by Wangensteen et al.[4] The initial hypothesis was that the factor that might influence most favorably the ultimate result of cancer surgery was the absence of cancer in all regional lymph nodes. Fear of having left behind residual cancer prompted a second operation, and reentry into the abdomen before the expiration of the 'silent' interval was proposed. Initially, Wangensteen reoperated upon patients with gastric, colon, and rectal cancer who he felt were at high risk of recurrence because of the extent of the primary tumor. The first report in 1951 suggested that the most favorable outcome occurred in patients with colon cancer. It was also pointed out that, at the time of the second-look, hepatic metastases presented a major challenge.

In 1954, Wangensteen and coauthors[12] updated their second-look experience from the University of Minnesota. A more systematic use of second or even several exploratory operations was reported in detail. Approximately 6 months after the initial excision and while the patients were still asymptomatic and had no clinical evidence of residual cancer, they were reoperated upon. If cancer was encountered at the second-look operation, it was excised, and subsequent exploratory operations called third or fourth looks were carried out at similar intervals until no more cancer was found. Once the patient had undergone a negative exploration, additional explorations were not recommended.

Selecting the most appropriate time for second look presents a challenge. By the time the second look is done, any residual local cancer should have grown large enough to be detected but still small enough so that it can be completely removed. Between 6 and 14 months were the intervals reported at which the patients still had resectable tumor. In spite of this, some unfortunate persons were found to have unresectable cancer, even though they were reexplored at 6 months. Variability in tumor growth rates existed then and continues to exist. The authors concluded that there was no reliable way to choose the best interval beween operations but suggested less than 6 months for patients with gastric cancer and approximately 8 months for those with colon cancer. False-negative explorations were feared, and it was common to have as many as 30 biopsy specimens from a single patient.

As early as 1954, it was reported that patients with cancer of the stomach or rectum declared free of cancer after a second operation subsequently had evidence of residual cancer. This was not true of those with colon cancer, and no residual cancer had become evident in those with negative second-looks. Therefore, the suggestion at this time

was that the best use of the second-look approach was in patients with colon cancer.

The Wangensteen series in 1954 reported 46 operations in 35 patients with cancer of the rectum: no cancer was found in 20; 13 remained alive; five were living with cancer; and two were dead of cancer. Of the 15 patients found to have cancer at second look, one was living 12 months after the last negative second look, 11 were dead of cancer, one died at operation, and one was alive with residual tumor awaiting a third look. Poor results were thought to be due to the anatomic restriction in the pelvic area and the inability to "clean out" the area adequately.

On the other hand, the 1954 report concerning colon cancer patients was more encouraging. Twenty-nine patients were reported to have undergone 45 operations. No cancer was found at second look in half (15), and all 15 were alive and well. Of the 14 who had a positive second, look, four were alive and free of tumor and six were dead from cancer. Three operative deaths occurred, and one was living with residual cancer. The report pointed out convincingly that a biologic marker would be helpful in decreasing negative second-look operations.

In 1969, Sosin and colleagues[27] reported the final results from the University of Minnesota of second-look procedures in both symptomatic and asymptomatic patients with cancer of the colon and rectum. Of 44 patients with rectal cancer undergoing second-look procedures, 24 were negative. Of these 24, seven developed recurrent cancer, seven had no evidence of disease, nine died of other causes, and there was one operative death. Of the 20 positive second looks, 16 developed recurrent tumor, one remained alive and well, and there were two operative deaths. The salvage rate for the group was clearly poor.

Results in a 98-patient intraabdominal colon cancer second-look group were more promising. Of 62 patients who underwent negative second-look procedures, 12 eventually developed recurrences, 10 died of causes other than cancer, two died at operation, and 41 remained alive and well. Of 36 with a positive second-look operation, 24 died of recurrent tumor, four were alive and well, two died of other causes without evidence of recurrent tumor, and six died at operation. The salvage rate in this group was reported as six of 36 (17%).

In a comparison of our data in 1985 with the Wangensteen experience, it becomes apparent that the result of second-look surgery remains better in those with colon cancer and poorer in those with cancer of the rectum. The biologic marker (CEA) has greatly improved the yield of positive abdominal reentries and has, for the most part, eliminated negative second-look procedures. In our experience, 139 of the 146 second-look procedures in asymptomatic patients were positive, compared to Wangensteen and Sosin's reports of 56 of 142 in 1969. Patient selection for further surgery was improved dramatically by the biologic marker. Better results were realized in those with colon cancer. Five-year survival in the 67 patients reoperated on through 1979 is 16, or 23.9% (Table 5).

TABLE 5. *Second-look Surgery Comparison*

| | Number |
|---|---|
| Wangensteen | |
| Negative | 62 |
| Positive | 36 |
| Salvage | 6 (6.2%) |
| O.S.U. | |
| Negative | 3 |
| Positive | 59 |
| Salvage | 16 (25.8%) |

Since there is considerable agreement that sequential CEA determinations will predict recurrence of colorectal cancer and a significant percentage of recurrences are hepatic, the surgeon performing a second-look operation must be prepared to deal with liver metastases. Major hepatic resection, regional infusion chemotherapy, and systemic chemotherapy are the choices to be considered. Fortner and co-workers[28] have reported that survival of patients with completely resected liver metastases not involving major ducts or vessels was 66% at 3 years. Fortner has reported that very high CEA levels do not contraindicate a second-look operation because resectable liver metastases frequently have values greater than 100 ng/ml. After resection, the CEA values returned to baseline in 89%. Very high values may take longer than a month to return to normal.

Wagner and Adson et al.[29] reevaluated patients undergoing liver resections for metastases of colorectal cancer and concluded that one-fourth of their patients with solitary or unilobar resectable lesions had prolonged survival after resection. A third report by Cady et al.[30] suggests that hepatic resection of metastatic colon cancer should be performed for patients with one, two and three lesions in one anatomic area, regardless of the size of the lesions.

Several reports have addressed the relative value of tests used in the follow-up of patients with colorectal cancer.[31,32] Sugarbaker et al.[33] indicated that the preoperative sequential management of plasma CEA levels yielded significant information about recurrence and that, when levels are rising, abdominal and pelvic CT scans are indicated. They compared laboratory studies and radiographic tests and concluded that the CEA assay was reliable in 71% and the CT scan in 67%. Staab et al.[34] reported a lead time between CEA elevation and the appearance of clinical symptoms of 4 and 5 months.

The use of the biologic marker CEA needs to be structured. The establishment of a postoperative baseline is required, and a good reporting system such as a computer print-out is helpful. If the CEA is elevated when the pri-

mary procedure is undertaken, the surgeon must search for occult metastases. The liver and periaortic nodes should be thoroughly examined and biopsy taken of any suspicious tissue. Most recurrences take place between 6 and 24 months after the primary operation, so this should be the period of closest CEA surveillance. Our experience and that of others suggests that a 1- to 2-month interval between CEA determinations during the first 2 years appears to be best, in order to establish precisely when the CEA starts to rise. To encounter the highest resectability and to improve the 5-year survival rate, the second operation should be undertaken before the CEA level exceeds 10 ng/ml.

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### Discussion

DR. BLAKE CADY (Boston, Massachusetts): I congratulate the authors on an interesting analysis of an attempt to pick up metastatic disease early by the use of carcinoembryonic antigen (CEA).

I had the opportunity in the past year to look at all of Dr. Wangensteen's follow-up papers. (Slide) It is interesting that during the time that Wangensteen had an asymptomatic second look program, he also had a series of patients that were symptomatic at the time of their exploration for metastatic disease, and it is interesting that the slide shows that the