CEA Monitoring Among Patients in Multi-institutional Adjuvant G.I. Therapy Protocols

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The Gastrointestinal Tumor Study Group (GITSG) has since 1975 included protocols for monitoring carcinoembryonic antigen (CEA) levels in its colorectal cancer adjuvant trials. Among the 563 patients on the colon cancer study (GI 6175) and the 207 patients on the rectal cancer study (GI 7175), one third had preoperative CEA determinations and more than 90% had some postoperative CEA monitoring. Colon cancer patients whose preoperative CEA was greater than 5 ng/ml had a greater probability of recurring than those whose values were lower (33% versus 18% recurrence with 21 months minimum follow-up; $p < 0.05$). The prognostic value of preoperative CEA was apparent only in patients with Dukes' C1 colon tumors. Preoperative CEA values were not of prognostic significance among the rectal adenocarcinoma patients. Although elevated levels of CEA after resection of either colon or rectum cancers were strongly associated with subsequent tumor recurrence, no single CEA value, arbitrarily defined as "elevated," provided an adequate screening test with both high sensitivity and high specificity. Postoperative CEA elevations were more strongly predictive of recurrence when part of a steadily rising trend. In the colon cancer study, the median monthly increase in CEA for disease-free patients was estimated to be zero, and for the relapsed patients 5.8%. The corresponding estimates for patients on the rectal cancer protocol were zero and 7.8%. Only 36 of the 344 disease-free patients on the colon protocol and 14 of the 94 disease-free patients on the rectal protocol (15%) exhibited a rate of increase of CEA as high as 3% per month over the entire period of observation. Two thirds of the relapsed patients on both studies showed a rate of increase this high or higher. The patterns of CEA rise in individual patients were quite varied, however, and monthly rates of increase as established in our study are not to be used as guidelines in patient management.

DESPITE MANY YEARS of investigation, the usefulness of carcinoembryonic antigen (CEA) monitoring in the clinical care of individual patients with colorectal adenocarcinoma is uncertain. Two questions remain to be answered: 1) how does CEA compare with conventional methods of diagnosing tumor recurrence (sensitivity and specificity, timing, and cost); and 2) if CEA can assist in the early identification of recurrence, is this knowledge useful to the clinician in increasing patient survival? Previous attempts to answer these questions have been based primarily on CEA data from individual institutions[1-3] that have found that CEA monitoring is either extraordinarily helpful[4] or completely unhelpful.[5]

In an attempt to study this issue with a large data base, the Gastrointestinal Tumor Study Group (GITSG) in 1975 included preoperative and serial postoperative CEA monitoring in the design of two multi-institutional* trials focused on the potential benefit of adjuvant therapies after clinically curative resection of Dukes B or C[6] colon or rectum cancers. Although the protocol for CEA monitoring in these studies was not designed to allow any evaluation of the effect of CEA monitoring on clinical decision-making or patient survival, the predictive value of preoperative and postoperative CEA monitoring and its limitations can be analyzed. The accuracy of CEA as a predictor of tumor recurrence in colon cancer patients as compared with rectal cancer patients has been investigated. The specificity and sensitivity of individual CEA values obtained from single plasma samples after surgery, as a screen for recurrent disease, have been determined and compared with the value of serial CEA changes in predicting tumor recurrence. Finally, the authors have speculated about the appropriate clinical application of this data to the management of individual patients with colorectal cancer.

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Materials and Methods

Description of Study Populations

Patients with Dukes' B2 or C colon or rectum cancers were accrued between 1975 and 1980 to two separate adjuvant therapy protocols. GITSG protocol 6175 was the study of the potential benefit of adjuvant therapy (chemotherapy, immunotherapy, both, and none) following clinically curative resection of Dukes' B2, C1, or C2 colon cancers. In this protocol, the Dukes' staging criteria was as follows: B2 patients had primary tumor that penetrated the serosa but no positive regional nodes; C1 patients had one to four positive nodes with or without serosal penetration; and C2 patients had five or more positive nodes with or without serosal penetration. Six hundred and twenty-one patients were randomized to this protocol, and 563 are currently fully eligible and evaluable for survival analyses. Median time since randomization is 46 months, and all surviving patients have been followed at least 21 months. GITSG protocol 7175 was designed to evaluate adjuvant therapy (chemotherapy, radiotherapy, both, and none) following curative resection of Dukes' B2, C1, or C2 rectal carcinoma. Two hundred and forty-five patients were entered into this study; 207 are now considered fully eligible and evaluable for survival analyses. Median time since randomization is 44 months, and all surviving patients have been followed at least 8 months. For both of these studies, interim evaluations of treatment effectiveness have been reported.[7,8]

Schedule and Method of CEA Determinations

The frequency of CEA determination as stipulated in the colon and rectum cancer protocols was identical. For patients on active treatment arms, CEAs were to be obtained before operation, one week after operation, and immediately before the first treatment (between 3 and 7 weeks after operation). CEA values during and after treatment were to be obtained monthly during the first 3 months, every 3 months for the remainder of the first year, and every six months from then on. Patients randomized to the control arm (surgery only) were to have CEA values obtained before operation, one week after operation, and at weeks 5, 10, 15, 25 after operation, and every 15 weeks thereafter. Actual compliance with the CEA schedule in these protocols was good. Approximately half of all patients had at least the number of CEA determinations stipulated in the protocol. Only about 15% of all patients had less than half of the required number of CEA determinations. The frequency of CEA monitoring was consistent among institutions, treatment groups, and tumor-staging categories. There was no association between frequency of CEA monitoring and recurrence.

All plasma CEA assays were performed at the individual institutions' laboratory using the modified Hansen Z-gel technique.[9] Interassay comparisons among the institutions and intra-assay analysis performed in the GITSG CEA reference laboratory at the Mallory Gastrointestinal Institute (Boston, Massachusetts) showed excellent reproducibility and acceptable deviation among the various laboratories.[10]

Evaluation of Patients for Recurrent Disease

Regardless of the treatment group selected, patients in both protocols were scheduled for regular clinic visits every 5 weeks during the first 6 months after surgery and every 15 weeks for the remainder of the first year. Physical examination, complete blood count, and liver function tests were performed at each visit. Liver/spleen scan, chest posterior–anterior, and lateral roentgenograms were obtained every 6 months. Sigmoidoscopic examination and large-bowel, contrast roentgenograms were performed every year. Histologic evidence of tumor was the fundamental criterion for recurrence. However, roentgenographic evidence was acceptable in cases of lung or bony metastases. In the rectal-cancer adjuvant study, liver metastases were also accepted on the basis of liver scan, and local recurrence was accepted on the basis of perineal pain occurring acutely after a pain-free interval.

Statistical Methods

The value of preoperative CEA levels to predict disease-free survival times was assessed using the Cox regression model.[11] Error rates associated with the use of single plasma sample postoperative CEA values as indicators of recurrent disease were calculated as follows:

$$\text{Sensitivity} = \frac{\text{Number of recurrent patients with elevated CEA}}{\text{Number of patients with recurrence}}$$

$$\text{Specificity} = \frac{\text{Number of disease-free patients with nonelevated CEA}}{\text{Number of patients disease-free}}$$

$$\text{False-negative rate} = \frac{\text{Number of recurrent patients with nonelevated CEA}}{\text{Number of patients with nonelevated CEA}}$$

$$\text{False-positive rate} = \frac{\text{Number of disease-free patients with elevated CEA}}{\text{Number of patients with elevated CEA}}$$

TABLE 1. *Preoperative CEA as Predictor of Recurrence*

Level of Preoperative CEA	GI 6175 (Colon) Total Patients	GI 6175 (Colon) Recurrences	GI 7175 (Rectal) Total Patients	GI 7175 (Rectal) Recurrences
All Patients	223	52 (23%)	93	34
CEA ≤5 ng/ml	137	25 (18%)	61	22 (36%)
CEA >5 ng/ml	86	27 (31%)	32	12 (38%)
Dukes B2 Patients	107	12 (11%)	37	9
CEA ≤5 ng/ml	68	7 (10%)	23	5 (22%)
CEA >5 ng/ml	39	5 (13%)	14	4 (29%)
Dukes C1 Patients	82	20 (24%)	41	18
CEA ≤5 ng/ml	51	7 (14%)	27	12 (44%)
CEA >5 ng/ml	31	13 (42%)	14	6 (43%)
Dukes C2 Patients	34	20 (59%)	15	7
CEA ≤5 ng/ml	18	11 (61%)	11	5 (45%)
CEA >5 ng/ml	16	9 (56%)	4	2 (50%)

The predictive value of serial postoperative CEA levels was studied using estimated slopes of linear regression of log (1 + CEA) against time from surgery for each patient with at least four postoperative CEA determinations before diagnosis of recurrent tumor. These slopes represent the percentage increase in CEA per unit time for a given patient. Cross-classifications of patients according to maximum level of CEA (above or below a given value) and disease status were evaluated with Pearson's chi square test, corrected for continuity.

Results

Prognostic Value of Preoperative CEA

Preoperative CEA values were reported for 223 (39%) of the 563 evaluable colon cancer patients and for 93 (45%) of the 207 rectal cancer patients. The median preoperative CEA for the 52 colon cancer patients who have recurred was 5.4 ng/ml, and for the 171 disease-free patients with preoperative CEA values available, 3.3 ng/ml. Application of the Cox regression model for censored data, using length of disease-free interval as the dependent variable, demonstrates that preoperative CEA levels have a significant inverse association with disease-free interval ($p = 0.03$). However, further investigation of the prognostic value of preoperative CEA within each Dukes' staging category showed that the level of preoperative CEA appeared unrelated to recurrence in patients who had no positive nodes (Dukes' B2) or in patients with more than four positive nodes (Dukes' C2). Preoperative CEA values were prognostic in patients whose primary tumors were classified as Dukes' C1 (by the GITSG criteria, having involvement of one to four positive nodes; $p < 0.02$). No association could be found between preoperative CEA levels and subsequent disease outcome among any of the patients with resected rectal cancers (Table 1).

Postoperative CEA Values and the Probability of Recurrence

Five hundred and forty-three colon cancer patients (96%) and 191 rectal cancer patients (92%) had at least one postoperative CEA value obtained. Few of these patients were found to have CEA values above 5ng/ml before beginning adjuvant treatment within the 3–7 weeks after curative resections of their colon and rectum cancer primaries. The authors assume that this confirms the clinical judgment of the surgeons that all gross disease was removed. This speculation is supported by the fact that those few colon cancer patients who did have CEAs greater than 5 ng/ml soon after the initial surgery had a significantly higher risk of recurrence ($p < 0.01$) than those whose CEA values remained lower than 5 ng/ml before initiation of adjuvant treatment (Table 2). Too few rectal cancer patients had elevated preadjuvant treatment CEAs to provide meaningful information about possible excess risk of recurrence.

In both the colon and rectum adjuvant studies, patients documented to have tumor recurrence were much more likely to have at least a single postoperative CEA elevation (preceding recurrence) than patients still free of disease. Thus, approximately two thirds of patients in both studies who had CEAs of greater than 10 ng/ml later recurred as compared with a recurrence rate of about 20% in patients whose CEA never exceeded 10 ng/ml. However, nearly half of all relapsed patients never had a CEA higher than 10 ng/ml. The error rates associated with four arbitrarily chosen levels of CEA as predictors of recurrence are given in Table 3 for colon cancer patients and Table 4 for rectal cancer pa-

TABLE 2. *Immediate Postoperative CEA as a Predictor of Recurrence*

Level of Pretreatment CEA	GI 6175 (Colon) Total Patients	GI 6175 (Colon) Recurrences	GI 7175 (Rectal) Total Patients	GI 7175 (Rectal) Recurrences
All Patients	423	113 (27%)	144	53 (37%)
CEA ≤5 ng/ml	359	85 (24%)	127	45 (35%)
CEA >5 ng/ml	64	28 (44%)	17	8 (47%)
Dukes B2 Patients	171	19 (11%)	49	12 (24%)
CEA ≤5 ng/ml	151	12 (8%)	43	11 (26%)
CEA >5 ng/ml	20	7 (35%)	6	1 (17%)
Dukes C1 Patients	181	55 (30%)	63	23 (37%)
CEA ≤5 ng/ml	147	41 (28%)	55	19 (35%)
CEA >5 ng/ml	34	14 (41%)	8	4 (50%)
Dukes C2 Patients	71	39 (55%)	32	18 (56%)
CEA ≤5 ng/ml	61	32 (53%)	29	15 (52%)
CEA >5 ng/ml	10	7 (70%)	3	3 (100%)

tients. Although the data in these tables demonstrate a strong association between elevated CEA levels and subsequent recurrence, the inverse relationship between sensitivity and specificity suggests that no arbitrarily chosen level of CEA elevation will provide a screening test able to predict tumor recurrence when applied to individual patient management.

Since follow-up is not complete on these patients, some of the "false-positives" may become "true-positives," and some of the "true-negatives" may become "false-negatives." This possibility is supported by the similarity that was observed in CEA patterns between patients with documented tumor recurrence and those with clinically suspected but not documented tumor recurrence. The classification of suspected tumor recurrence was based on detection of abdominal masses by physical examination, positive liver scan, or patients whose death was attributed to but not proven to be caused by tumor. When the error rates in Table 3 are recalculated with patients having suspected recurrence included among those with documented recurrence, the false-positive rates are reduced substantially. For example, the proportion of disease-free patients among those whose maximum CEA exceeded 10.0 ng/ml is reduced from 0.38 to 0.24, while the proportion of relapsed patients among those whose CEA never exceeded 10.0 ng/ml (the false-negatives) increased only slightly, from 0.17 to 0.19. Nevertheless, since almost 90% of patients still living have been followed for at least 2 years after their primary tumor surgery, we believe the rates as presented in Tables 3 and 4 may not change substantially.

Serial Postoperative CEA Values and the Probability of Tumor Recurrence

The relationship between tumor recurrence and the rate of postoperative CEA rise was examined in all patients with at least four postoperative CEA values after resection of their colon or rectum cancers. Four hundred and fifty-six patients in the colon cancer protocol (81%) and 141 patients in the rectal cancer protocol (64%) had such data available. Linear regression of log (1 + CEA) against time from surgery was performed for each patient. The slope of the regression line represents the percentage increase in CEA per 30-day interval. The time periods analyzed for each patient were those between curative surgery and documented recurrence

TABLE 3. *Measures of Accuracy of Various Postoperative Levels of CEA as Predictors of Recurrence: GI 6175 (colon)*

	Total Pts.	Recurrences	Sensitivity	Specificity	False + Rate	False − Rate
Total Patients with Postop CEA Monitoring	543	149	—	—	—	—
Maximum Postop CEA						
>2.5	405	134	.90	.31	.67	.04
>5.0	242	102	.68	.64	.58	.16
>10.0	128	80	.54	.88	.38	.17
>20.0	83	56	.38	.93	.33	.20

TABLE 4. *Measures of Accuracy of Various Postoperative Levels of CEA as Predictors of Recurrence: GI 7175 (rectal)*

	Total Pts.	Recurrences	Sensitivity	Specificity	False + Rate	False − Rate
Total Patients with at Least One Postop CEA	191	69	—	—	—	—
Maximum Postop CEA						
>2.5	126	54	.78	.41	.57	.23
>5.0	83	48	.70	.71	.42	.19
>10.0	51	37	.54	.77	.27	.23
>20.0	28	24	.35	.97	.14	.28

or the time of the last CEA determination, whichever was earlier.

The distribution of postoperative CEA slopes was different for relapsed patients as compared with patients still disease-free. The median monthly increase in CEA for disease-free patients was estimated to be zero, and for relapsed patients, 5.8%. The corresponding estimates for patients on the rectal-cancer protocol were zero and 7.8%. Only 36 of the 344 disease-free patients on the colon protocol (10%) and 14 of the 94 disease-free patients on the rectal protocol (15%) exhibited a rate of increase of CEA as high as 3% per month over their entire period of observation; approximately two thirds of the relapsed patients on both studies showed a rate of increase this high or higher. We considered the predictive value of CEA elevations in the context of whether a rising pattern of CEAs was observed for the patient. These data are given in Tables 5 and 6. It is apparent that a CEA elevation in and of itself was not strongly predictive of recurrence unless it was part of a steadily rising trend. It is also apparent that serially rising CEAs are strongly suggestive of recurrent disease even in the absence of any single values as high as 5 or 10 ng/ml. These results were true regardless of Dukes' stage of the primary tumors.

The slopes of postoperative CEA rise, estimated from our linear regression model, do not accurately quantitate the rate of increase in individual patients since the patterns of postoperative CEA change are quite varied. Monthly rates of increase as estimated from the authors' data are, therefore, not to be used as guidelines in patient management. They demonstrate only that a rising postoperative CEA may be more predictive of subsequent relapse than any arbitrarily defined abnormal CEA value assayed in a single serum sample.

There were differences in the degrees of serial postoperative CEA rise according to the first site of documented tumor recurrence. In the colon-cancer adjuvant protocol, liver recurrences were preceded by the most rapid serial postoperative CEA elevations. This was not

TABLE 5. *Postoperative CEA Elevations and Rates of Increase in CEA Levels as Indications of Recurrence: Colon Cancer Patients*

	Total Patients	Recurrences	Proportion Recurrent
Total patients with at least four postoperative CEA determinations	456	112	.25
Maximum CEA ≤ 5 ng/ml, monthly rise ≤ 3%	232	23	.10
Maximum CEA > 5 ng/ml, monthly rise ≤ 3%	117	18	.15
Maximum CEA ≤ 5 ng/ml, monthly rise > 3%	21	10	.48
Maximum CEA > 5 ng/ml, monthly rise > 3%	86	61	.71
Maximum CEA ≤ 10 ng/ml, montly rise ≤ 3%	319	33	.10
Maximum CEA > 10 ng/ml, monthly rise ≤ 3%	30	8	.27
Maximum CEA ≤ 10 ng/ml, monthly rise > 3%	34	18	.53
Maximum CEA > 10 ng/ml, monthly rise > 3%	73	53	.73

TABLE 6. *Postoperative CEA Elevations and Rates of Increase in CEA Levels as Indications of Recurrence: Rectal Cancer Patients*

	Total Patients	Recurrences	Proportion Recurrent
Total patients with at least four postoperative CEA determinations	141	47	.33
Maximum CEA ≤ 5 ng/ml, monthly rise ≤ 3%	61	8	.13
Maximum CEA > 5 ng/ml, monthly rise ≤ 3%	33	6	.18
Maximum CEA ≤ 5 ng/ml, monthly rise > 3%	12	4	.33
Maximum CEA > 5 ng/ml, monthly rise > 3%	35	29	.83
Maximum CEA ≤ 10 ng/ml, monthly rise ≤ 3%	82	10	.12
Maximum CEA > 10 ng/ml, monthly rise ≤ 3%	12	4	.33
Maximum CEA ≤ 10 ng/ml, monthly rise > 3%	16	7	.44
Maximum CEA > 10 ng/ml, monthly rise > 3%	31	26	.84

TABLE 7. *Levels of Postoperative CEA by Site of Recurrence: GI 6175 (colon)*

	No Recurrence	Local/ Regional	Liver	Other	Lungs	Single Other	Multiple Other	Site Unconfirmed
Total patients	394	29	37	8	18	38	14	5
No. patients with maximum postop CEA >10 ng/ml	48	8	28	3	9	20	10	—
Median "maximum postoperative CEA" (ng/ml)	3.8	4.2	21.0	8.3	9.1	10.6	42.3	—
Median monthly percentage increase in CEA	0%	3.5%	11.7%	9.2%	4.7%	7.0%	1.5%	—

true in the patients with rectal cancer recurrence. All patients with liver and multiple site recurrences tended to show the highest absolute CEA elevations (Tables 7 and 8).

Interval Between Postoperative CEA Elevations and Tumor Recurrence

The data from these protocols cannot pinpont the lead time between postoperative CEA elevation and documented recurrence. In several of the participating institutions, postoperative CEA elevations triggered immediate history and physical exams, the performance of conventional tests for recurrence before their protocol schedule, and in some cases, second-look surgery despite negatives on all conventional tests and lack of symptoms in the patients. Naturally, if recurrence were documented in such a setting, "lead time" would be shorter than if CEA elevations were ignored and protocol stipulated conventional tests for recurrence were performed on schedule. Nevertheless, our data do show that the higher the CEA level, the greater the proportion of patients recurring in the 200-day interval following that elevation. Tables 9 and 10 show the proportions of patients recurring and the time intervals to recurrence after each of three arbitrary levels of postoperative CEA elevation. Approximately half the patients on both studies whose CEA rose above a level of 20 ng/ml relapsed within 200 days of their first such elevation; only 21% of colon cancer patients and 36% of rectal cancer patients whose CEA never exceeded 5 ng/ml recurred within 200 days of the first elevation above 5 ng/ml.

Our data also show that the higher CEA levels in patients in whom recurrence was eventually documented tended to be concentrated in the 200-day interval before documentation of recurrence. The median CEA for relapsed colon cancer patients during this interval immediately preceding documented tumor recurrence was 8.0 ng/ml. The median level of all earlier postoperative CEA's for these patients was 2.2 ng/ml, quite comparable with the overall median postoperative CEA level of 1.9 ng/ml in the colon cancer patients remaining disease-free. A similar pattern was evident in the rectal cancer patients. The median CEA for relapsed rectal cancer patients in the 200-day interval immediately preceding documented recurrence was 5.6 ng/ml, compared with median levels of 2.0 ng/ml for relapsed patients more than 200 days before documented recurrence and 2.0 ng/ml for all disease-free rectal cancer patients.

Discussion

The design of these studies does not allow any answer to questions concerning the effect of CEA monitoring on clinical decision-making or patient survival. These

TABLE 8. *Levels of Postoperative CEA by Site of Recurrence: GI 7175 (rectal)*

	No Recurrence	Regional	Liver	Liver + Other	Lungs	Single Other	Multiple Other
Total patients	120	20	12	11	16	7	4
Maximum postop CEA >10 ng/ml	11	12	9	6	4	3	1
Median "maximum postoperative CEA"	3.0	15.0	29.8	12.0	4.0	7.6	5.8
Median monthly percentage increase in CEA	0%	15.2%	7.6%	13.6%	4.1%	7.6%	2.4%

TABLE 9. *Time to Recurrence After First CEA Elevation Above a Specified Value: GI 6175*

CEA Level Defined as "Elevated"	Total Patients with at Least One Elevation*	Recurrence within 200 Days of First Elevation	Later Recurrences	Patients Remaining Disease-Free
5 ng/ml	242	52 (21%)	50 (21%)	140 (58%)
10 ng/ml	128	53 (41%)	27 (21%)	48 (38%)
20 ng/ml	83	39 (47%)	17 (20%)	27 (33%)

* Total patients analyzed = 543.

data do, however, provide insight into the association between elevated CEA values and colorectal cancer.

In patients whose colon cancers were pathologically staged Dukes' C1, preoperative CEA values of greater than 5 ng/ml were associated with a statistically significant increased risk of recurrence compared with those patients whose preoperative values were lower. This prognostic benefit did not pertain to any of the other Dukes' grades of colon cancer or any of the rectal cancer patients. As with any result for a specific subgroup of a study population, this must be considered with caution because of an increased probability of finding one or more "statistically significant" differences when a large number of comparisons are made. These data are somewhat consistent with those from earlier single institution series reported by Wanebo et al.[12] and Goslin et al.[13] In the latter study, no prognostic significance in preoperative CEA values could be found among patients after curative resection of Dukes/Kirklin[14] B2 lesions, but preoperative CEA showed strong prognostic value for patients with Dukes/Kirklin C primary tumors. Of the Dukes/Kirklin C patients that could be stratified by preoperative CEA levels of 5 ng/ml, the majority fit the classification of Dukes C1 used in the GITSG pathologic criteria (resectable colon cancers extending through the entire thickness of the bowel wall with microscopic involvement of four or fewer mesenteric lymph nodes). However, the association of elevated preoperative CEA with recurrence was much stronger in the earlier series than in our Dukes C1 patients.

Postoperative CEA elevations in this multi-institutional study, whether analyzed as single plasma sample elevations or serial CEA rises, were associated with more frequent subsequent tumor recurrence. This association was found regardless of the Dukes' classification of either colon or rectum cancers. No effect on the association was found by differences in treatment success of the two adjuvant therapy protocols.

There are several ways in which significant bias could have entered into this analysis. Variation in the degree to which the study protocol was followed, especially the frequency of CEA determination, could have been influenced by factors related to the probability of recurrence. If patients with Dukes B2 colon cancers were monitored less frequently than those with Dukes C2 lesions, then the association of serial CEA elevations with tumor recurrence might simply reflect the association between Dukes' staging and recurrence. In addition, if the extent to which a patient was evaluated for recurrence by conventional tests was influenced by the patient's CEA value, results would favor an association between elevated CEA value and documented recurrence. The consistency found in the frequency of CEA monitoring among patient groups with differing Dukes' tumor staging and the protocol requirement of conventional diagnostic tests for all patients at least semiannually decrease the likelihood of these biases.

Patients who recurred without any preceding plasma CEA elevations above 5 ng/ml were investigated to determine if frequency of CEA monitoring or proportion of poorly differentiated primary tumors were different from relapsed patients whose tumor recurrences were preceded by CEA elevation. Forty-seven patients on the colon study and 21 patients on the rectal study (nearly one third of all relapsed patients) did not have CEA elevations above 5 ng/ml preceding documented recurrence. A slightly greater proportion of these pa-

TABLE 10. *Time to Recurrence After First CEA Elevation Above a Specified Value: GI 7175*

CEA Level Defined as "Elevated"	Total Patients with at Least One Elevation*	Recurrence within 200 Days of First Elevation	Later Recurrences	Patients Remaining Disease-Free
5 ng/ml	83	31 (.36)	17 (.19)	35 (.45)
10 ng/ml	51	25 (.49)	12 (.24)	14 (.27)
20 ng/ml	28	17 (.55)	7 (.30)	4 (.15)

* Total patients analyzed = 191.

tients had poorly differentiated primary tumors (7/21, 33%) on the rectal study and 7/47 (17%) on the colon study compared with overall rates of relapsed patients of 23% and 12% respectively. The frequency of CEA monitoring was approximately the same for patients who recurred without preceding CEA elevations and those patients with recurrent disease who had preceding CEA elevations. It seems clear, therefore, that despite other studies showing that CEA is an unreliable predictor of tumor recurrence in patients with largely undifferentiated primary tumors,[15] neither the degree of tumor differentiation nor variations in the frequency of CEA monitoring could account for many of the "false-negatives" in these two adjuvant studies.

In both the colon cancer and the rectum cancer adjuvant protocols, analysis of CEA data by associating a single plasma sample CEA "elevation" and subsequent risk for tumor recurrence again confirms the inadequacy of CEA as a screening test no matter if the marker is applied before or after "curative" resection of primary tumor. As expected, if the arbitrary CEA value defined as "elevated" is high enough, excellent specificity will be compromised by unacceptable sensitivity. Conversely, when the lower "abnormal" CEA values are chosen, sensitivity will improve but specificity becomes unacceptable.

Any potential clinical application of CEA data to individual patient decision-making will have to be based on serial postoperative CEA monitoring.[4,12,16] The data presented here strongly suggest that most CEA elevations that are truly associated with recurrent disease will occur in the context of a general rising trend of CEA values over time. Slope data defined retrospectively in this present analysis cannot be generalized to prospective clinical decision making. However, the indication that a clearly defined rise in CEA over time predicts subsequent recurrence more accurately than any level of elevation for a single CEA determination suggests new hypotheses to be tested. Logically, in any such subsequent protocol, the determination of potential beneficial effects on clinical decision making by prospective use of serial CEA rises would depend upon rigidly stipulated dignostic and therapeutic intervention in one group of patients who had CEA follow-up, and in another comparable group of patients who did not have CEA follow-up.

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