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Pre- and Postoperative Carcinoembryonic Antigen Determinations in Hepatic Resection for Colorectal Metastases

Predictive Value and Implications for Adjuvant Treatment Based on Multivariate Analysis

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Objective
The object of this study was to evaluate the prognostic significance of pre- and postoperative serum carcinoembryonic antigen (CEA) levels in the resectional treatment of colorectal hepatic metastases. The main question was whether postoperative CEA levels correlated with survival and the time to recurrence.

Summary Background Data
Despite numerous investigations on prognostic factors in colorectal cancer, only sparse data are available to estimate the patient's individual risk for tumor recurrence postoperatively. It is controversial whether preoperative CEA values are of prognostic significance, and after observing the kinetics of CEA decline, elevated CEA levels postoperatively were found to be an ominous sign. CEA therefore could indicate the presence of a tumor burden after resection.

Methods
One hundred sixty-six patients undergoing hepatic resection for colorectal metastases with curative intent were prospectively documented and underwent multivariate analysis for indicators of prognosis.

Results
Abnormal preoperative CEA levels were not of prognostic significance compared with values within the normal range (survival, 36 *vs.* 30 months; $p = 0.12$; disease-free survival, 12 *vs.* 10 months; $p = 0.82$). The postoperative serum CEA level, however, was the most predictive factor with regard to survival and the disease-free interval. Patients in whom CEA levels were abnormal before surgery and returned into the normal range after resection had significantly better survival times (37 *vs.* 23 months, $p = 0.0001$) and disease-free survival times (12 *vs.* 6.2 months, $p = 0.0001$) compared with patients with persistently abnormal values.

Conclusions

Pre- and postoperative determination of the serum CEA level is mandatory to judge whether a curative resection has been performed and whether tumor has been left behind after the operation. Postoperative CEA levels also should be used as a stratification criterion in adjuvant treatment studies after hepatic resection to indicate patients with a high risk of tumor recurrence.

In patients with hepatic metastases of colorectal cancer, resectional treatment offers the only chance for long-term survival.[1] Neither systemic nor regional chemotherapy was proved to be as effective as a hepatic resection with regard to the disease-free survival time. Several prognostic factors have been established that facilitate the decision about whether to perform a resection in a patient or not. After surgery, some patients have long-term disease-free survival, but the majority of them have recurrent tumors within the first 2 years after the resection.[2–5] However, only sparse data are available to estimate the patients' risks for tumor recurrence and to allot them to adjunctive treatment modalities.

Carcinoembryonic antigen (CEA) was reported many times to be an indicator of tumor recurrence, both locoregional and metastatic in colorectal cancer. Furthermore, it may serve to monitor the response to treatment in patients undergoing regional or systemic chemotherapy, not only in colorectal, but also in lung and breast cancer.[6,7] Several studies used the course of CEA levels as a response criterion.[8,9]

In the treatment of primary colorectal cancer, a positive correlation between tumor stage and the proportion of patients with abnormal CEA values before and after surgery was proved.[10,11] In addition, the CEA value showed the highest predictive value for tumor recurrence.[10] In patients who undergo hepatic resection for colorectal metastases, it is still controversial whether preoperative serum CEA levels are of prognostic value in regard to resectability.[12–16] In a limited number of patients, the kinetics of CEA decline were determined after surgery,[16–18] and it was concluded that "elevated CEA levels postoperatively seem to be a prognostic ominous sign."[4]

It was the purpose of this study to evaluate the prognostic significance of pre- and postoperative serum CEA levels. We used data prospectively documented in 166 patients undergoing hepatic resection for colorectal metastases to answer the following questions. Can elevated CEA serum levels before surgery serve as a prognostic criterion in comparison with patients with normal CEA levels? Are CEA levels before and after surgery of prognostic significance in multivariate analysis? Do postoperative CEA levels correlate with the the time to tumor recurrence and the median survival rate?

PATIENTS AND METHODS

Patients

From October 1, 1981 to September 30, 1991, we performed hepatic resections in 99 (59%) men and 67 (41%) women. Their median age was 59 years (range, 30 to 79 years). In all of them, the primary tumor had been resected for cure.

The indication for resection of hepatic metastases was made if the patient fulfilled the following criteria: (1) the metastases seemed to be restricted to one hepatic lobe (maximum number, three) and were estimated to be amenable to surgical resection and (2) there were no signs of extrahepatic disease in preoperative diagnostic procedures (x-ray of the chest, abdominal ultrasonography, bone scintiscan, computed tomography (CT) of the abdomen, and CT scan of the pelvis in the case of primary cancer of the rectum). Surgery was done in another three patients with solitary lung metastases scheduled for subsequent lung resection; these patients were excluded from the analysis.

At laparotomy, the percentage of liver replacement (PLR) by the tumor was estimated and documented by bimanual palpation and intraoperative ultrasonography. Twenty-three patients had metastases invading to adjacent organs. Of them, the tumors in 14 patients could be resected with no evidence of residual disease (R0 resection, no macroscopic tumor, and negative resection margins). Nine patients underwent resection with positive margins and were excluded from this analysis; the details were published elsewhere.[19] Three patients had discontinuous intra-abdominal spread. Two of them had lymph node metastases at the hepatoduodenal ligament, and one patient had a locoregional recurrence after anterior resection. They all underwent radiotherapy after surgery and were omitted from the study. Another five patients with metastases confined to the liver also were excluded from analysis because of positive resection margins. Six patients died after the operation; one of them had positive resection margins (operative mortality rate, 3.6%). Thus, the study group consisted of 141 pa-

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Table 1. PATIENT SELECTION (EXCLUSION) CRITERIA FOR THE STUDY

	Number
No. of patients who underwent liver resection	166
Resection specimen margins positive	14
Metastases confined to the liver	5/140
Metastases invading to adjacent organs (one postoperative death)	9/23
Discontinuous extrahepatic tumor treated by additional radiotherapy	3
Postoperative mortality	6
Synchronous lung metastases	3
Study group/R0-resection*	141

* No residual tumor macroscopically and according to the pathologist report.

tients who underwent hepatic resection with no evidence of residual tumor (Table 1).

CEA Determinations

Serum CEA levels were determined before and after surgery. Blood samples were obtained within 1 week before the operation and at the end of the first postoperative week. We used a commercially available enzyme-linked immunosorbent assay (Abbott, Wiesbaden, Germany). The interassay variance was between 3.2% and 8.8% in the linear range of the assay between 1 and 90 ng/mL of CEA. CEA values greater than 5 ng/mL were considered abnormal.

In the case of abnormal postoperative values, further blood samples were taken at 1- to 2-week intervals, and the minimum CEA value underwent statistical analysis. In four patients, no postoperative CEA values were obtained. The median postoperative in-hospital stay of the patients was 12 days (range, 6 to 73 days).

All data on patients and CEA values were prospectively documented and recorded on the main-frame computer of the German Cancer Research Center.

Follow-Up

The patients were followed every 3 months during the first 2 postoperative years. The checkup consisted of a physical examination, chest x-ray study, ultrasonography of the liver and abdomen, and a determination of the CEA level. After the first 2 years, 6-month intervals for follow-up were used up to postoperative year 5, and thereafter, yearly checkups were performed. All patients were followed for at least 1 year. The median follow-up time was 47 months (range, 12 to 108 months). By September 30, 1992, it was known whether the patients were alive and were with or without evidence of disease (all patients). The date of death was known in all 89 patients (61%) who died. The cause of death was tumor dependent in 85 patients, not related to the tumor in 2, and unknown in another 2 patients.

Statistical Analysis

Survival rates were estimated according to the method of Kaplan and Meier.[20] To calculate significant differences between subgroups by univariate analysis, we used the log-rank test.[21] By multivariate regression analysis (Cox proportional-hazards testing[22]), we assessed the independent prognostic significance of different factors. The following factors that possibly influence survival underwent analysis: (1) location (colon *vs.* rectum), (2) the Dukes' stage of the primary tumor (Astler-Coller modification), (3) tumor differentiation (grading), (4) synchronous *versus* metachronous metastases, (5) the time interval from the primary to metastases in metachronous disease, (6) PLR (classified as up to 25%, 25% to 50%, and more than 50%), (7) unilobar or bilobar disease, (8) the number of metastases resected (single, two to three, and four and more), (9) the patient's sex, (10) the patient's age (younger than 40, 41 to 50, 51 to 60, 61 to 70, and older than 71 years), (11) preoperative CEA levels (less or more than 5 ng/mL), and (12) postoperative CEA levels (less or more than 5 ng/mL). Cox regression analysis was performed twice with survival and disease-free survival as dependent variables. All statistical evaluations were done by use of the SAS package (SAS Institute, Cary, NC).

RESULTS

Survival After Hepatic Resection

The median survival rate of our patients was 30 months (range, 3 to 108 months), including the operative mortality rate of 3.6%, and was 34 months without calculating postoperative deaths. Tumor recurrence was detected in 104 patients (71%), and the median recurrence-free time interval was 11.6 months (range, 2 to 104+ months).

Survival Rate Distribution for Different Strata

Univariate analysis revealed the postoperative CEA level ($p = 0.002$), time interval from the primary tumor to hepatic metastases ($p = 0.016$), PLR ($p = 0.019$), patient's sex (men in favor of women, $p = 0.031$), and patient's age ($p = 0.047$) as significant prognostic factors

Table 2. RESULTS OF MULTIVARIATE ANALYSIS FOR PROGNOSTIC FACTORS

Variable	Beta	p value	z:ph Ratio
Dependent variable survival			
Postoperative CEA	1.311	0.0002	1.46
Sex	0.802	0.0032	2.02
PLR	0.47	0.029	0.71
Time interval to primary tumor	0.019	0.047	0.22
Dependent variable disease-free survival			
Postoperative CEA	1.433	0.0000	1.71
No. of metastases resected	0.274	0.013	1.92
Synchronous *vs.* metachronous mets	0.057	0.034	0.65

for survival. All other factors did not reach the p = 0.05 level.

In regard to the recurrence-free survival, again, the postoperative CEA level resulted in the highest p value (0.00006); furthermore, the nodal status of the primary tumor (p = 0.0004), unilobar *versus* bilobar disease (p = 0.006), the time interval from the primary tumor to hepatic metastases (p = 0.008), and synchronous *versus* metachronous disease (p = 0.018) were statistically significant factors.

Multivariate Analysis of Independent Prognostic Factors

Multivariate analysis detected only four independent prognostic factors that influenced survival (the postoperative serum CEA level, patient's sex, PLR, and time interval to the primary tumor). Only three independent criteria that influenced disease-free survival were found (the postoperative serum CEA level, number of metastases resected, and synchronous *vs.* metachronous disease; Table 2). The postoperative serum CEA level was the one with the highest beta and p value in both analyses. All other factors did not significantly contribute to prognosis.

Preoperative CEA Examinations (Table 3)

The individual CEA values ranged between 1 and 4053 ng/mL (mean, 135.7 ng/mL; confidence interval, 95%, 48.8 to 469.7 ng/mL; median, 16 ng/mL). Neither univariate nor Cox regression analysis detected preoperative CEA levels as a prognostic factor for survival or disease-free survival. There was no significant difference with regard to the different amounts of elevated CEA. Patients who had "negative" CEA levels (range, 0 to 2 ng/mL) had a median survival of 37 months; patients with CEA levels from 3 to 5 ng/mL had a survival time of 35 months; and the survival of patients who presented with CEA levels of 6 to 20 ng/mL was 29 months. Those with a CEA concentration between 21 and 50 ng/mL had a survival of 32 months, and patients with CEA values exceeding 50 ng/mL had a 25-month median survival (p = 0.12, Fig. 1).

Table 3. MEDIAN SURVIVAL AND DISEASE-FREE SURVIVAL RATES AFTER HEPATIC RESECTION DEPENDENT ON PRE- AND POSTOPERATIVE CEA VALUES

	No. of Patients	Survival	Disease-Free Survival
CEA Preoperative			
0–2 ng/mL	20 (14.2%)	37 mo	11 mo
3–5 ng/mL	17 (12.1%)	35 mo	7 mo
6–20 ng/mL	44 (31.2%)	29 mo	13 mo
21–50 ng/mL	23 (16.3%)	32 mo	12 mo
> 50 ng/mL	37 (26.2%)	25 mo	6 mo
		p = 0.12	p = 0.14
0–5 ng/mL	37 (26.2%)	36 mo	12 mo
> 5 ng/mL	104 (75.8%)	30 mo	10 mo
		p = 0.21	p = 0.82
CEA Postoperative			
0–2 ng/mL	73 (53.3%)	37 mo	15.5 mo
3–5 ng/mL	32 (23.4%)	34 mo	10.2 mo
6–20 ng/mL	18 (13.1%)	29 mo	7 mo
21–50 ng/mL	7 (5.1%)	25 mo	4 mo
> 50 ng/mL	7 (5.1%)	14 mo	5 mo
		p = 0.0007	p = 0.0001
0–5 ng/mL	105 (77.7%)	37 mo	12 mo
> 5 ng/mL	32 (22.3%)	23 mo	6.2 mo
		p = 0.0001	p = 0.0001

Predictive Value of Postoperative CEA Values (Table 3)

After surgery, the individual CEA values ranged between 1 and 236 ng/mL (mean, 9.1 ng/mL; confidence interval, 95%, 3.5 to 13.2 ng/mL; median, 3 ng/mL).

By contrast with preoperative determinations, it was obvious that the normal postoperative CEA values were correlated with better survival rates and higher median time lapses to recurrence. One patient only with an elevated postoperative CEA had a disease-free interval of more than 15 months (median, 6.2 months). By contrast, the median time to recurrence was 15.5 months in patients with postoperative CEA levels of 0 to 2 ng/mL and 10 months in patients with CEA levels of 3 to 5 ng/mL (p = 0.0001). None of the patients with abnormal postoperative CEA levels survived for more than 35 months (Fig. 2). At that time, 17 patients (32.8%) in the group with normal postoperative CEA values were alive.

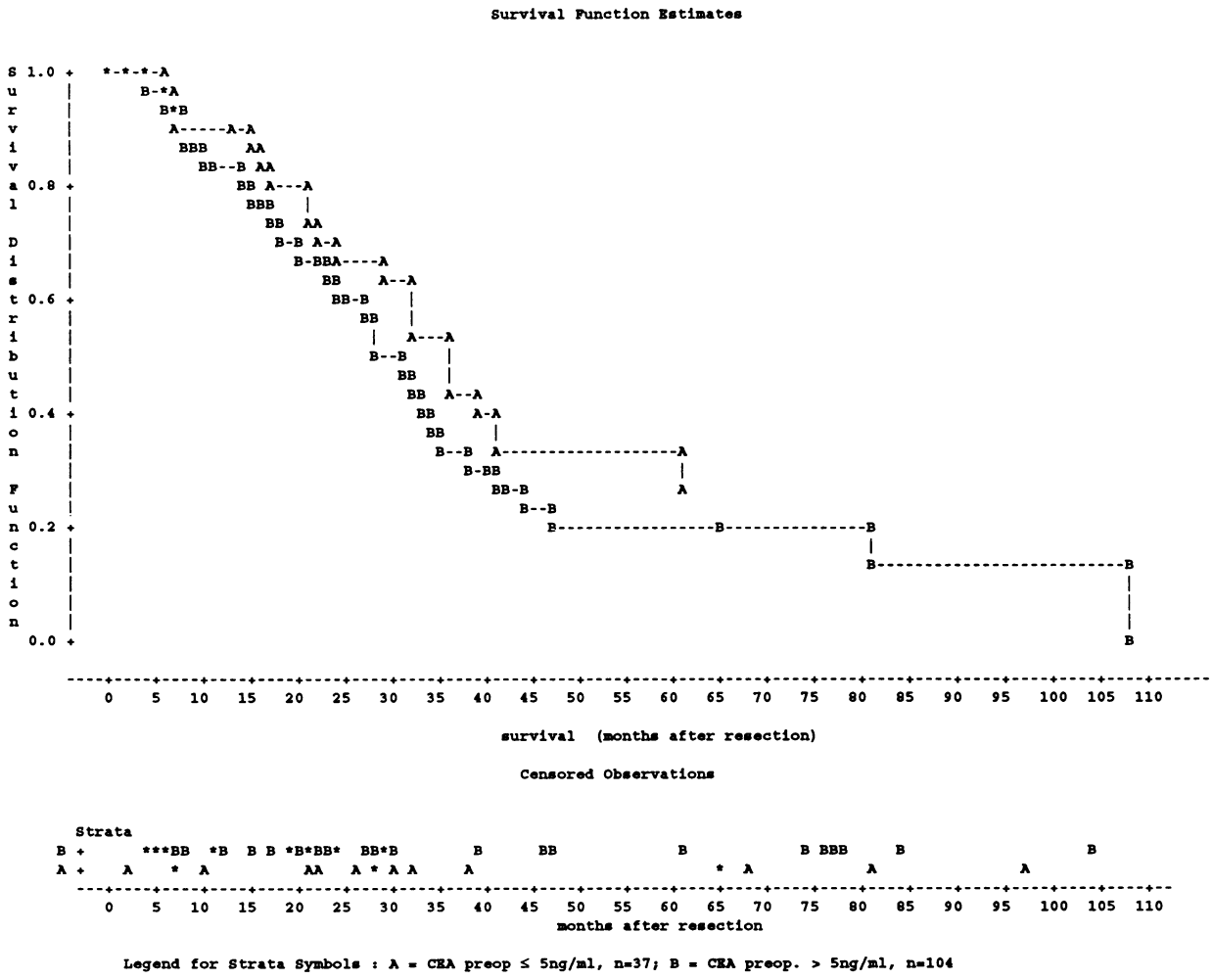

Figure 1. Survival after hepatic resection, according to preoperative CEA values. A, preoperative CEA levels up to 5 ng/mL; B, preoperative CEA more than 5 ng/mL. The censored observations are listed (p = 0.21, by log-rank test).

CEA Decline After Surgery and Predictive Value (Table 4)

Of 104 patients with preoperative abnormal serum CEA levels, in 68 patients, the CEA level after surgery returned to normal. Their median survival rate and disease-free interval was significantly better (p = 0.0002 and 0.0001, respectively) than those of patients whose CEA values remained elevated (Figs. 2 and 3).

In an attempt to evaluate whether the extent of the decrease in the CEA level after surgery was of prognostic importance, the postoperative CEA levels were divided by the preoperative ones, resulting in a per cent CEA decrease. Hence, 14 patients had a more than 97% decrease, and this was followed by a 17-month survival rate. In 26 patients, a drop in the CEA level of 90% to 97% was followed by a 32-month median survival. Twenty-nine patients had a decline of CEA of 75% to 90% and a median survival of 40 months; 30 patients had a decrease of CEA of 75% or less, and their survival rate was 24 months. These differences were statistically not significant (p = 0.17, by the Wilcoxon test; p = 0.14, by the log-rank test).

DISCUSSION

Serial determinations of CEA are used to assess treatment effects in different tumors. It is accepted that the production and excretion of CEA by tumor cells is a linear function of cell number, and CEA can be used to calculate the doubling time of tumors and to define a semiquantitative relationship between CEA levels and the tumor volume.[23] Recently, monitoring of CEA was used to assess whether a complete destruction had been reached by cryosurgical treatment of hepatic metastases.[24] All investigators assume that posttreatment elevated CEA values indicate residual tumor.

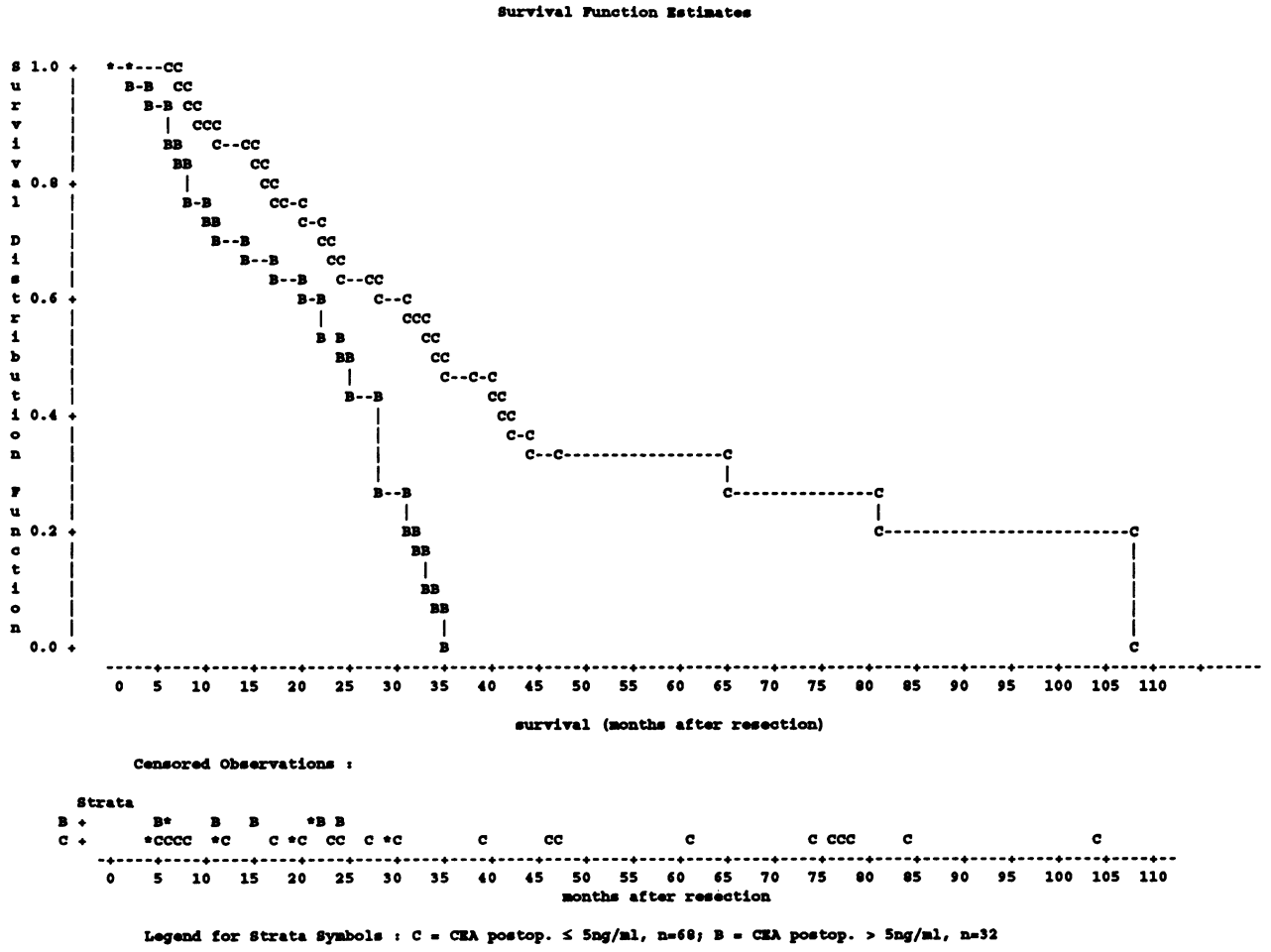

Figure 2. Survival after hepatic resection, according to postoperative CEA values in patients with preoperative abnormal levels. C, postoperative CEA levels up to 5 ng/mL; B, postoperative CEA levels more than 5 ng/mL. The censored observations are listed (p = 0.0002, by log-rank test).

In colorectal hepatic metastases, most authors found the majority of patients had elevated CEA levels before surgery.[10,12,16,18,25] Among our patients, 73.7% had an abnormal preoperative CEA level. It is controversial whether there is a cutoff level of CEA that indicates nonresectable metastases.[12,16,26] Decision rules using cutoff values in symptomatic patients to predict tumor recurrence were found inadequate for asymptomatic patients.[26] By contrast, slope analysis was found to be helpful to discriminate patients with recurrence.[27] Recently, simplified plans, using CEA as a monitoring tool during the follow-up of patients, were proposed[28] and have been accepted as the basis for the indication to perform a hepatic resection.[16] Consequently, postoperative CEA values should indicate residual tumor.

Preliminary analysis of CEA values indicated that patients cured by hepatic resection may be distinguishable from those with a high probability of residual disease and subsequent high risk for tumor recurrence.[4,29] To investigate this in a larger number of patients was the aim of our study.

The median survival time of our patients and their disease-free interval after surgery were in the same ranges as those reported by other authors.[2–4,14,18,30] Also, the prognostic factors found in our univariate analysis were similar to those in other studies.[1,14,30]

Preoperative values of CEA were not significantly correlated with survival or disease-free survival in our patients. Several other authors who investigated this question also reported no prognostic significance.[12–14,16] Younes et al.[15] divided CEA values into less than 5 ng/mL, less than 50 ng/mL, and more than 50 ng/mL and performed both univariate and multivariate analyses. Besides the number of hypotensive episodes, the number of metastases resected, and the site of the primary tumor, the preoperative CEA level was part of an equation used to predict the relative risk of recurrence after hepatic resection. In another series, CEA also was called an important factor for survival, but no statistical analysis was given.[31]

Although the preoperative CEA value, when elevated,

Table 4. MEDIAN AND DISEASE-FREE SURVIVAL DEPENDING ON COMPARISON OF PRE- AND POSTOPERATIVE CEA VALUES

	No. of Patients	Survival	Disease-Free Survival
CEA preoperative			
Normal	37	36 mo	9 mo
CEA preoperatively abnormal			
Postoperatively normal	68	37 mo	14 mo
Postoperatively abnormal	32	23 mo	6.2 mo
		p = 0.0002	p = 0.0001
CEA-Decrease postoperatively			
> 97%	14	17 mo	9 mo
90%–97%	26	32 mo	6 mo
75%–90%	29	40 mo	13 mo
<75%	30	24 mo	8 mo
		p = 0.13	p = 0.14

seems to be of limited prognostic significance, the median survival of our patients with normal preoperative CEA values was not significantly different from that of patients whose CEA values returned to normal after hepatic resection. Similarly, in patients undergoing second-look procedures because of rising CEA levels, the survival rate was best in patients with CEA values less than 10 ng/mL.[25] This may be the result of two factors. First, a minimal tumor burden was detected and removed during surgery. Second, in addition to treatment effects, inherent biologic variables may be reflected by CEA serum values. The capacity of human cell lines to grow and to form metastases when injected into the spleens of nude mice was reported to be associated with CEA production.[32] The cell lines that secreted the highest amounts of CEA produced the highest tumorigenicity. Cell lines that secreted no detectable CEA produced neither splenic tumors nor hepatic colonies.

In colorectal primary tumors, postoperative CEA levels predicted recurrence and survival, independent of tumor stage.[10] In a multivariate analysis, this was the most predictive factor (postoperative CEA level, $p = 0.0001$; preoperative CEA level, $p = 0.01$). The authors concluded that postoperative CEA levels can indicate patients who may benefit from adjuvant treatment. However, as in our series, the CEA level at recurrence was not predictive of postrecurrence survival.

Fortner et al.[11] reported that 84% of their patients who underwent hepatic resection had elevated CEA levels at the time of the diagnosis of hepatic metastases. In 89% of these patients in whom CEA was measured after surgery, the value returned to normal, and the higher levels required longer returns to normal—up to 14 weeks postsurgery. Later,[4] there was evidence that a persistent elevation in CEA levels after hepatic resection indicated a residual tumor. Consequently, these patients were attributed to the least favorable postresectional stage of disease. In 63% of these patients, cancer was found at the reexploration.

Steele et al.,[16] in a multi-institutional trial, found preoperative CEA values to be a poor predictor of resectability. Also, patients who had undergone noncurative resections or had unresectable lesions showed a significant increase in postoperative CEA levels. Their median CEA value 61 to 180 days postsurgery was significantly higher than the median value observed in the curatively resected group, thus indicating residual tumor.

Before this, Steele et al.[29] analyzed patients with recurrence after hepatic resection. Serial plasma CEA kinetics indicated that cured patients may be distinguishable from those with a high probability of minimal residual disease, but the numbers were too small to draw definite conclusions. Curative resection of hepatic metastases leads to an increase in median survival; noncurative resection provides a limited benefit to patients.[16] Our data indicate that, in cases of persistently elevated CEA values, the resection of hepatic metastases was not curative. Under these circumstances, the resection cannot be classified R0, according to the terms of the International Union Against Cancer. These patients should undergo additional treatment.

Hepatic clearance of CEA may be a pitfall when reduced decomposition occurs because of restricted hepatic function.[33] After metastasectomy a two-phase decrement of CEA decrease was reported.[17,18] In a first phase, up to 89% of CEA is removed from the circulation within a few hours. However, in individual patients, the CEA half-life was measured and ranged from 0.8 to 25 days. After the resection of major parts of normal hepatic tissue (trisegmentectomy), this has to be taken into consideration. In two of our patients, after an extended right hepatectomy (segments 4 to 8, according to Couinaud[34]), minimal CEA values were obtained 16 and 23 days after surgery.

Thus, a determination of serum CEA levels before surgery in patients with hepatic metastases is a must. It provides the basis for a postoperative judgment whether the resection performed was curative or not. Within prospective studies of adjuvant treatment, the postoperative CEA levels should be used as a criterion for stratification. This factor may be of equal significance with the pathologist's report. For further studies of adjunctive treatment in patients after resections of colorectal hepatic metastases, those with elevated CEA levels should no longer considered as being in an adjuvant situation of treatment. Elevated CEA levels indicate residual and measurable

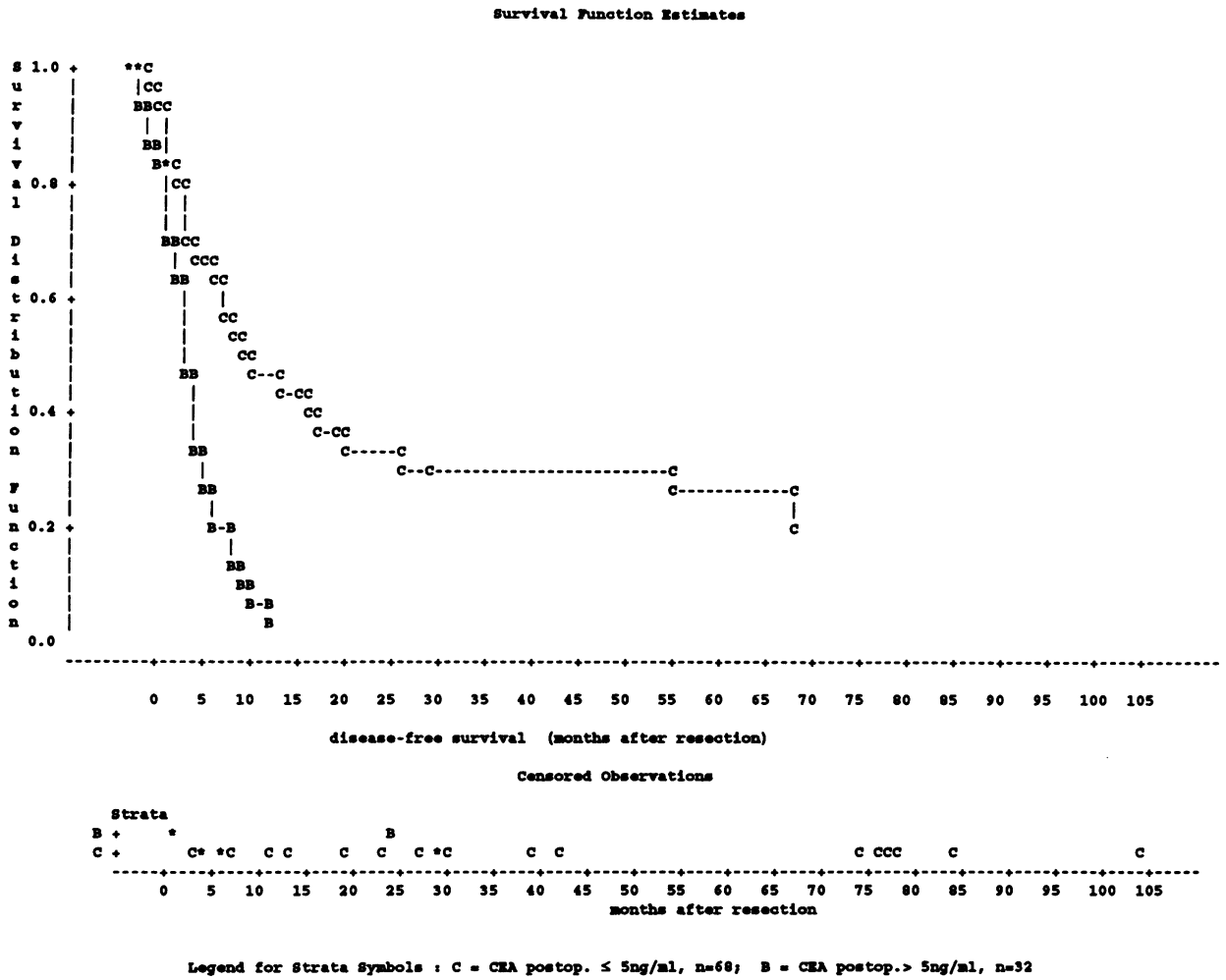

Figure 3. Disease-free survival after hepatic liver resection, according to postoperative CEA values in patients with preoperative abnormal CEA levels. C, postoperative CEA level up to 5 ng/mL; B, postoperative CEA level more than 5 ng/mL. The censored observations are listed (p = 0.0001, by log-rank test).

disease.[29] Further treatment studies should be designed to include the group of patients with a high risk for tumor recurrence (persistent elevation of CEA) and those with a low risk (CEA returned to normal).

The significance of postoperative CEA determinations resembles the situation in medullary thyroid carcinoma in which serum pentagastrin-stimulated calcitonin is a sensitive indicator of residual disease.[35] For prostatic cancer, prostate-specific antigen (PSA) levels also are of undoubted value because "a detectable postoperative serum PSA value after radical prostatectomy almost uniformly implies persistence of tumor, and small amounts of residual prostatic tissue may been left behind."[36]

The cost effectiveness of CEA determinations does not only include CEA determinations but also other evaluation tests prompted by abnormal CEA values.[37] In terms of adjuvant treatment after hepatic resection, the costs might arise because of chemo- or immunotherapy. Perioperative CEA determinations allow us to assign only those patients to the adjunctive treatment arm who have indications that are highly suspicious for residual disease. This may help to select the right candidates for treatment and save costs.

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References

1. Hughes KS, Rosenstein R, Simon R, et al. Resection of the liver for colorectal carcinoma metastases—a multiinstitutional study of long-term survivors. Dis Colon Rectum 1988; 31:1–4.
2. Bozzetti F, Bignami P, Morabito A, et al. Patterns of failure following surgical resection of colorectal liver metastases: rationale for a multimodal approach. Ann Surg 1987; 205:264–269.

3. Ekberg H, Tranberg KG, Andersson R, et al. Pattern of recurrence in liver resection for colorectal secondaries. World J Surg 1987; 11: 541–547.
4. Fortner JG. Recurrence of colorectal cancer after hepatic resection. Am J Surg 1988; 155:378–382.
5. Hohenberger P, Schlag P, Schwarz V, Herfarth C. Tumour recurrence following liver resection for colorectal metastases—implications and results of further treatment. J Surg Oncol 1990; 44:245–251.
6. Shinkai T, Saijo N, Tominaga K, et al. Serial plasma carcinoembryonic antigen measurements for monitoring patients with advanced lung cancer during chemotherapy. Cancer 1986; 57:1318–1323.
7. Kiang DT, Greenberg LJ, Kennedy BJ. Tumor marker kinetics in breast cancer. Cancer 1990; 65:193–199.
8. Balch C, Urist MM, Soong S, McGregor M. A prospective phase II clinical trial of continuous FUDR regional chemotherapy for colorectal metastases to the liver using a totally implantable drug infusion pump. Ann Surg 1983; 198:567.
9. Quentmeier A, Schlag P, Hohenberger P, et al. Assessment of serial CEA determinations in monitoring therapeutic progress and prognosis of metastatic liver disease treated by regional chemotherapy. J Surg Oncol 1989; 40:112–118.
10. Chu DZ, Erickson CA, Russell MP, et al. Prognostic significance of carcinoembryonic antigen in colorectal carcinoma. Serum levels before and after resection and before recurrence. Arch Surg 1991; 126:314–316.
11. Fortner JG, Silva JS, Golbey R, et al. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. Ann Surg 1984; 199:3096–3106.
12. Moertel CG, O'Fallon JR, Go VLW, et al. The preoperative carcinoembryonic antigen test in the diagnosis, staging, and prognosis of colorectal cancer. Cancer 1986; 58:603–610.
13. August DA, Sugarbaker PH, Ottow RT. Hepatic resection of colorectal metastases. Ann Surg 1985; 201:210–218.
14. Doci R, Gennari L, Bignami P, et al. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. Br J Surg 1991; 78:797–801.
15. Younes RN, Rogatko A, Brennan MF. The influence of intraoperative hypotension and perioperative blood transfusion on disease-free survival in patients with complete resection of colorectal liver metastases. Ann Surg 1991; 214:107–113.
16. Steele G, Bladey R, Mayer R, et al. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group protocol 6584. J Clin Oncol 1991; 9:1105–1112.
17. Lokich J, Ellenberg S, Gerson B, et al. Plasma clearance of carcinoembryonic antigen following hepatic metastasectomy. J Clin Oncol 1984; 2:462–465.
18. Kortz WJ, Myers WC, Hanks JB, et al. Hepatic resection for metastatic cancer. Ann Surg 1984; 199:182–184.
19. Hohenberger P, Schlag P, Herfarth Ch.. Extended liver resection for colorectal metastases infiltrating to adjacent organs. Langenbecks Arch Chir 1993; 378:109–114.
20. Kaplan L, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1985; 53:457–481.
21. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163–170.
22. Cox DR. Regression models and life table. J Stat Soc 1972; 34: 187–220.
23. Bronstein BR, Steele G Jr, Ensminger W, et al. The use of limitations of serial plasma CEA levels as a monitor of changing metastatic liver tumor volume in patients receiving chemotherapy. Cancer 1980, 46:266–272.
24. Onik G, Rubinsky B, Zemel R, et al. Ultrasound-guided hepatic cryosurgery in the treatment of metastatic colon carcinoma. Cancer 1991; 67:901–907.
25. Wanebo HJ, Llaneras M, Martin T, Kaiser D. Prospective monitoring trial for carcinoma of colon and rectum after surgical resection. Surg Gynecol Obstet 1989; 169:479–487.
26. Denstman F, Rosen L, Khubchandani IT, et al. Comparing predictive decision rules in postoperative CEA monitoring. Cancer 1968; 58:2089–2095.
27. Boey J, Cheung HC, Lai CK, Wong J. A prospective evaluation of serum carcinoembryonic antigen (CEA) levels in the management of colorectal carcinoma. World J Surg 1984; 8:279–286.
28. Sugarbaker PH, Gianola FJ, Dwyer A, Neuman NR. A simplified plan for follow-up of patients with colon and rectal cancer supported by prospective studies of laboratory and radiologic test results. Surgery 1987; 102:79–87.
29. Steele G, Osteen RT, Wilson RE. Patterns of failure after surgical cure of large liver tumours. Am J Surg 1984; 147:554–559.
30. Scheele J, Stangl R, Altendorf-Hoffmann A. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 1991; 110:13–29.
31. Sugarbaker PH. Surgical decision making for large bowel cancer metastatic to the liver. Radiology 1990; 174:621–626.
32. Tibbetts LM, Doremus CM, Tzanakakis GN, Vezeridis MP. Liver metastases with 10 human colon carcinoma cell lines in nude mice and association with carcinoembryonic antigen production. Cancer 1993; 71:315–321.
33. Thomas P, Zamcheck N. Role of the liver in clearance and excretion of circulating carcinoembryonic antigen (CEA). Dig Dis Sci 1983; 28:216–224.
34. Bismuth H. Surgical anatomy and anatomical surgery of the liver. World J Surg 1982; 6:3–9.
35. Brunt LM, Well SA. Advances in the diagnosis and treatment of medullary thyroid carcinoma. Surg Clin North Am 1987; 67:263.
36. Androle GL. Serum prostatic-specific antigen: the most useful tumor marker. J Clin Oncol 1992; 10:1205–1207.
37. Sandler RS, Freund DA, Herbst CA, Sandler DP. Cost effectiveness of postoperative carcinoembryonic antigen monitoring in colorectal cancer. Cancer 1984; 53:193–198.