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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Positive Postoperative CEA is a Strong Predictor of Recurrence for Patients After Resection for Colorectal Liver Metastases

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ABSTRACT

Background. The role of carcinoembryonic antigen (CEA) in surveillance and follow-up of patients with colorectal cancer continues to be debated. The objective of this study was to assess the utility of postoperative CEA as a predictor of recurrence for patients with resected colorectal liver metastases (CLM).

Methods. Patients were identified from a prospectively maintained CLM database, and were studied retrospectively. Patients with extrahepatic disease or initially unresectable CLM were excluded. All patients in this study received adjuvant systemic chemotherapy after resection.

Results. Between 1997 and 2007, a total of 318 consecutive patients were studied, with 168 patients (53 %) experiencing recurrence within 2 years. Various postoperative CEA cutoffs were tested as independent predictors of recurrence. A postoperative CEA $\geq$15 ng/ml obtained the highest hazard ratio (1.87; 95 % CI 1.09–3.2; $p = 0.023$) and was chosen to be included in the survival analysis in the multivariate model. A postoperative CEA $\geq$15 ng/ml had a specificity of 96 % and positive predictive value of 82 % for recurrence. On multivariate analysis, age $\geq$70 years, the presence of positive lymph node at primary tumor resection, disease-free interval $\leq$12 months, number of lesions >1, largest lesion $\geq$5 cm, presence of positive margins, and postoperative CEA $\geq$15 ng/ml were independent predictors of recurrence within 2 years.

Conclusion. This study demonstrates a postoperative CEA $\geq$15 ng/ml to be a predictive test for recurrence.

The carcinoembryonic antigen (CEA) is a common test obtained in the course of treatment of patients with colorectal cancer. The role of CEA in the follow-up of patients after resection of stages I–III colorectal cancer has been established,[1,2] and the role of preoperative and postoperative CEA as a prognostic criteria in stages I–III colorectal cancer is also well accepted. For colorectal liver metastases (CLM; stage IV), the role of preoperative CEA has also been extensively studied. The meta-analysis by Abbas et al., using data from prior studies that investigated preoperative CEA as a prognostic factor, clearly documents preoperative CEA as an independent predictor of survival.[3–7] Preoperative CEA has therefore been incorporated into many useful prognostic scoring systems for CLM, including the clinical risk scores (CRS).[8–10] Some studies are also suggesting postoperative CEA to be an independent prognostic factor for recurrence after CLM,[11,12] although the use of postoperative CEA in this setting is still largely extrapolated from studies in stage I–III disease.[2]

The objective of the current study was to assess the prognostic value of postoperative CEA in patients after resection of CLM, with the goal of determining if this could be a useful, inexpensive, and widely available test for postoperative surveillance.

METHODS

Subjects and Data Collection

This study was performed with permission from the Institutional Review Board of the Memorial Sloan-

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Kettering Cancer Center (MSKCC). Patients submitted to hepatectomy for CLM were identified from a prospectively maintained database containing demographic, clinical, operative, pathological, and follow-up data. Further data were obtained from patient charts and hospital electronic records.

The clinical risk score (CRS) based on previously published studies was calculated for each patient.[9] The clinical criteria consisted of nodal status of the primary tumor, disease-free interval (DFI) from the primary tumor to the discovery of the liver metastases $\leq$12 months, number of tumors >1, preoperative CEA level $\geq$200 ng/ml, and size of the largest tumor $\geq$5 cm. Each criterion was assigned one point and patients with scores of 0, 1, or 2 were classified as low CRS, and patients with scores of 3, 4, or 5 as high CRS.

All patients in this analysis received adjuvant systemic chemotherapy consisting of fluourouracil plus either oxaliplatin or irinotecan in a 10-year practice at MSKCC, attempting to detect all recurrences over a long follow-up time. Patients who did not receive documented adjuvant systemic chemotherapy or received intra-arterial chemotherapy were excluded from this study. Patients who had previous metastasectomies, had detectable extrahepatic disease during the pre- or intraoperative course, or were treated with tumor ablation exclusively were not included. Preoperative imaging to evaluate the extent of intrahepatic disease and to exclude extrahepatic metastatic sites included computed tomography and/or magnetic resonance imaging of the chest, abdomen, and pelvis. Fluorodeoxyglucose positron emission tomography (FDG-PET) was used selectively according to the judgment of the treating physician. CEA assessment in the postoperative course was carried out with at least one measure in the first 6 months after operation. If the patient had more than one CEA assessment in the period, only the first elevated CEA (CEA $\geq$5 ng/ml) was considered in this period.

Follow-up time was calculated from the date of liver resection to the date of the last clinical encounter, captured by the MSKCC medical record system, or the date of death. Disease-free survival (DFS) and overall survival (OS) were calculated based on the survivorship status at last follow-up.

Statistical Analysis

Statistical comparisons between patients who experienced or did not experience recurrence were performed by Fisher's exact test (for continuous variables) and the Wilcoxon rank-sum test (for categorical variables). Values were expressed as median (interquartile range), or percentage, as appropriate. Survival probabilities were estimated using the Kaplan–Meier method and compared with the log-rank test. Cox regression models were developed to determine factors independently associated with recurrence and death. Best threshold for postoperative CEA was determined using the maximal χ^2 method. Factors that presented $p < 0.1$ univariate analysis were entered into a multivariate analysis to test for significant effects while adjusting for possible confounders. A $p < 0.05$ was considered significant for univariate and multivariate analyses. All statistical analyses were conducted using STATA v 8.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Between 1998 and 2007, a total of 318 patients with CLM treated with potentially curative hepatic resection and adjuvant systemic chemotherapy were found to have had a CEA assessment in the first 6 months postoperation. One hundred and sixty-eight patients (52.8 %) experienced recurrence within 2 years and were compared with the 150 patients (47.2 %) who did not exhibit recurrence. Clinical and pathological data of each group are summarized in Table 1. The groups were comparable in sex, American Society of Anesthesiologists (ASA) score (ASA 3 vs. ASA 1–2), site of primary tumor, preoperative CEA, and pre- and postoperative chemotherapy administered for the primary tumor. The pathological stage of the primary tumor was associated with borderline significance between the groups. Comparing patients who presented with recurrence within 2 years and those who did not, significant differences were noted in median DFI (2.8 vs. 11.5; $p = 0.009$), presence of positive lymph nodes in the primary tumor (69 vs. 51 %), median preoperative CEA (17 vs. 12.6 ng/ml; $p = 0.001$), median number of liver lesions (2 vs. 1; $p < 0.001$), median size of the largest lesion (4 vs. 3.4 cm; $p = 0.003$), bilateral liver disease (49 vs. 37 %), presence of positive margins (21 vs. 7 %), and preoperative chemotherapy for CLM (46 vs. 26 %). Patients who recurred had a higher CRS score: high CRS (3, 4, and 5) was present in 55 % of patients with recurrence compared with 25 % in the group with no recurrence, in the first 2 years ($p < 0.001$).

Postoperative Carcinoembryonic Antigen Assessment

In the analysis of the relationship of pre- and postoperative CEA to recurrence, comparisons were performed looking for CEA as continuous variables, in receiver operating characteristic curves (electronic supplementary Fig. 1), and CEA as a discrete variable (greater than or less than 5 ng/ml; greater than or less than 15 ng/ml). Diagnosis tests were applied and included the same values of CEA (postoperative CEA $\geq$5 or $\geq$15 ng/ml); postoperative

TABLE 1 Clinicopathological characteristics according to presence of recurrence within 2 years

Characteristics	Total [N = 318 (%)]	Recurrence [N = 168 (52.8)]	No recurrence [N = 150 (47.2)]	*p* value
Age[a]	58.6 (50.4–67)	57.8 (49.8–65.4)	59.6 (51.6–69.3)	0.1
Male sex	185 (58.2)	97 (57.7)	88 (58.7)	0.91
ASA score[b]				1
1–2	226 (71)	119 (70.8)	107 (71.3)	
3	92 (28.9)	49 (29.2)	43 (28.7)	
Primary site				0.54
Colon	226 (71)	122 (76.2)	104 (69.3)	
Rectum	92 (29)	4.6 (27.4)	46 (30.7)	
Pathological grade[b]				0.85
Low–intermediate	285 (89.6)	150 (89.3)	135 (90)	
High	33 (10.4)	18 (10.7)	15 (10)	
Stage at the time of primary surgery				0.065
0	2 (0.6)	0	2 (1.3)	
I	28 (8.8)	12 (7.1)	16 (10.7)	
IIA	51 (16)	24 (14.3)	27 (18)	
IIB	4 (1.3)	2 (1.2)	2 (1.3)	
IIIA	10 (3.1)	2 (1.2)	8 (5.3)	
IIIB	84 (26.4)	43 (25.6)	41 (27.3)	
IIIC	11 (3.5)	8 (4.8)	3 (2)	
IVA	128 (40.3)	77 (45.8)	51 (34)	
DFI (months)[a]	7.6 (0–19.5)	2.8 (0–15.3)	11.5 (0–23)	**0.009**
Preoperative CEA, ng/ml[a]	16 (5.5–55)	17 (7.8–67.7)	12.6 (4.3–38.7)	**0.001**
Number of lesions[a]	2 (1–3)	2 (1–4)	1 (1–2)	**<0.001**
Size of largest lesion, cm[a]	3.5 (2.4–5.8)	4 (2.7–6.3)	3.4 (2.1–5)	**0.003**
Bilateral disease	138 (43.4)	82 (48.8)	56 (37.3)	**0.042**
Margins	46 (14.5)	35 (20.8)	11 (7.3)	**0.001**
Positive node at primary	191 (60)	115 (68.5)	76 (50.7)	**0.001**
Preoperative CEA ≥200 ng/ml	36 (11.3)	24 (14.3)	12 (8)	0.11
Number of lesions >1	182 (57.2)	118 (70.2)	64 (42.7)	**<0.001**
Size of largest lesion ≥5 cm	105 (33)	65 (38.9)	40 (26.7)	**0.024**
DFI ≤12 months	199 (62.6)	117 (69.6)	82 (54.7)	**0.008**
CRS				**<0.001**
0	15 (4.7)	7 (4.2)	8 (5.3)	
1	72 (22.6)	16 (9.5)	56 (37.3)	
2	102 (32)	53 (31.6)	49 (32.7)	
3	86 (27)	57 (33.9)	29 (19.3)	
4	36 (11.3)	29 (17.3)	7 (4.7)	
5	7 (2.2)	6 (3.6)	1 (0.7)	
Chemotherapy				
Primary neoadjuvant	40 (12.6)	20 (11.9)	20 (13.3)	0.74
Primary adjuvant	248 (79)	133 (79.6)	115 (78.2)	0.78
Liver preoperative	117(36.8)	78 (46.4)	39 (26)	**<0.001**
Postoperative CEA[a,c]	5.5 (2.8-8.7)	3.2 (1.9-6)	6.5 (5.3-13.4)	**<0.001**

The bold values represent *p* values showing significant differences

Data are expressed as *n* (%) unless otherwise specified

ASA American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *DFI* disease-free interval, *CRS* clinical risk scores

[a] Expressed as median (p25–p75)

[b] ASA 1—total of 15 patients (4.72 %)

[c] First postoperative elevated CEA

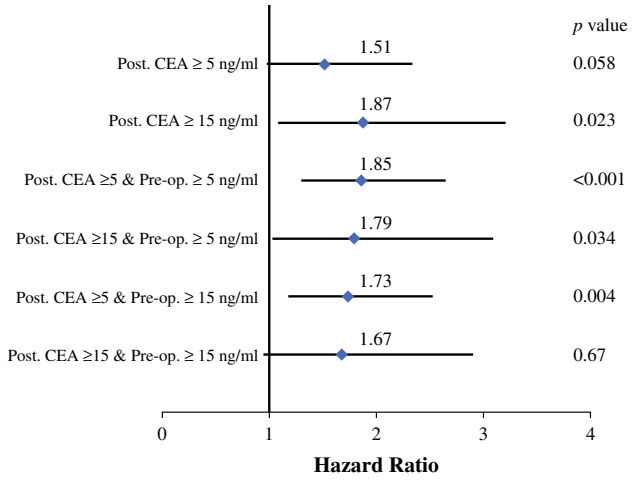

FIG. 1 Hazard ratio comparison of putative CEA values entered separately in the Cox regression. CEA carcinoembryonic antigen, Post. postoperative, Pre-op preoperative

CEA ≥15 ng/ml presented the highest specificity (96 %) and the highest positive predictive value (81.8 %).

Assessing the value of postoperative CEA as an independent prognostic factor to recurrence within 2 years, values of pre- and postoperative CEA were entered individually in the univariate analyses, and each one was entered separately in the Cox regression model with the other predictors. A total of six models were realized: postoperative CEA ≥5 mg/dl [hazard ratio (HR) 1.51; 95 % CI 0.99–2.3; $p = 0.058$]; postoperative CEA ≥15 mg/dl (HR 1.87; 95 % CI 1.09–3.2; $p = 0.023$); post- and preoperative CEA ≥5 mg/dl (HR 1.85; 95 % CI 1.31–2.62; $p < 0.001$); postoperative CEA ≥15 mg/dl and preoperative CEA ≥5 mg/dl (HR 1.79; 95 % CI 1.04–3.08; $p = 0.034$); postoperative CEA ≥5 mg/dl and preoperative CEA ≥15 mg/dl (HR 1.73; 95 % CI 1.19–2.52; $p = 0.004$); and both CEA levels ≥15 mg/dl (HR 1.67; 95 % CI 0.96–2.89; $p = 0.67$). Each of these variables and HRs are presented in Fig. 1. Among the CEA cutoffs tested and identified as independent predictors, postoperative CEA ≥15 ng/ml obtained the highest HR (1.87; 95 % CI 1.09–3.2; $p = 0.023$); for this reason, it was chosen to be included in the survival analysis in the multivariate model.

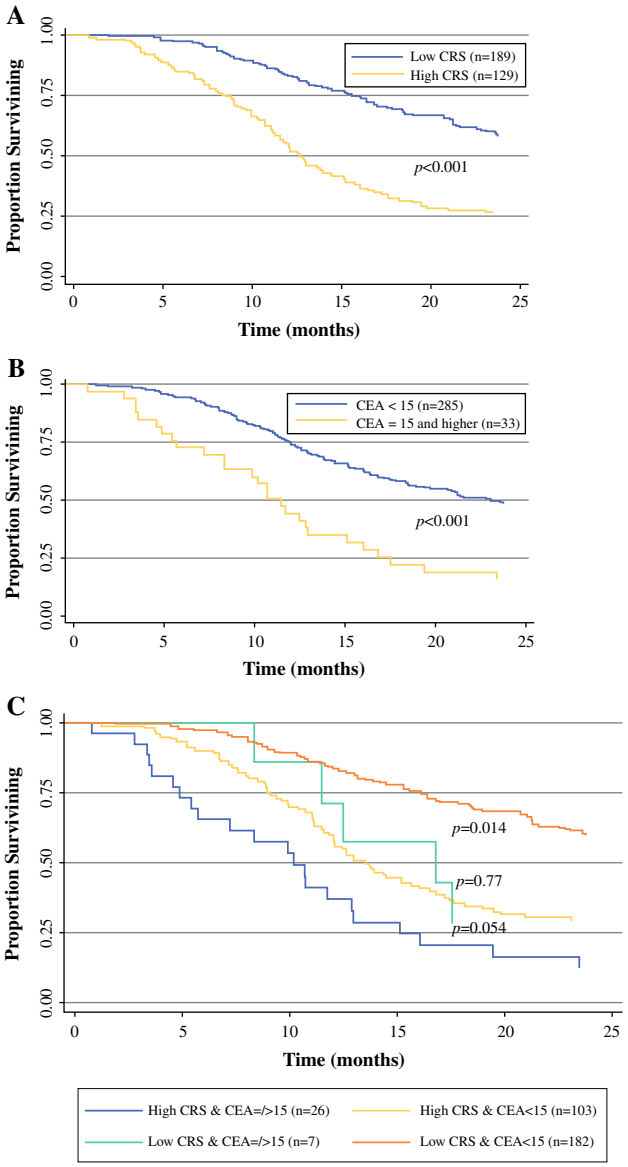

FIG. 2 Kaplan–Meier estimates of recurrence for patients after CLM with curative-intent, as related to a CRS (low vs. high; $p < 0.001$); b postoperative CEA (CEA ≥15 ng/ml or lower; $p < 0.001$); or c combinations of CRS and postoperative CEA levels (general distribution, $p < 0.001$; *high* CRS, differing CEA levels, $p = 0.014$; *low* CRS, differing CEA levels, $p = 0.054$; *high* CRS and *low* CEA vs. *low* CRS and *high* CEA, $p = 0.77$). CLM colorectal liver metastases, CRS clinical risk scores, CEA carcinoembryonic antigen

Survival Analysis

Median follow-up for all patients was 60, 37 months median follow-up for the group who recurred within 2 years, and 87 months for the group without recurrence within 2 years. Median survival was 60 months, and median follow-up for survivors was 96 months. Median survival data were statistically worse for patients who presented postoperative CEA ≥15 ng/ml in the first 6 months versus patients who did not present these levels of CEA (29 vs. 73 months, respectively) [$p < 0.001$].

Median DFS was 21 months. Stratifying for risk of recurrence, analyses were performed according to CRS split in patients with high (3, 4, and 5) and low (0, 1, and 2) CRS. DFS was statistically worse for patients who presented with high CRS (13 months) compared with the patients with low CRS (not reached) [$p < 0.001$; Fig. 2a]. For patients who presented for liver resection with a

TABLE 2 Univariate and multivariate analyses for independent predictors of recurrence within 2 years after curative-intent treatment

Characteristics	Univariate		Multivariate	
	p value	HR	95 % CI	*p* value
Age ≥70 years	**0.037**	0.53	0.33–0.85	**0.008**
Male sex	0.52	–	–	–
ASA (1–2 vs. 3)	0.97	–	–	–
Primary site (colon vs. rectum)	0.56	–	–	–
CRS criteria				
Presence of nodal disease	**<0.001**	1.78	1.28–249	**0.001**
DFI ≤ 12 months	**0.004**	1.46	1.03–2.08	**0.033**
Preoperative CEA ≥200 ng/ml	**0.051**	0.78	0.45–1.35	0.377
Number of lesions >1	**<0.001**	2.01	1.38–2.94	**<0.001**
Size of largest lesion ≥5 cm	**<0.001**	1.92	1.36–2.71	**<0.001**
Bilateral disease	**0.022**	0.77	0.54–1.09	0.138
Presence of positive margins	**<0.001**	2.07	1.4–3.07	**<0.001**
Postoperative CEA ≥ 15 ng/ml	**<0.001**	1.87	1.09–3.2	**0.023**

The bold values represent *p* values showing significant differences

HR hazard ratio, CI confidence interval, *ASA* American Society of Anesthesiologists, *CRS* clinical risk scores, *DFI* disease-free interval, CEA carcinoembryonic antigen

normal CEA, postoperative CEA ≥15 ng/ml discriminated a significant difference in median time to recurrence (12 vs. 23 months; $p < 0.001$) [Fig. 2b]. Of note, patients with low CRS and CEA ≥15 ng/ml behaved similarly as patients with high CRS and CEA ≤15 ng/ml when recurrence was assessed ($p = 0.77$; Fig. 2c).

The univariate and multivariate analyses for predictors of recurrence within 2 years are shown in Table 2. On multivariable analysis, age ≥70 years, the presence of positive lymph node at primary tumor resection, DFI ≤12 months, number of lesions >1, largest lesion ≥5 cm, presence of positive margins, and postoperative CEA ≥15 ng/ml were independent predictors of recurrence within 2 years.

DISCUSSION

First described by Gold and Freeman in 1965, CEA has been in common use in clinical practice.[13] It is a cell surface glycoprotein originally isolated during fetal gut, liver, and pancreatic development, and was noted to disappear from circulation during the second trimester of gestation.[14] In 1969, Thomson et al. described high serum CEA in 97 % of patients with colon cancer.[15] This protein was found to be a ligand for E- and L-selectin on colon cancer.[16]

Studies have examined the role of preoperative CEA as a prognostic factor of recurrence and survival since the middle 1980s.[17–28] As a pre-hepatectomy test, CEA is included in many prognostic scoring systems, including clinical risk score.[7–9] The role of CEA in the follow-up of patients after resection of primary colorectal cancer is also well accepted. The American Society for Clinical Oncology recommends that postoperative CEA be assessed every 3 months for at least 3 years for stages II–III.[2] For resected stage IV disease, the use of CEA in follow-up has been largely extrapolated from its use in stage II–III disease. In a sample of 110 patients who underwent curative intent liver resection for CLM, Hara et al. recently demonstrated that positive postoperative CEA level presents post-test probabilities of recurrence of 70–90 %, compared with 10 % when CEA level is negative.[29] In many situations, CEA level has been used as a surrogate of tumor burden. Although a high CEA level is not a formal contraindication to surgery, these patients tended to be subjected to increased radiologic scrutiny prior to surgery. In the current study, postoperative CEA was found to not only be an independent predictor of recurrence but was also found to be highly specific (96 %) and accurate (positive predictive value = 82 %). This value was not statistically different to high CRS patients in general and patients with high CRS and postoperative CEA <15 ng/ml (14 months). It suggests that, different to preoperative CEA, postoperative CEA is not the only surrogate to tumor load, assuming a role as a predictor of recurrence, or even a marker of silent recurrence.

Many molecular tests have been proposed for stratifying the risk of recurrence after liver resection, including carbohydrate antigen 19-9, DNA ploidy or flow cytometric proliferation, p53, k-ras, thymidine synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, microsatellite instability/hMSH2 or hMLH1, circulating mutant DNA, and loss of heterozygosity on the long arm of chromosome 18.[2,30] None have been sufficiently predictive

of outcome to warrant recommendation by the American Society of Clinical Oncology guidelines for routine use.[2] Our results indicate that the first CEA after hepatectomy is a very good test for risk stratification. It is an inexpensive test, costing approximately 25 United States dollars, and is widely available.[31] Thus, we recommend it as a basis of comparison for any other new test being proposed for the assessment of risk of recurrence, with cost, usefulness, and ease of performance as the basis of comparison.

CONCLUSIONS

In this study, we have shown that postoperative CEA collected in the first 6 months is an additional tool to predict recurrence in patients with CLM who underwent curative-intent treatment. The cutoff of 15 ng/ml results in a high specificity and positive predictive value for recurrence. In addition to the CRS, postoperative CEA is an independent predictor of long-term outcomes in patients treated by hepatectomy for CLM. Clinical trials to determine whether the combination of these two parameters can be used to help determine the frequency of scanning in the follow-up of patients treated for metastatic colorectal cancer will help define cost-effective care.

CONFLICT OF INTEREST Raphael L.C. Araujo, Mithat Gönen, Peter Allen, Ronald DeMatteo, Peter Kingham, William Jarnagin, Michael D'Angelica, and Yuman Fong declare no conflicts of interest.

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