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# Monitoring Carcinoembryonic Antigen in Colorectal Cancer: Is it Still Useful?

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**Abstract: The results of a study conducted to determine the usefulness of carcinoembryonic antigen (CEA) monitoring in the follow-up of patients with resected colorectal cancer are reported herein. The subjects of this study were 125 patients in whom CEA had been determined preoperatively and 239 patients in whom CEA had been monitored postoperatively. The results revealed increased preoperative CEA in only 24% of the subjects, and that this increment was correlated with subsequent more advanced tumor stage and a higher recurrence rate ($P < 0.01$). The postoperative CEA level exceeded the threshold in 71% of the patients affected by recurrence, 94.4% of whom developed liver metastases and 50%, nonhepatic recurrence. This marker showed elevated sensitivity for liver metastases (99%), whereas the sensitivity was lower for nonhepatic recurrence of the disease (94%). Thus, we concluded that CEA monitoring can be useful for preoperative colorectal tumor grading, even if its validity in the early diagnosis of recurrence is problematic, especially in terms of radical repeated surgery and survival.**

**Key Words:** tumor marker, preoperative stage, liver metastasis, carcinoembryonic antigen.

## Introduction

Carcinoembryonic antigen (CEA) has been the prototype of colorectal tumor markers for over 30 years. Although it is anachronistic to discuss its role in the early diagnosis of colorectal cancer, it cannot be denied that it is monitored in most patients followed up postoperatively[1] and that it is still the topic of numerous scientific papers.

We conducted a long-term follow-up, over almost 20 years, of colorectal cancer within the framework of the Italian National Research Council, and thereafter verified the results to determine whether this marker is still valid today. Our study was aimed at assessing the efficacy of CEA levels for determining the preoperative tumor stage and making an accurate early diagnosis of recurrence.

## Materials and Methods

All of the patients in this study series had undergone radical surgery for colorectal cancer graded according to Astler-Coller's classification. Follow-up included CEA monitoring, conducted every 3 months for years 1, 2, and 3, every 6 months for years 4 and 5, then yearly up to year 10. The antigen was determined using the radioimmunoassay method (n.v.: 0–5 ng/ml).

A retrospective analysis revealed two groups of patients who attended the controls regularly for a minimum of 1 year to a maximum of 10 years. Preoperative CEA levels were determined on the morning of surgery in the first group of 125 patients. The prognostic reliability of the CEA level, and the correlation between the preoperative CEA level and the postoperative tumor stage, were statistically assessed in all the patients in this group and in a subgroup of 93 patients who had been followed up for over 2 years. The recurrence rate in our series was 72.9% within this period.[2,3] The second group was made up of 239 patients in whom the CEA level was monitored postoperatively. In this group, 194 patients were disease-free, 18 presented solely with liver recurrence, 22 were affected by nonhepatic recurrence, and 5 presented with both liver and nonliver recurrence. The sensitivity, specificity, positive prognostic value (PPV), negative prognostic value (NPV), and the diagnostic

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accuracy (DA) of the CEA level for disease recurrence and liver and nonliver metastases were determined in this group.

Statistical analysis was performing using multiple contingency tables with the *P*-value referring to the chi-squared distribution.

## Results

The preoperative CEA levels were within the normal range of ≤5.0 ng/ml in 95 patients (76%) while they were elevated to >5 ng/ml in 30 patients (24%). In the subgroup of patients with a normal preoperative CEA level, 73 (76.8%) were free from disease, whereas 12 (12.6%) developed recurrence with a 10% dropout rate. The postoperative follow-up period ranged from 12 to 120 months with a mean of 45.7 months. In the subgroup of patients with an elevated preoperative CEA level, 15 (50%) were disease-free and 12 (40%) developed recurrence, with a 10% dropout rate. The postoperative follow-up period ranged from 12 to 93 months with a mean of 50.3 months. The difference between the number of recurrences in patients with an elevated CEA level and those with a normal CEA level was statistically significant ($P < 0.01$). Of the 12 patients with a normal preoperative CEA level who presented with postoperative recurrence, all 5 affected by liver metastases had an elevated CEA level, whereas only 1 of the 7 affected by nonhepatic recurrence had an elevated CEA level. Moreover, 70 of the 93 patients followed up for over 2 years had presented with normal preoperative CEA levels. Of these, 50 (71.4%) were free from disease, 11 (15.7%) developed recurrence, and the dropout rate was 13% after a follow-up period ranging from 24 to 120 months, with a mean of 56.3 months. The remaining 23 patients had presented with preoperative CEA concentrations exceeding 5 ng/ml. Of these, 8 (34.8%) were disease-free, 12 (52.2%) developed recurrence, and the dropout rate was 13% after a follow-up period ranging from 31 to 93 months, with a mean of 60.7 months. The difference in recurrence between the two subgroups was statistically significant ($P < 0.01$).

The correlation between the preoperative CEA level and the Astler-Coller tumor stage (Table 1) showed more patients in "A + B1 + B2" classes when the CEA level was <5 ng/ml (65.3% *vs* 56.7%) and more patients in "C1 + C2 + D" classes when the CEA level was >5 ng/ml (43.3% *vs* 34.7%). The postoperative CEA level revealed false positive results of >5 ng/ml in 23/194 (11.8%) patients who were free from disease after a follow-up period of 12 to 120 months, with a mean of 51.4 months. The CEA level was positive in only one determination in 10 of these patients, in more than one determination in 7, with a minimum of 2 and a maximum of 5, then normalizing, and consistently in 6, 2 of whom were hepatitis C virus (HCV)-positive and 1 who had vesicle papillomatosis.

**Table 1.** The relationship between tumor stage according to Astler-Coller and the preoperative carcinoembryonic antigen (CEA) levels

| Stage | Patients with CEA ≤5 ng/ml ($n = 95$) | Patients with CEA >5 ng/ml ($n = 30$) |
|---|---|---|
| A + B1 + B2 | 65.3% | 56.7% |
| C1 + C2 + D | 34.7% | 43.3% |

Increased CEA levels were observed in 32 (71.1%) of the 45 patients with recurrence, 18 of whom had hepatic recurrence, 22 nonhepatic recurrence, and 5 mixed metastases. In the 18 patients with only liver metastases, the CEA levels exceeded the normal threshold 17 times (94.4%), being the first sign of recurrence 13 of the 17 times (76.5%) with a mean advance in diagnosis of 1.7 months. The mean CEA level in the first positive determination was 38.5 ng/ml, the minimum being 6 ng/ml, and the maximum 273 ng/ml.

We also studied the 22 patients with nonhepatic recurrence, 16 of whom had local or anastomotic recurrence, 4 pulmonary metastases, 1 brain metastasis, and 1 supraclavical lymph node metastasis. The CEA levels were abnormal in 11 (50%) and normal in the other 11, being the first sign of recurrence in 6/11 patients (54.5%) with a mean advance in diagnosis of 6.6 months. The mean CEA level of the first increment was 24.9 ng/ml, the minimum being 6 ng/ml, and the maximum 80 ng/ml. The marker was increased in 37.5% of patients (6/16 times) with local or anastomotic recurrence, and in 100% of the four patients with pulmonary metastases.

The CEA levels of sensitivity, specificity, PPV, NPV, and DA in the patients with hepatic and those with nonhepatic recurrence were assessed (Table 2). It was found that CEA sensitivity and diagnostic accuracy in the patients affected by liver metastases were more significant than in those with nonhepatic recurrence, at 99% *vs* 94% and 89% *vs* 84%, respectively. On the contrary, minor specificity of the CEA level depended on the false positive results of 43% and 32%, respectively.

## Discussion

Even if the usefulness of CEA screening for colorectal cancer was disclaimed,[4–6] considering that only 24% of our patients presented with abnormal preoperative

**Table 2.** The specificity, sensitivity, PPV, NPV, and DA of CEA concentrations in relation to liver and nonliver metastases

| | Neoplastic recurrence | Liver metastases | Nonhepatic recurrence |
|---|---|---|---|
| Specificity | 58% | 43% | 32% |
| Sensitivity | 93% | 99% | 94% |
| PPV | 73% | 94% | 50% |
| NPV | 88% | 88% | 88% |
| DA | 85% | 89% | 84% |

PPV, positive prognostic value; NPV, negative prognostic value; DA, diagnostic accuracy

CEA levels, its preoperative determination may be justified by the fact that elevated concentrations seem to be correlated with a higher recurrence rate[1,7–10] ($P < 0.01$ in our series) and more severe tumor staging.[7,11] We believe that this point is not merely speculative. As it is difficult to perform accurate pre- or intraoperative anatomopathologic staging, elevated preoperative CEA levels provide a means of determining those patients at higher risk of recurrence for whom an aggressive multimodal approach, from surgery to intraportal chemotherapeutic flash[10] and positioning of a total implantable system,[12] with more intensive follow-up,[7] are recommended.

Another aspect that must be considered when assessing the usefulness of determining CEA levels is the postoperative normalization of the serum concentrations of this marker. This should take place within 4 months after surgery and when it does not, it is likely that the surgery was not radical enough and that the disease will probably recur within a year.[8] In fact, both of our patients in whom the postoperative CEA did not normalize developed recurrence within 9 months after surgery. If the improved survival of patients who have undergone resection of colorectal cancer is linked not only to early diagnosis of the primitive cancer, but also to early diagnosis and treatment of recurrence, repeated postoperative monitoring of the CEA level is important. This diagnostic method is commonly adopted by members of the American Society of Colon and Rectal Surgeons.[13] It is inexpensive, can be repeated often, and a recent meta-analysis by Bruinvels et al.[14] indicated that among all the follow-up tests, CEA determination prolonged survival by 9%.

In reality, when we consider the overall recurrence rate, the quantification of this antigen does not seem invalidating, especially when we refer to data in the literature that reveal a pathological increase of the marker in a very wide range of between 44% and 88.6%.[1,7,15–25] In our series, the CEA level increased in 71% of the patients who developed recurrence, and statistical analysis showed its diagnostic accuracy to be equal to 85%, with a relatively low percentage of error. Moreover, the sensitivity of the antigen was 93% as a result of the low number of false negatives, while the low specificity (58%) was linked to the false positives. Even if the latter resulted in an increase in costs, false positives are less serious than false negatives as they do not influence the possible benefits of CEA in diagnosing recurrence. Moertel et al.[1] calculated that false positives could be reduced by raising the upper limit of the CEA levels from 5 ng/ml without provoking a concomitant, but more dangerous, increase in false negatives.

If hepatic and nonhepatic recurrence are separated, CEA can furnish a precise orientation as it is known to be more specific for liver metastases.[1,8,9,18,19,25,26] In the present series, abnormal CEA levels were observed in 94.4% of the patients who developed liver metastases, showing a sensitivity of 99%. This percentage falls between those reported by Sardi et al.[27] and Wanebo et al.[25] of 100% and 95%, respectively, although relatively lower percentages were reported by other authors, including Hohenberger et al.,[28] Moertel et al.,[1] McCall et al.,[19] and Rocklin et al.,[16] who reported 73.7%, 78%, 80%, and 85%, respectively. These data enabled us to verify that the reliability of the CEA levels in our series[3] was certainly greater that of liver ultrasonography (US). This finding is in agreement with those of other authors[21,24,29] and the reason why we eliminated liver US from our follow-up protocol. Establishing a diagnosis of nonhepatic recurrence is more complex. In the present series, the CEA levels increased in only 50% of the patients and diagnostic accuracy was 84%. This is much lower than that achieved using other examinations, especially for local or anastomotic recurrence which is associated with a CEA increase varying between 20% and 40%,[7,30,31] being 37.5% in our series. The real dilemma is linked to the fact that even if serum CEA monitoring can facilitate the early diagnosis of recurrence, especially liver recurrence, it does not seem to increase the incidence of radical repeated surgery and survival. In fact, no significant statistical differences have been observed between "second-look CEA-directed" and non-"second-look CEA-directed" operations.[1,19,32,33]

In conclusion, we believe that although preoperative CEA monitoring can open up new frontiers in intraoperative multimodal treatment, its true efficacy, both pre- and postoperatively, for improving survival is doubtful even if it is unquestionably the best and earliest marker of liver metastasis. The dilemma about whether or not to analyze CEA is probably as significant as that regarding the usefulness of colorectal follow-up for improving survival. However, for patients

being followed up for colorectal cancer, CEA is "without doubt, the most useful examination."[24]

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