

CEA as a prognostic index in colorectal cancer

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Introduction: The carcinoembryonic antigen, CEA, is the tumor marker most used in colorectal patients, principally during follow up after radical surgery. High serum CEA level before surgery is often associated with worse prognosis, in some studies. **Objective:** The purpose of this study was to evaluate the preoperative carcinoembryonic antigen levels (CEA) and the frequency of recurrence. **Material and Methods:** Eighty-three patients with colorectal cancer at Dukes stages A, B or C were evaluated retrospectively. The patients' follow up was at least two years or to death. CEA was determined in serum by enzyme immunoassay (Sorin Biomedica), normal value 0-5ng/ml. **Results:** Disease recurrence was observed in 32 patients (38.5%), 13 Dukes B and 19 Dukes C. Seventy five per cent of the patients with CEA higher than 10ng/ml relapsed and 80% of the patients without recurrence had normal CEA. Disease recurrence in patients with preoperative elevated CEA occurred during the first year of follow up in 56% of the patients. **Conclusion:** Although the tumor stage is today the most valuable prognostic variable in colorectal cancer, the preoperative CEA value can provide some additional information in the prognosis of the patient.

UNITERMS: CEA. Colorectal cancer. Recurrence.

INTRODUCTION

Colorectal cancer is one of the most common cancers in industrialized cities. In Brazil, it is the 4th largest cause of cancer in women and the 6th in men. In 1995, 22000 persons had colorectal cancer and 3000 died from this cancer in this country.

The carcinoembryonic antigen (CEA), first described by Gold and Freedman⁽¹⁾ in 1965, is a glycoprotein present in a high number (90%) of colorectal adenocarcinoma. Serum determination of CEA is the the most widely used tumor marker in these patients. The main function of this marker is to detect early recurrence during follow up after radical surgery. The serum dosage of CEA at diagnosis has low sensitivity because patients with colorectal cancer can have normal levels of serum CEA. The relationship between high CEA serum levels in the preoperative period and worse

prognosis has been investigated in several studies^{2,3,4,5}, so far without definite conclusion. Patients with high CEA serum levels before surgery could have a higher incidence of recurrence than patients with normal levels.

The aim of this study was to retrospectively evaluate the serum CEA levels before surgery in operable colorectal cancer patients as a predictor of recurrence. The possible relationships between serum levels of CEA and sex, age, diameters of the tumor, histological differentiation, tumor site (colon or rectum) and Dukes stage have also been evaluated.

PATIENTS AND METHODS

We retrospectively reviewed 83 patients with colorectal adenocarcinoma treated at the Gastroenterology division of the Hospital São Paulo. The mean age of the patients was 57 years (29-83 years), there being 42 women and 41 men. 44 had colon cancer and 39 rectal cancer. All had operable cancer. Staging was performed according to Dukes' stages (Dukes A in 3, Dukes B in 46 and Dukes C

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in 34). All the patients were followed for at least two years or up to death.

Serum samples were taken preoperatively, within 30 days of surgery and stored at -20°C . Serum levels of CEA were measured by Elisa, using the Sorin Biomedica kit. Normal values are from 0-5ng/ml.

We calculated the sensitivity, specificity and positive and negative predictive value for CEA as an index of tumor recurrence. Statistical analysis consisted of Kruskal-Wallis analysis of variance or Chi square test. Significance was defined as $p < 0.05$.

RESULTS

The mean and standard mean error of CEA values in Dukes stages A, B and C were 2 ± 1.96 ; 5.8 ± 5.82 ; 23.6 ± 23.59 (Table 1). There was no significant difference with respect to sex ($p=0.94$), age before or after 45 years ($p=0.94$), cancer site ($p=0.77$), diameter of the tumor ($p=0.96$), or histological differentiation ($p=0.87$).

The CEA values were differentiated in all three stages by the Kruskal-Wallis analysis ($p= 0.043$), in which patients with Dukes stage A were the same as those with stage B, but those with stage C were different from both A and B. Among the 46 patients with Dukes stage B, 9 (34%) had elevated serum CEA levels and among the 34 patients with stage C, 17 (50%) had elevated CEA serum level. The 3 patients with Dukes' stage A had normal serum CEA levels (Table 2).

Twenty six patients (31%) had CEA levels greater than 5ng/ml (Table 2). Disease recurrence was found in 32 patients, 13 Dukes B and 19 Dukes C, 22 had metastases, most frequently in the liver (57%), and 10 had local recurrence. CEA levels were elevated in 7 of the 12 patients who developed liver metastases. Before the completion of 1 year of follow up, 12 patients had relapsed. Among the 32 patients with recurrence of the disease during the follow up, 16 had preoperative elevated CEA serum levels and 16 had normal CEA levels. In 9 of the 16 patients with an elevated preoperative CEA, the recurrence appeared during the first year of follow up, while in the 16 with normal serum CEA level the diagnosis of recurrence was done after 1 year in 81% of the patients (Table 3). This difference was significant by the Chi square test ($p= 0.04$).

Recurrence of the disease was observed in seventy five per cent of the patients with preoperative CEA levels greater than 10ng/ml. On the other hand, among the 51 patients without recurrence during the follow up, 41 (80%)

Table 1
Mean \pm epm of CEA serum levels in Dukes stages.

	Dukes A	Dukes B	Dukes C
X \pm epm	1.93 \pm 0.88	5.82 \pm 1.86	23.6 \pm 6.33

had normal CEA serum levels (Table 4). The Chi-square test between the patients with or without recurrence according to the serum CEA levels either normal or elevated, was statistically different ($p= 0.008$).

The sensitivity, specificity, the positive predictive value and the negative predictive value are described in Table 5.

The frequency of recurrence according to Dukes stage was 28% for the B stage and 56% for the C stage. In Dukes stage B, the CEA level was elevated in 30% of the patients who developed recurrence, and normal in 82% of patients without recurrence. In Dukes stage C, 19 patients developed recurrence, of which 12 (63%) had a CEA level greater than 5ng/ml. Among the other 15 patients without relapse, 10 (67%) had normal serum levels. These differences were not significant by the Chi square test ($p>0.05$).

DISCUSSION

Thirty years after its description by Gold and Freedman⁽¹⁾, the CEA remains the tumor marker most studied in colorectal cancer, its main function being the monitoring of patients after the surgical resection of the tumor. The preoperative CEA level as a prognostic index is not yet defined, although many authors believe that the CEA level offers an additional criterion for evaluating the prognosis of colorectal cancer.

As in the majority of previous studies^(2,4), we also did not observed any differences of CEA levels when comparing sex, age, tumor site, tumor diameter or histological differentiation. Carpellan et. al.⁽⁶⁾, observed higher CEA sensitivity levels for rectal cancer than for colon cancer,

Table 2
Number of patients with CEA $>$ or $<$ 5ng/ml according to the Dukes stage

Dukes stage	<5	>5
A	3	0
B	37	9
C	17	17

Table 3
Number of patients with CEA > or < 5ng/ml and the time of recurrence

Time of Recurrence	CEA < 5ng/ml	CEA >5ng/ml
< 1 year	3	9
>1 year	13	7

attributing these differences to the fact that rectal cancer is more often infiltrative and annular.

The sensitivity of CEA at the time of diagnosis of the tumor at Dukes stages A or B was 18%.and 50% at stage C, which was a result similar to Chu et al⁽⁷⁾. The mean serum levels were higher for tumors in Dukes stage C than for stages B or A. The differences in serum CEA were statistically significant. The CEA level differentiated Dukes stage A from C, and C from B, but not A from B.

We observed, as in previous studies, that 38.5% of the patients relapsed. This percentage was higher in the patients with nodal involvement (Dukes C). In this group, the frequency of recurrence was 58% and the CEA level was elevated in 60% of the patients. The Gastrointestinal Tumor Study Group⁽⁸⁾ reported that patients with 4 or more nodal involvements and CEA level greater than 5ng/ml had a higher risk of recurrence and decreased survival.

CEA preoperative levels were normal in 50% of the patients who developed recurrence and elevated in the others, and therefore patients with normal serum CEA level can develop recurrence during follow up. The sensitivity was lower than in the studies of Wang⁽⁹⁾ and Tate⁽¹⁰⁾ but similar to McCall⁽¹¹⁾. Seventy five per cent of patients with CEA level higher than 10ng/ml developed recurrence, but on the other hand, among the 50 patients

Table 5
Number of patients with CEA > or < 5ng/ml and with or without recurrence

	CEA < 5ng/ml	CEA >. 5ng/ml
Recurrence	16	16
Without Recurrence	41	10

without recurrence, the CEA level were normal in 80%. Tsushiya et al⁽⁴⁾ observed that patients with preoperative CEA level greater than 10ng/ml in Dukes stage B or C had decreased survival rates. In the group of patients with elevated preoperative CEA and recurrence, this occurred in the first year of follow up. Chu⁽⁷⁾ and Groslin⁽³⁾ also reported that patients with elevated CEA level had recurrence after the first 6 months. Carpelan⁽¹²⁾ found a significant difference in survival in patients with preoperative serum CEA above 5ng/ml and those with a lower CEA level. Northover⁽¹³⁾ reported that the risk of recurrent disease within two years of primary surgery was more than double in those whose serum CEA was raised preoperatively.

In this study we can conclude that preoperative CEA higher than 10ng/ml was associated with poorer prognosis. In these patients the recurrence would be more frequently in the first year of follow up. The results from this series are consistent with several published works. Although the information provided by the tumor stage is still the most valuable prognostic variable today, the preoperative elevated CEA level provides additional information on the prospects for survival, suggesting a more aggressive tumor and probably identifying a subgroup of patients for adjuvant therapy.

Table 4
Sensitivity(S), specificity(E), positive predictive value (PPV) and negative predictive value (NPV)

S= $\frac{\text{N}^{\circ} \text{ of patients with recurrence and preoperative CEA } > 5}{\text{N}^{\circ} \text{ of patients with recurrence}}$	S= $\frac{16}{32}=50\%$
E= $\frac{\text{N}^{\circ} \text{ of patients without recurrence and preoperative CEA } < 5}{\text{N}^{\circ} \text{ patients without recurrence}}$	E= $\frac{41}{51}=80,4\%$
PPV= $\frac{\text{N}^{\circ} \text{ of patients with elevated CEA and recurrence}}{\text{N}^{\circ} \text{ of patients with elevated CEA}}$	VPP= $\frac{16}{26}=61,5\%$
NPV= $\frac{\text{N}^{\circ} \text{ of patients with normal CEA and without recurrence}}{\text{patients with normal CEA}}$	VPN= $\frac{41}{57}=72\%$

RESUMO

Introdução: O antígeno carcinoembrionário, CEA é o marcador tumoral mais usado em pacientes com câncer colorretal, principalmente no acompanhamento clínico após ressecção cirúrgica do tumor. Níveis séricos elevados de CEA no pré-operatório são frequentemente associados, em alguns estudos, a pior prognóstico. **Objetivo:** Comparar os níveis séricos de CEA no pré-operatório e a frequência da recorrência no acompanhamento clínico. **Material e Métodos:** Oitenta e três pacientes com câncer colorretal estadiados em Dukes A, B, e C foram avaliados retrospectivamente. Os pacientes foram acompanhados, por no mínimo dois anos ou até o óbito. O CEA sérico foi determinado por Elisa (Sorine Biomédicas, valor normal 0-5 ng/ml). **Resultados:** A recorrência foi observada em 32 pacientes (38.5%), sendo 13 pacientes Dukes B e 19 Dukes C. Setenta e cinco por cento dos pacientes com CEA maior que 10ng/ml apresentaram recorrência e oitenta por cento dos pacientes sem recorrência tinham níveis séricos de CEA dentro do valor de normalidade. Nos pacientes com CEA elevado no pré-operatório e que desenvolveram recorrência, esta ocorreu no primeiro ano de acompanhamento em 56% dos pacientes. Dezesesseis pacientes foram a óbito durante o acompanhamento, 11 destes tinham CEA sérico aumentado no pré-operatório. **Conclusão:** Embora, o estadiamento clínico seja a variável mais usada na avaliação do prognóstico, os valores de CEA no pré-operatório podem fornecer algumas informações adicionais sobre o prognóstico do doente.

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