

DETERMINATION OF CARCINOEMBRYONIC ANTIGEN LEVELS IN PERIPHERAL AND DRAINING VENOUS BLOOD IN PATIENTS WITH COLORECTAL CARCINOMA

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ABSTRACT - Background - The problem of the relationship between blood carcinoembryonic antigen (CEA) levels and tissue CEA content in colorectal carcinoma, and the mechanisms for CEA release from tumor cells in tissue adjacent to the neoplasm is important to understanding the biology of colorectal carcinoma. It has not been adequately explained whether CEA in the peripheral blood is drained mainly by portal system blood or by the lymphatic system, or indeed by both systems. **Aim** - To study the behavior of CEA levels in peripheral blood (CEA-p) and venous effluent blood (CEA-d) among patients with colorectal tumors, who underwent curative operation. **Method** - A total of 28 patients were studied (12 male [42.9%] and 16 female [57.1%], mean age 66.1 years [range: 43 - 84]). Immediately after laparotomy, peripheral venous blood was extracted by antecubital venous puncture and venous effluent blood was collected from the main drainage vein of the lesions. Values of CEA-p, CEA-d and the gradient between CEA-d and CEA-p that were less than 5.0 ng/mL were considered normal. Results - Eight (28.6%) patients were stage A in Duke's classification, nine (32.1%) stage B and 11 (39.3%) stage C. The neoplasm was located in the rectum of 14 patients (50.0%), in the transverse colon in five (17.9%), in the sigmoid in four (14.3%), in the cecum and/or ascending colon in three (10.7%), and in the descending colon in two (7.1%). The histopathological examination revealed well-differentiated adenocarcinoma in all the patients. Only one patient (3.6%), Duke's classification stage C, presented neoplasm with venous invasion. The gradient between the CEA-p and CEA-d levels were normal in 25 patients (88.3%) and high in three (10.7%). The mean value for CEA-p was 3.8 ± 4.1 ng/mL (0.1-21.1 ng/mL) and for the drained CEA (CEA-d) it was 4.5 ± 4.3 ng/mL (0.3-20.2 ng/mL), without significant difference between these values. There was a significant difference between the mean value for CEA-p and CEA-d levels greater than 5 ng/mL. **Conclusion** - The CEA-p and CEA-d levels in the colorectal carcinoma patients were not shown to be different. The results from this study suggest that, in colorectal neoplasm without venous invasion, there may not be notable CEA drainage from the tumor by the portal vein effluent blood.

HEADINGS - Carcinoembryonic antigen. Colorectal neoplasms. Colonic neoplasms. Portal system.

INTRODUCTION

Colorectal carcinoma is one of the most common malignant diseases in the western world and its incidence is rising⁽²²⁾. Despite the use of various diagnostic procedures, many patients present an advanced stage tumor at the time of surgery⁽⁶⁾. The overall five-year survival rate for patients with tumors that can be extirpated is only 50%^(15, 22, 32). Among such patients, the main cause of death is the metastases that lead to loco regional or distant relapse in the late stages of the disease^(15, 27, 29).

Carcinoembryonic antigen (CEA) has been widely utilized as a marker for detection, staging, verification of relapse after extirpation of the primary tumor^(8, 9), determination of the therapeutic response and estimation of the prognosis or survival⁽²⁸⁾. Its clinical usefulness has been proven in various types of tumors of the gastrointestinal tract, and it forms a valuable tool for the management of colorectal carcinoma cases^(16, 32).

Histopathological, immunohistochemical and pathophysiological studies have described increased CEA levels in peripheral blood^(16, 25, 26, 32). This has gradually made it possible to understand the mechanism for its elevation^(23, 24). However, the problem of the

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relationship between blood CEA levels and tissue CEA content, and the mechanisms for CEA release from tumor cells in tissue adjacent to the neoplasm and its consequent entry into peripheral blood, remain insufficiently clarified^(4,5). In addition, it has still not been adequately explained whether CEA in the peripheral blood is drained to the thoracic duct mainly by portal system blood or the lymphatic system, or indeed by both systems⁽¹⁵⁾.

This study aimed to investigate the relationship between the CEA levels in peripheral blood (CEA-p) and the portal vein effluent blood (CEA-d) among patients with colorectal neoplasm who underwent curative surgery.

METHOD

A total of 28 patients were studied, 12 were male (42.9%) and 16 were female (57.1%). These patients had colorectal carcinoma in stages A, B or C, according to the Duke's classification. They underwent operation with curative intent in the Surgical Gastroenterology Department of "Hospital do Servidor Público Estadual", São Paulo, SP, Brazil, from 1999 to 2001 (Table 1).

The term curative has been utilized to designate the absence of macroscopic disease at the end of the surgical procedure.

Twenty-four patients (85.7%) were caucasians, two (7.1%) were oriental and two (7.1%) were black.

The following were considered to be inclusion criteria: the presence of adenocarcinoma of the large intestine confirmed by histopathological study of the extirpated lesion, absence of distant metastases at the preoperative examinations and in the abdominal cavity inventory made during the operation, and extirpation of the neoplastic lesion with curative intent. The exclusion criteria were the presence of distant metastases and incomplete extirpation of the neoplastic lesion.

The clinical and morphological data were obtained by consulting the patients' hospital records or interviewing the patients or their relatives at the return outpatient visits.

All the patients had their histological diagnosis of colorectal carcinoma confirmed via review of thin sections stained using hematoxylin and eosin (HE) method and analyzed by a pathologist.

The neoplasm was considered to be Duke's stage A when it did not reach the external muscle layer of the intestinal wall; Duke's stage B when it extended right through the wall including the adventitious adipose tissue; and Duke's stage C when it involved lymph nodes, independent of the depth of parietal invasion.

The preoperative evaluation consisted of the clinical and proctologic examinations, colonoscopy, determination of the serum level of CEA,

TABLE 1 - Clinical and morphological characteristics and peripheral and venous draining blood CEA values of the patients operated for colorectal carcinoma

Case	Age (yrs)	Sex	Tumor location	Dukes	Vein invasion	Peripheral CEA (ng/mL)	Venous draining CEA (ng/mL)	CEA d-p*
1	56	M	Cecum	A	NO	1.50	1.70	NO
2	53	M	Descending	C	NO	1.90	1.50	NO
3	57	M	Rectum	C	NO	7.50	8.50	NO
4	84	F	Rectum	B	NO	2.30	5.90	NO
5	46	F	Transverse	C	NO	3.10	4.80	NO
6	71	F	Rectum	C	NO	9.40	10.60	NO
7	75	M	Sigmoid	B	NO	5.80	6.00	NO
8	43	F	Rectum	C	NO	0.30	0.30	NO
9	62	M	Rectum	B	NO	5.40	6.00	NO
10	63	F	Sigmoid	B	NO	4.80	3.60	NO
11	63	M	Cecum	A	NO	2.50	2.50	NO
12	80	F	Cecum	B	NO	1.60	2.60	NO
13	69	M	Transverse	C	NO	5.10	4.90	NO
14	69	M	Rectum	C	NO	1.90	1.60	NO
15	67	M	Sigmoid	C	YES	2.10	1.60	NO
16	56	F	Transverse	B	NO	6.10	7.00	NO
17	83	M	Rectum	B	NO	0.10	1.10	NO
18	80	F	Rectum	A	NO	2.60	13.00	YES
19	55	F	Descending	C	NO	2.50	3.20	NO
20	55	F	Sigmoid	C	NO	1.20	1.60	NO
21	76	F	Rectum	C	NO	21.10	2.60	NO
22	76	F	Rectum	A	NO	0.90	1.10	NO
23	63	F	Rectum	B	NO	0.30	20.20	YES
24	74	M	Rectum	A	NO	1.10	2.50	NO
25	61	M	Rectum	A	NO	2.00	1.70	NO
26	76	F	Transverse	B	NO	4.50	4.40	NO
27	63	F	Transverse	A	NO	2.90	2.50	NO
28	56	F	Rectum	A	NO	5.60	4.20	NO

*CEA d-p = gradient between drained venous effluent CEA and peripheral CEA (NO = ≤5.0 ng/mL; YES = >5.0 ng/mL)

abdominal ultrasonography and computed tomography of the abdomen. All the colorectal lesions were extirpated in a curative manner.

Immediately after the laparotomy, peripheral venous blood and blood from venous drainage in the region of the tumor were collected from all the patients. The peripheral venous blood was extracted by antecubital venous puncture. The venous effluent blood was collected from the main drainage vein of the colorectal neoplastic lesion. A ligature was applied to the main drainage vein close to the lesion using non-absorbable thread. Venous blood was then collected from the vein segment between the ligature and the intestine through a catheter inserted into the ileocecal vein for cecal lesions; the right colon vein for ascending colon lesions; the middle colon vein for transverse colon lesions; the left colon vein for descending colon lesions; the sigmoid vein for sigmoid lesions; and the superior rectal vein for rectal lesions.

The serum samples from the peripheral and portal bloods were stored in a freezer at -70°C until the CEA analyses were performed. For assaying the CEA, a solid-phase fluoroimmunoassay was utilized (Delfia CEA Kit, Pharmacia, Turku, Finland). This was based on a direct technique in which two monoclonal antibodies are directed against two antigen sites of the CEA molecule. The fluorescence of each sample being proportional to the CEA concentration. The precision of the method was estimated by the intra-assay coefficient of variation (c.v.) to be 3.4 and 2.4% for low and high values, respectively. The inter-assay c.v. was 4.6 and 2.8% for the same parameters. The sensitivity of this CEA assay was 0.2 ng/mL and the highest point on the recognition curve was 500 ng/mL.

The cut-off level was 2.5 ng/mL. Rises in CEA levels in peripheral blood (CEA-p) and the drainage vein of the neoplasm (CEA-d) up to 5 ng/mL were considered normal. CEA-p and CEA-d levels greater than 5 ng/mL were considered abnormal. Gradients between CEA-d and CEA-p levels (d-p gradient) higher than 5 ng/mL were defined as abnormal gradient levels and levels of less than this were defined as normal⁽²⁸⁾.

Surgical specimens were fixed in 10% formalin solution and embedded in paraffin, thin sections were taken from this for histopathological diagnosis. Three sections were examined, consisting of a central section through the neoplastic lesion and two parallel sections bordering the central one. The sections were stained with HE.

The variables considered for the purposes of statistical analysis were age, sex, location of the lesion within the large intestine, peripheral CEA level, CEA level in the drainage vein of the carcinoma, Duke's classification, and presence or absence of vein invasion by the neoplasm in the product from the surgical extirpation. Parametric and non-parametric statistical tests were used according to the nature of the samples. The quantitative variables were represented by absolute frequency (N) and relative frequency (percentage). The statistical models utilized were arithmetic mean, median, standard deviation, Pearson correlation,

Mann-Whitney test and Wilcoxon test for two related paired samples. For every test, the level for rejection of the null hypothesis was set at 0.05 (95% significance level), in accordance with the current standards for biological studies.

RESULTS

The mean age was 66.1 ± 11 years and the median was 68.0 years (range, 43-84 years) (Table 2).

The neoplasm was located in the rectum of 14 patients (50%), transverse colon in 5 (17.9%), sigmoid colon in 4 (14.3%), cecum and/or ascending colon in 3 (10.7%), and in the descending colon in 2 (7.1%) (Table 1).

Eight patients (28.6%) were classified as Duke's stage A, 9 (32.1%) as stage B and 11 (39.3%) as stage C (Table 1). Neither the preoperative evaluation nor the intraoperative inspection of the peritoneal cavity demonstrated metastatic disease.

In 17 patients (60.7%), the CEA-d value was greater than the CEA-p value, whereas in 9 patients (32.1%) the CEA-p level was greater than for CEA-d and in 2 cases (7.1%) the CEA-d and CEA-p values were equal (Table 1). There was no statistically significant correlation ($P = 0.619$) between the corresponding CEA-p and CEA-d values for each patient (Table 2).

The mean CEA-p value was 3.8 ± 4.1 ng/mL (range, 0.1-21.1 ng/mL) and the mean for CEA-d was 4.5 ± 4.3 ng/mL (range, 0.3-20.2 ng/mL). There was no statistically significant difference between these values ($P = 0.098$) (Table 2). Of the 28 patients in the present study, 8 (28.6%) presented CEA-p levels over 5 ng/mL and another 8 patients (28.6%) had CEA-d levels greater than 5 ng/mL (Table 1). In these patients, the mean value for CEA-p was 8.25 ng/mL and 9.65 ng/mL for CEA-d, with a statistically significant difference ($P < 0.001$) between them. Five patients (17.8%) simultaneously presented CEA-p and CEA-d levels greater than 5 ng/mL (Table 1).

When the altered CEA-p and CEA-d values were considered, the CEA-d level was greater than the CEA-p level in six (21.4%) patients and, conversely, the CEA-p value was greater than the CEA-d value in three (10.7%) patients (Table 1).

In 25 (89.3%) patients, the gradient between the CEA-p and CEA-d levels was normal (≤ 5 ng/mL) and high (> 5 ng/mL) in 3 (10.7%) (Table 1), though there was no statistically significant difference ($P = 0.063$).

Four (14.3%) patients with CEA levels of more than 5 ng/mL presented CEA-d level higher than the CEA-p level, and none of them had a gradient between the CEA-d and CEA-p levels of more than 5 ng/mL.

Only one patient (3.6%), staged as Duke's C, showed venous invasion. In this patient, the lesion was located in the sigmoid and the CEA-p and CEA-d levels were normal (Table 1).

TABLE 2 - Mean ages and mean peripheral CEA and venous effluent CEA values obtained from patients operated for colorectal carcinoma

Variable	Mean	Standard deviation	Minimum	Maximum	Number (n)
Age (yrs)	66.1	11.0	43	84	28
Peripheral CEA (ng/mL)	3.8	4.1	0.1	21.1	28
Venous effluent CEA (ng/mL)	4.5	4.3	0.3	20.2	28

Wilcoxon (Z) = -1.493 $P = 0.136$ (NS)
 Pearson correlation (r) = 0.937 $P < 0.0001$
 NS = not significant

DISCUSSION

CEA determination is widely utilized as a practical tool for assessing hematogenic metastasis and/or relapse among colorectal carcinoma patients, since almost all such patients show a rise in serum CEA preceding the manifestation of signs, symptoms or diagnosis of metastasis and/or relapse of the tumor^(1, 2, 7, 17, 21). High preoperative CEA serum levels that do not present reduction to normal levels after extirpation of the colorectal neoplasm are associated with a worse prognosis and may identify specific subgroups for adjuvant therapy^(13, 22).

The serum level of peripheral CEA is influenced by the production of CEA by neoplastic cells⁽³¹⁾, tumor necrosis^(11, 15, 30), release of CEA in tissue adjacent to the tumor and its penetration of the lymphatic system and/or blood stream^(16, 32), metabolism and hepatic excretion^(3, 18), reabsorption through the colorectal wall⁽¹⁴⁾, dilution by the blood stream system^(23, 25, 26) and the formation of immunocomplexes⁽¹⁹⁾.

Except when performing the laparotomy, it is difficult to determine the levels of CEA-d due to problems with blood collection⁽²⁸⁾. During the operation, however, blood from the venous effluent of the tumor can be collected without risk, since it is easy to insert the venous catheter into the dilated veins after ligature close to the lesion⁽²⁸⁾. In the present study, no technical difficulties were experienced in blood collection from the venous effluent of the neoplasm at its different locations, during the operation.

When the CEA levels in effluent blood are greater than those in peripheral blood, it is possible that the CEA mainly penetrates the portal system via the drainage vein of the neoplasia⁽¹⁹⁾. Low CEA values in peripheral blood, in comparison with venous effluent blood, are probably the result of metabolic degradation of CEA in the liver. In the present study in 17 patients (60.7%) all without venous invasion by the neoplasm, the CEA-d was higher than the CEA-p, although this elevation was not statistically significant. On the other hand, HARLOZINSKA et al.⁽¹¹⁾ and TABUCHI et al.⁽²³⁾ demonstrated a relationship between raised CEA levels in portal and peripheral blood and the presence of vein invasion by colorectal neoplasm. In contrast, when the CEA levels in venous effluent from the lesion are equal to or less than those in peripheral blood, which occurred in 11 (39.3%) of the patients in the present study, authors conjectured that the tumor antigens produced in the region of the neoplasm may be collected and drained preferentially by the lymphatic vessels in the region of the lesion, thereby reaching the peripheral blood via the thoracic duct^(10, 19, 20).

It has been argued by several authors that the gradient between CEA-d and CEA-p more correctly reflects the quantity of antigens released by tumor cells than the isolated CEA-d and CEA-p levels, since the CEA-d levels correspond to the total amount of circulating CEA-p and the CEA released by neoplastic cells^(4, 5, 15, 23, 25). This gradient could be more useful for estimating prognosis or survival than the CEA-p and CEA-d levels in isolation⁽²⁸⁾. It would be accurate if the venous effluent were the only drainage route for CEA. This would systematically imply greater CEA concentration in the mesenteric portal blood drained from the region of the tumor. Nonetheless, other drainage routes for CEA, such as the lymphatic system, may contribute to the serum levels of this marker^(10, 19, 20).

In the present study, it was observed that the majority (89.3%) of the patients presented a gradient between the CEA-d and CEA-p levels that was within the values considered normal and only three patients (10.7%) had a high gradient between CEA-d and CEA-p. There was no significant difference between these two situations. But 8/28 patients (28.6%) presented CEA-p levels of more than 5 ng/mL and another eight patients (28.6%) had CEA-d levels greater than 5 ng/mL. In these patients

the mean value for CEA-p was 8.25 ng/mL and 9.65 ng/mL for CEA-d, with a statistically significant difference ($P < 0.001$). Nevertheless, only four (14.3%) patients with CEA levels of more than 5 ng/mL presented a CEA-d level higher than the CEA-p level, and none of them showed a gradient between the CEA-d and CEA-p levels of more than 5 ng/mL.

Depending on the morphological and biological variables of the neoplasm, such as absence of venous invasion, one may postulate that CEA preferentially escapes through the lymphatic system⁽¹²⁾. This would cause a notable diminution in CEA levels in the venous effluent blood (CEA-d).

The histological differentiation of colorectal tumors has been considered to be an important determinant of the serum and portal levels of CEA⁽³¹⁾. Nevertheless, this matter is considered controversial since studies have published conflicting results. ROGNUM⁽²⁰⁾ reported that moderately differentiated tumors were associated with higher serum CEA levels than well or poorly differentiated tumors. Moderately or poorly differentiated tumors were more frequently associated with greater serum CEA levels, which could be related to the greater malignant potential and greater incidence of hepatic metastases observed among patients with such tumors⁽¹³⁾. All the patients in the present study had moderately differentiated colorectal carcinoma and consequently, the tumor differentiation did not provide a reliable variable.

Study of other histopathological variables (hepatic metastases, tumor invasion of the colorectal wall, lymph node and venous invasion, and the Duke's classification) in relation to elevated CEA levels in peripheral blood and venous effluent has demonstrated that in most cases locally advanced lesions present greater serum CEA levels⁽¹¹⁾. Of these variables, venous invasion has been most significantly associated with high CEA levels^(15, 23, 24). CEA levels have been described as greater among patients with venous invasion than in those without and gradually increasing according to the degree of invasion⁽¹¹⁾. Additionally CEA levels have been related to the vessel invasion located in the wall layers of the neoplastic lesions. Patients with venous invasion in the subserous and/or extramural veins have shown serum CEA levels greater than for patients with vessel invasion in the submucosal layer or lamina propria muscle layer⁽¹¹⁾. In addition to this, it has been demonstrated that, among patients with venous invasion, the CEA level of the venous effluent (CEA-d) was higher after mechanical stimulation of the neoplastic lesions during the operation. However these levels in patients without venous invasion did not alter, even following such stimulus⁽¹¹⁾. In the present study, only one patient (3.6%), whose CEA-p and CEA-d values were normal, presented venous invasion by the colorectal neoplasm and the other histopathological variables did not demonstrate significant differences. It is possible that in these cases the increased CEA level in the venous effluent depends, among other factors, on the capacity of the cells that determine venous invasion by the tumor, for producing sizeable quantities of CEA.

CONCLUSIONS

The present study has not indicated any significant elevation in CEA in portal blood, in relation to peripheral blood, in neoplasms without venous invasion. It is possible that in such cases, lymphatic vessels drain most of the CEA and it reaches the blood stream via the thoracic duct and therefore the differences in CEA levels in peripheral and portal blood are a consequence of histopathological variables in colorectal carcinoma.

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Waisberg J, Contim-Neto L, Oliveira MSL, Matheus CO, Nagashima CA, Goffi FS. Determinação dos níveis do antígeno carcinoembrionário no sangue periférico e no efluente venoso em doentes com carcinoma colorretal. *Arq Gastroenterol* 2004;41(2):88-92.

RESUMO - Racional - O problema da relação entre os níveis de CEA no sangue e o conteúdo de CEA tissular no carcinoma colorretal e os mecanismos de liberação do CEA das células neoplásicas nos tecidos vizinhos à neoplasia e sua conseqüente entrada dentro do sangue periférico são importantes para o entendimento da biologia do carcinoma colorretal. Ainda não foi convenientemente elucidado se o CEA no sangue é drenado principalmente pelo sangue do sistema portal ou pelos linfáticos para o ducto torácico ou, ainda, por ambos os sistemas. **Objetivo** - Estudar o comportamento dos níveis do CEA no sangue periférico (CEA-p) e no sangue do efluente venoso (CEA-d) de doentes com tumores colorretais operados curativamente. **Método** - foram estudados 28 doentes, sendo 12 (42,9%) homens e 16 (57,1%) mulheres. A média de idade foi de 66,1 anos (43 a 84 anos). Imediatamente após a laparotomia, o sangue venoso periférico foi extraído por punção venosa antecubital e o sangue do efluente venoso coletado da veia principal de drenagem das lesões. Os valores de CEA-p, CEA-d e do gradiente entre o CEA-d e CEA-p abaixo de 5,0 ng/mL foram considerados normais. **Resultados** - Oito (28,6%) doentes foram classificados no estágio A de Dukes, 9 (32,1%) no estágio B e 11 (39,3%) no estágio C. A neoplasia estava localizada no reto em 14 (50,0%), no cólon transverso em 5 (17,9%), no cólon sigmóide em 4 (14,3%), no ceco e/ou cólon ascendente em 3 (10,7%), e no cólon descendente em 2 (7,1%) enfermos. O exame histopatológico revelou adenocarcinoma bem diferenciado em todos os enfermos. Em apenas um (3,6%) doente a neoplasia, estadiada como Dukes C, exibiu invasão venosa. O gradiente entre os níveis de CEA-p e de CEA-d estava normal em 25 (89,3%) doentes e elevado em 3 (10,7%). O valor médio do CEA-p foi de $3,8 \pm 4,1$ ng/mL (0,1 a 21,1 ng/mL) e do CEA-d foi de $4,5 \pm 4,3$ ng/mL (0,3 a 20,2 ng/mL), sem diferença significativa entre esses valores. Houve diferença significativa entre a média dos valores dos níveis do CEA-p e do CEA-d maiores que 5 ng/mL. **Conclusão** - Os níveis de CEA-p e do CEA-d nos doentes com carcinoma colorretal não se mostraram diferentes. Os resultados deste estudo sugerem que, nas neoplasias colorretais sem invasão venosa, o CEA não é drenado expressivamente pelo sangue do efluente venoso portal do tumor.

DESCRIPTORIOS - Antígeno carcinoembrionário. Neoplasias colorretais. Neoplasias do cólon. Sistema porta.

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