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• BRIEF REPORTS •

Biliary carcinoembryonic antigen levels in diagnosis of occult hepatic metastases from colorectal carcinoma

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Abstract

AIM: To prospectively explore the role of carcinoembryonic antigen (CEA) in gallbladder bile in patients with colorectal carcinoma and the morphological and clinical features of neoplasia and the occurrence of hepatic metastases.

METHODS: CEA levels in the gallbladder and peripheral blood were studied in 44 patients with colorectal carcinoma and 10 patients with uncomplicated cholelithiasis. CEA samples were collected from the gallbladder bile and peripheral blood during the operation, immediately before extirpating the colorectal neoplasia or cholecystectomy. Values of up to 5 ng/ml were considered normal for bile and serum CEA.

RESULTS: In the 44 patients with colorectal carcinoma who underwent operation with curative intent, the average level of serum CEA was 8.5 ng/ml (range: 0.1 to 111.0 ng/ml) and for bile CEA it was 74.5 ng/ml (range: 0.2 to 571.0 ng/ml). In the patients with uncomplicated cholelithiasis who underwent cholecystectomy, the average level of serum CEA was 1.9 ng/ml (range: 1.0 to 3.5 ng/ml) and for bile CEA it was 1.2 ng/ml (range: 0.3 to 2.9 ng/ml). The average duration of follow-up time was 16.5 months (range: 6 to 48 months). Four patients who underwent extirpation of the colorectal carcinoma without evidence of hepatic metastasis and with an average bile CEA value of 213.2 ng/ml presented hepatic metastases between three and seventeen months after removal of the primary colorectal neoplasia. Three of them successfully underwent extirpation of the hepatic lesions.

CONCLUSION: High CEA levels in gallbladders of patients undergoing curative operation for colorectal carcinoma may indicate the presence of hepatic metastases. Such patients must be followed up with special attention to the diagnosis of such lesions.

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INTRODUCTION

Colorectal carcinoma is the second most common cancer type in the Western world and the liver is the organ most affected by its distant metastases[1,2]. At the time when primary tumor is extirpated, hepatic metastases are encountered in 20 to 25 % of the patients. Approximately half of the patients who have had colorectal lesions extirpated in an apparently curative manner will develop hepatic metastases postoperatively[1,3,4].

The majority of relapse monitoring programs for operated colorectal carcinoma include determinations at regular intervals of the serum concentration of carcinoembryonic antigen (CEA) and hepatic imaging via abdominal ultrasonography, tomography and/or magnetic resonance[3,5]. Nonetheless, even with such investigations, around 10 to 30 % of hepatic metastases will remain undiagnosed[4]. When lesions are present in the liver, extirpation is the treatment of choice. However, this is only possible in 20 % of such patients and only 25 % of these will achieve survival of more than 5 years[1,3,4].

In 1965, Gold and Freedman[6] described the presence of CEA in extracts from malignant tumors and fetal intestinal tissue. Today, assaying of blood CEA is utilized preoperatively and postoperatively among colorectal carcinoma patients for the detection of disease relapse[7-10].

In 1989, Yeatman *et al*[11] suggested that CEA concentration in bile could constitute a marker for detecting hepatic metastases at an earlier stage. Their hypothesis was based on the observation that CEA derived from hepatic metastases could be excreted both in bile and in blood. Since the bile volume is less than the plasma volume, rises in the detectable CEA concentration occur earlier in the gallbladder than in peripheral blood[11-13]. Yeatman and Paul *et al*[11-14] found elevated CEA concentrations in bile among patients with colorectal carcinoma and proven hepatic metastases and among patients who underwent curative extirpation without any hepatic involvement could be detected via imaging methods.

The role of CEA level in gallbladder bile remains controversial with regard to its contribution towards early detection of hepatic metastases in patients undergoing curative operation for colorectal carcinoma[15-23].

The aim of this study was to prospectively analyze the results of CEA determinations in peripheral blood and gallbladder bile among a series of patients treated by curative operation for colorectal carcinoma, relating them to morphological features of the neoplasia and hepatic relapse.

MATERIALS AND METHODS

Patients

Between 1998 and 2001, 44 patients experienced extirpation of colorectal carcinoma with curative intent. The term curative was utilized to designate an absence of macroscopic disease at the termination of the surgical procedure, verified in the report on the anatomopathological examination of the extirpated neoplastic lesions and associated structures. Samples of gallbladder bile and peripheral blood were collected during the operation, immediately before the start of excision of the neoplasia, for all patients.

This investigation was made in accordance with the ethical standards accepted by the Helsinki Declaration of the World Medical Association, adopted in 1964 and amended in 1996. The patients were aware of the study protocol and signed a statement of free and informed consent upon entering the present study.

The following were considered to be inclusion criteria: achievement of curative operation, absence of distant metastases and presence of adenocarcinoma of the large intestine confirmed by means of histopathological study of the extirpated lesion. Patients submitted to operations that were evaluated as non-curative were not included in this sample.

The clinical and morphological data were obtained by consulting the hospital records of the patients included in the study, or by interviewing the patients or their relatives at return outpatient visits.

Thirty-nine patients (88.6 %) were white, three were oriental (6.8 %) and two were black (4.5 %). Twenty-one patients (47.7 %) were male and 23 (52.3 %) were female. The average age was 63±14.7 years (range: 29 to 90 years). All patients had their preoperative diagnosis of colorectal carcinoma confirmed by biopsy specimens obtained via colonoscopy. For this, the thin sections were stained using the hematoxylin-eosin (HE) method and analyzed by a pathologist.

Neoplasia was considered to be Dukes A when it did not reach the external muscle tunica of the intestinal wall, Dukes B when it extended throughout the wall and also reached the adventitious adipose tissue, and Dukes C when lymph nodes were compromised, independent of the depth of parietal invasion.

Preoperative investigation of the presence of an extra-intestinal lesion was made via abdominal ultrasonography, abdominal tomography and chest radiography, and did not reveal metastases in any of these patients.

In ten patients with uncomplicated cholecystolithiasis who underwent elective cholecystectomy via laparotomy, blood and gallbladder bile samples were collected under the same conditions as for the patients with colorectal carcinoma. These served to furnish CEA levels in gallbladder bile for comparison purposes. All these patients were white, of whom seven (70 %) were female and three (30 %) were male. The average age was 50.8±20.1 years (range: 23 to 74 years old).

Sample collection

Blood and bile sample collection was performed during the operation. After making an inventory of the abdominal cavity, 5 ml samples of gallbladder bile were obtained via puncture of the fundic region of the gallbladder using a caliber 23 needle coupled to a plastic syringe of capacity 10 ml. Then, using another syringe of capacity 20 ml, the remainder gallbladder bile was evacuated, followed by occlusion of the location of the puncture by a pouch suture using thin atraumatic absorbable thread made of polyglycolic acid. At the start of the operation, prior to removing the colorectal neoplasia, 5 ml blood samples was collected via peripheral venous puncture in the non-dominant upper limb, divested of intravenous infusion of any solution, using a caliber 37 needle coupled to a plastic syringe of capacity 10 ml.

CEA assay

The serum and bile samples were stored in a freezer at -70 ℃ until the CEA analyses were done. A solid-phase fluoroimmunometric assay system was utilized (Delfia CEA Kit, Pharmacia, Turkü, Finland) for assaying the serum and bile CEA. The precision of the method was estimated via the coefficient of variation (c.v.), with intra-assay c.v. of 3.4 % and 2.4 % for low and high values, respectively, and inter-assay c.v. of 4.6 % and 2.8 % for the same parameters. The sensitivity of this CEA assay was 0.2 ng/ml and the upper limit on the recognition curve was 500 ng/ml. Whenever this value was exceeded, dilutions were needed for adjustment of the reactions.

The limit of normality adopted for bile CEA was 5 ng/ml which was based on the analysis of the values obtained in the group of patients who underwent cholecystectomy.

Statistical analysis

Considering the nature of the samples, non-parametric statistical tests were utilized in the evaluation of the results. Quantitative variables were represented by absolute frequency (*n*) and relative frequency (%). The statistical models utilized were arithmetic mean, standard deviation, Mann-Whitney test, Wilcoxon test and Kruskal-Wallis test. The normality of the data were tested using the Kolmogorov-Smirnov test and the homogeneity of the variance was verified using the Levene test.

In all tests, the level for the rejection of the null hypothesis was set at 0.05 % (significance level of 95 %), in accordance with the current standards in biological studies.

RESULTS

In the group of patients with colorectal carcinoma, there was a single lesion in 43 patients (97.7 %) and multiple lesions in one of them (2.3 %). The neoplasia was located in the rectum in 24 patients (54.5 %), in the cecum-ascending colon in 6 (13.7 %), in the transverse colon in 6 (13.6 %), in the sigmoid in 4 (9.1 %), in the descending colon in 2 (4.5 %), in the left flexure in 1 (2.3 %), and the lesion involved the cecum and rectum simultaneously in 1 patient (2.3 %). With regard to the degree of histopathological differentiation of the neoplasia, all the lesions were considered to be moderately differentiated. All the patients operated for colorectal carcinoma evolved without notable intercurrences and were discharged from hospital. The average duration of follow-up for the patients was 16.5 months (range: 6 to 48 months).

Concerning the Dukes classification, 2 patients (4.6 %) were classified as class A, 21 (47.7 %) as class B, and 21 (47.7 %) as class C.

Thirteen patients (29.5 %) classified as Dukes C were submitted to adjuvant chemotherapy using intravenous 5-fluorouracil over seven sessions.

In the patients with colorectal carcinoma, the average value was 8.5±18.7 ng/ml (range: 0.1 to 111.0 ng/ml) for serum CEA, and was 74.5±130.3 ng/ml for bile CEA (0.2 to 571 ng/ml) (Table 1).

In the group of patients with uncomplicated cholelithiasis, the average value was 1.94±0.8 ng/ml (range: 1.0 to 3.5 ng/ml) for serum CEA, and was 1.24±0.9 ng/ml for bile CEA (range: 0.3 to 2.9 ng/ml) (Table 2). The patients in this group were discharged from hospital with uneventful recovery.

Seventeen patients (38.6 %) presented a serum CEA value of more than 5.0 ng/ml, while 27 patients (61.4 %) exhibited a blood CEA level less than or equal to 5.0 ng/ml. With regard to bile CEA, 29 patients (65.9 %) exhibited values of more than 5.0 ng/ml, whereas 15 patients (34.1 %) had determinations of less than or equal to 5.0 ng/ml. In 35 patients (79.5 %), the bile CEA level was greater than the serum CEA level, and in nine patients (20.5 %), the serum CEA level was higher than the bile CEA level. Thirteen patients (29.5 %) simultaneously presented serum CEA and bile CEA values of more than 5 ng/ml. In 11 patients (25.0 %), the determinations obtained for serum CEA and bile CEA were less than or equal to 5.0 ng/ml.

The bile CEA values in the patients operated for colorectal carcinoma were significantly greater than those determined in the blood ($P<0.0001$) (Table 1). On the other hand, in the group of patients who underwent cholecystectomy, the bile CEA

values were significantly less than those of serum CEA (P=0.46) (Table 2). The bile CEA levels in patients with colorectal carcinoma were significantly greater (P<0.0001) than those that underwent cholecystectomy. Comparison of the bile CEA/serum CEA ratios for the colorectal carcinoma and cholecystectomy patients showed significantly greater values in the group with neoplasia of the large intestine than in those with cholecystectomy (P<0.0001) (Table 3).

Table 1 Average values for serum and bile CEA obtained from patients operated for colorectal carcinoma

Variables	Average (ng/ml)	S.D.	Minimum (ng/ml)	Maximum (ng/ml)	*n*
Serum CEA	8.5	18.7	0.1	111.0	44
Bile CEA	74.5	130.26	0.2	571.0	44

Wilcoxon (Z)=-4.614, P<0.0001 (Serum CEA *vs* Bile CEA), Notes: S.D.=standard deviation.

Table 2 Average values for serum and bile CEA obtained from patients operated for uncomplicated cholelithiasis

Variables	Average (ng/ml)	S.D.	Minimum (ng/ml)	Maximum (ng/ml)	*n*
Serum CEA	1.9	0.8	1.0 ng/ml	3.5 ng/ml	10
Bile CEA	1.2	0.9	0.3 ng/ml	2.9 ng/ml	10

Wilcoxon (Z)=-1.992, P<0.46 (Serum CEA *vs* Bile CEA), Notes: S.D.=standard deviation.

Table 3 Average values of the bile CEA/serum CEA ratio obtained from patients operated for colorectal carcinoma and cholelithiasis

Group	Variables	Average	S.D.	Minimum	Maximum	*n*
Colorectal carcinoma	Bile CEA/serum CEA	22.1	48.5	0.02	287.0	44
Cholelithiasis	Bile CEA/serum CEA	0.6	0.3	0.3	1.9	10

Mann-Whitney (U)=63.5, P<0.0001 (colorectal carcinoma group *vs* cholelithiasis group), Notes: S.D.=standard deviation.

In this study, there was no significant relationship between Dukes classification and serum CEA values (P=0.60) or bile CEA values (P=0.78). Besides, the bile and serum CEA values showed a non-significant relationship with the localization of the neoplastic lesions in the right colon, left colon or rectum (P=0.93 and P=0.53, respectively).

Four patients (9.1 %) with colorectal carcinoma showing elevated bile CEA levels who were operated on with curative intent presented evolution to hepatic metastases. They were initially diagnosed due to a rise in postoperative serum CEA levels, with an average of 8.6 ng/ml (range: 0.3 to 22.8 ng/ml). Only two of them presented increased serum CEA levels at the time of operation, although all four presented elevated bile CEA levels, with an average of 228.4 ng/ml (range: 6.6 to 571 ng/ml). They corresponded to 13.8 % of the 29 patients with elevated bile CEA. In these four patients, hepatic metastases developed on average around 9.7 months (range: 3 to 17 months) after removal of the primary colorectal lesion. Three of them were staged as Dukes C and one as Dukes B (Table 4). With the exception of the single Dukes B patient, who presented disease relapse with hepatic metastases disseminated in both lobes, the other three patients were submitted to hepatectomy for the removal of their metastases. Two of them died after removal of the hepatic lesions: one around nine months afterwards and the other 21 months afterwards. Although no necropsy was performed on these patients, there was no evidence of neoplasia recurrence up to the time of death. The third of these patients is still alive, without active disease, around eight months after extirpation of the hepatic metastases. The remaining 40 patients are alive, without signs of disease relapse, six to 48 months after removal of the primary colorectal lesion.

Table 4 Location of the lesion, Dukes staging and serum and bile CEA values, obtained from the patients operated for colorectal carcinoma with hepatic metastases during the follow-up

Case	Location	Dukes	Serum CEA (ng/ml)	Bile CEA (ng/ml)
1	Transverse colon	B	22.8	510.0
2	Rectum	C	2.1	292.0
3	Rectum	C	9.4	44.1
4	Sigmoid	C	6.6	6.6
Average			10.2	213.2

DISCUSSION

An ability to predict the appearance of hepatic metastases in patients operated on for colorectal carcinoma with curative intent could influence the use of adjuvant chemotherapy and intensify the follow-up of patients with indications for surgical treatment for lesions that could be extirpated[18,20,24-26].

Determination of bile CEA levels may be a potentially sensitive method for diagnosing hepatic metastases of colorectal carcinoma, since hepatic lesions smaller than 1 cm^3 are able to produce elevations of CEA concentrations in bile[11,16,22,26].

Huang and Tang[17] studied serum and bile CEA obtained by drainage using a preoperative duodenal tube in patients with benign affections and colorectal carcinoma, with and without hepatic metastases. These authors verified that the difference between bile CEA values in patients operated upon for colorectal carcinoma with and without hepatic metastases was significant, thus showing that the bile CEA level assisted in confirming the existence of hepatic lesions. Novell and Moura *et al*[19, 22] studied the levels of serum and bile CEA in patients with colorectal carcinoma and suggested that a determination of the bile CEA level might be useful in diagnosing concealed hepatic metastases. In the four patients of the present study who evolved with hepatic metastases, and in 29 other patients (65.9 %) who did not present metastases, the bile CEA values were also significantly greater than those for serum CEA. The average follow-up duration of 16.5 months was not yet sufficient for a conclusive evaluation of bile CEA determination as a predictive parameter for the appearance of hepatic metastases in these patients. An average follow-up for at least 60 months would increase the possibility of finding hepatic relapse of the disease and would furnish more consistent support for an assessment of the usefulness of bile CEA.

In patients with hepatic metastases of colorectal carcinoma, the concentrating capacity of the gallbladder has been singled out as the mechanism responsible for the elevated bile CEA levels in comparison with serum CEA levels[18,27-29]. The finding of elevated bile CEA values in the absence of hepatic metastases may also be credited to the fact that bile CEA is derived not only from the hepatic metastases but also from the primary tumor[29]. This situation is thought to contribute to the existence of a direct relationship between serum and bile CEA levels[13]. That is, when serum CEA levels are significantly elevated, bile CEA levels will also be, and consequently the serum CEA levels produced by the primary tumor may elevate the bile levels, even in the absence of hepatic metastases. These events could justify the findings in the present sample, in which 25 patients (86.2 %) with elevated bile CEA levels had not

presented hepatic metastases at the time of last follow-up consultation. Nonetheless, other studies[13,14,17,30] have suggested that increased CEA levels in bile in the presence of hepatic metastases are exclusively produced by neoformation in the liver, without originating in the portal circulation, indicating that patients with elevated bile CEA have silent hepatic metastatic disease. Paul *et al*[14] suggested that the bile CEA predicted hepatic disease only when collected after the removal of the primary tumor, which would avoid any significant contribution of serum CEA to bile CEA levels. It remains to be proven whether the finding of elevated serum and bile CEA levels during the extirpation of colorectal carcinoma, as occurred in 27 patients (61.4 %) of this study would constitute a selecting criterion for monitoring bile CEA levels after operation.

Yeatman *et al*[11] found elevated bile CEA levels in 70 % of their patients with colorectal carcinoma extirpated in a curative manner that had normal intraoperative hepatic ultrasonography. Over the average follow-up of 30 months for this group of patients, 13 % of them presented hepatic metastases. The result was close to that found in the present study, which observed that 9.1 % of patients had hepatic metastases over an average follow-up of 16.5 months. Li Destri *et al*[23] found a diagnostic accuracy for bile CEA of 91 % among patients operated for colorectal carcinoma with or without hepatic metastases, and 89.5 % among patients who evolved with hepatic metastases. Ishida *et al*[21] analyzed the relationship of CEA values in gallbladder bile collected during operation and in peripheral blood, with the appearance of metachronic hepatic metastases of colorectal carcinoma. In 49 patients without evidence of hepatic metastases at the time of operation, the elevated levels of bile CEA were predictive of the appearance of metachronic hepatic metastases with a 75 % sensitivity rate, 85 % specificity and 84 % accuracy. In another study, Ishida *et al*[15] showed that patients with elevated bile CEA or elevated bile CEA / serum CEA ratio could be candidates for hepatic relapse.

In the present study, four patients (9.1 %) operated for colorectal carcinoma with curative intent developed hepatic metastases after removal of the neoplastic lesion. Since the average follow-up duration for the patients was 16.5 months, it was possible that the number of patients affected by hepatic metastases and elevated bile CEA increased with the prolongation of the follow-up. This could make the determination of bile CEA levels a predictive parameter for the development of hepatic lesions.

However, other studies did not share the idea that bile CEA had a predictive value in relation to the development of hepatic metastases. Dorrance *et al*[20] determined serum and bile CEA levels in 26 patients submitted to curative surgery and followed up for an average of 63.5 months. Twelve patients (46.1 %) survived without relapse and 14 (53.8 %) died because of recurrence of neoplasia. The average value of serum CEA in the group free of disease was significantly greater than that in the group with relapse. The accuracy of serum CEA as a predictive indicator for concealed hepatic metastases was 77 %, in comparison with 72 % for bile CEA, without significant difference. The authors concluded that determination of intraoperative bile CEA levels was not more accurate than serum CEA as a predictive indicator for the occurrence of metastases among patients undergoing potentially curative surgery for colorectal carcinoma. Panaguzzi *et al*[16] studied the follow-up of patients operated for colorectal carcinoma without hepatic metastases although with elevated bile CEA levels. They concluded that, although the bile CEA levels were elevated in patients with hepatic metastases, these levels did not represent a predictive parameter for their presence in colorectal carcinoma. Garcia *et al*[18] determined the concentration of bile CEA in 24 patients with colorectal carcinoma, all of them exhibited elevated bile CEA, of whom 21 did not present evidence of hepatic metastases, while three had such lesions in the liver. These authors followed up their patients for an average of 32.3 months. Three of them developed hepatic metastases. The authors stressed that there was no clear relationship between the bile CEA values and the appearance of hepatic metastases, although they recognized that their sample was not large enough for definitive conclusions.

In our sample, nine patients (20.5 %) presented bile CEA values less than the respective values for serum CEA. One possible explanation for this fact is that the liver purification mechanisms for CEA produced by primary colorectal neoplasia might not be saturated and consequently the levels excreted into the bile would be less than into blood.

Bile CEA has apparently emerged as a promising tool for identifying patients with undiagnosed hepatic metastases. In patients with verified recurrence of neoplasia, the sensitivity of CEA determination in bile is greater than that for values found in the blood. Consequently, there could be a broadening of the indication for hepatectomy or radiofrequence ablation[31] due to hepatic metastases. Local or systemic chemotherapy procedures[32] could be introduced earlier, as could radioimmunoguided surgery or also treatments using anti-CEA monoclonal antibodies. To prove the real value of bile CEA for detecting hepatic relapses at an earlier stage, prospective studies with an adequate length of follow-up time, and standardized intervals between extirpation of colorectal neoplastic lesion and withdrawal of the bile samples, are needed.

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