ABSTRACT

The relevance of colorectal adenocarcinoma lies in its high incidence, with the liver being the organ most frequently affected by distant metastases. Liver metastases occur in 40 to 50% of patients with colorectal adenocarcinoma, accounting for approximately 80% of deaths in the first three postoperative years. Nevertheless, despite this, they are occasionally susceptible to curative treatment.

OBJECTIVE: The present investigation focuses on the relationship between the level of carcinoembryonic antigen (CEA) in gallbladder bile and the presence of liver metastases secondary to colorectal adenocarcinoma.

RESULTS: The CEA level in peripheral serum was 2.0 ng/ml (range: 0.7 to 3.8 ng/ml) in the control group, 11.4 ng/ml (range: 0.5 to 110.3 ng/ml) in group I, and 66.9 ng/ml (range: 2.1 to 670 ng/ml) in group II. In the portal system, serum mean values found were 1.9 ng/ml (range: 0.4 to 5.0 ng/ml) in the control group, 13.3 ng/ml (range: 0.8 to 33.3 ng/ml) in group I, and 70.8 ng/ml (range: 1.8 to 725 ng/ml) in group II. Mean values found in gallbladder bile were 4.1 ng/ml (range: 1.0 to 8.6 ng/ml) in the control group, 14.3 ng/ml (range: 0.0 to 93.0 ng/ml) in group I, and 154.8 ng/ml (range: 14.0 to 534.7 ng/ml) in group II.

CONTEXT: The relevance of colorectal adenocarcinoma lies in its high incidence, with the liver being the organ most frequently affected by distant metastases.

INTRODUCTION

Value of CEA level determination in gallbladder bile in the diagnosis of liver metastases secondary to colorectal adenocarcinoma

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INTRODUCTION

The relevance of colorectal adenocarcinoma lies in its high incidence, with the liver being the organ most frequently affected by distant metastases. Liver metastases occur in 40 to 50% of patients with colorectal adenocarcinoma, accounting for approximately 80% of deaths in the first three postoperative years. Nevertheless, despite this, they are occasionally susceptible to curative treatment.

The CEA level in peripheral serum was 2.0 ng/ml (range: 0.7 to 3.8 ng/ml) in the control group, 11.4 ng/ml (range: 0.5 to 110.3 ng/ml) in group I, and 66.9 ng/ml (range: 2.1 to 670 ng/ml) in group II. In the portal system, serum mean values found were 1.9 ng/ml (range: 0.4 to 5.0 ng/ml) in the control group, 13.3 ng/ml (range: 0.8 to 33.3 ng/ml) in group I, and 70.8 ng/ml (range: 1.8 to 725 ng/ml) in group II. Mean values found in gallbladder bile were 4.1 ng/ml (range: 1.0 to 8.6 ng/ml) in the control group, 14.3 ng/ml (range: 0.0 to 93.0 ng/ml) in group I, and 154.8 ng/ml (range: 14.0 to 534.7 ng/ml) in group II.

METHODS

The procedures that follow were in accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

From December 1993 to February 1996, 45 patients hospitalized in the Surgical Gastroenterology Discipline ward with a diagnosis of colorectal adenocarcinoma were enrolled. Patients with associated diseases, such as cholelithiasis, obstruction of the biliary pathways, intestinal inflammatory diseases, chronic or acute liver diseases and pancreatitis, were not included. For the classification of patients with and without liver metastases, three preoperative parameters were used, based on imaging techniques (computer tomography [CT], magnetic resonance imaging [MRI] and computed arterial portography [CTAP]) and intraoperative assessment. Thus, group I, which included 30 patients without liver metastases, and group II, which included 15 patients with liver metastases were created. Eighteen organ-donor patients were used as the control group. None had cholelithiasis, obstruction of the biliary pathways, cirrhosis, liver schistosomiasis or pancreatitis. With regard to gender, the control group was composed of 13 males and 5 females, with ages ranging from 19 to 66 years, mean age 35.6 years. In group I, 9 males and 21 females were studied, with ages ranging from 28 to 83 years, mean age 57.2 years; whereas in group II, 7 males and 8 females were studied, with ages ranging from 30 to 80 years, mean age 58.3 years (Table 1).

As for Dukes classification, group I was composed of 6 patients presenting Dukes A classification, 8 Dukes B, 12 Dukes C, and 4 were not classified as they underwent no tumor resection.
Forty-one patients were submitted to IMR and CTAP in addition to CT. The 4 patients who failed to undergo CTAP already presented liver metastases detected by CT and IMR. Imaging was always analyzed by two single examiners from the Imaging Diagnosis Department, who considered the scanning either positive or negative, according to the presence or absence of images suggesting liver metastases. The surgical inventory was made by the surgeon following the collection of both gallbladder bile and portal system blood. Following the macroscopic assessment of the liver, bimanual palpation was performed. Whenever the surgeon had any doubt, biopsy of the lesion was performed.

Peripheral venous blood was collected during anesthesia induction, by direct puncture of an upper limb vein. Ten ml was collected into a dry tube, which was centrifuged to separate serum.

At surgery, all patients were submitted to material collection soon after the abdominal cavity was opened, prior to the handling of the tumor or to the surgical inventory. In the control group, bile collection was performed before the liver was excised. Gallbladder bile was collected by puncture of the gallbladder fundus after a purse string suture using absorbable material.

All collected material was centrifuged and the separated serum was stored in a freezer at -20°C, until level determination was performed. The CEA level determination in serum was performed by using the Delfia® method. The CEA level determination in serum was performed by using the Delfia® method.

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Table 1. Distribution of mean, maximum and minimum values and standard deviation of CEA levels in peripheral serum

| Control | Group I | Group II |
|---------|---------|---------|
| n       | 16      | 30      | 15      |
| mean    | 2.0     | 11.4    | 66.0    |
| standard deviation | 0.9 | 24.6    | 668.8   |
| minimum | 0.7     | 0.5     | 2.1     |
| maximum | 3.8     | 110.3   | 670.0   |

Table 2. Distribution of mean, maximum and minimum values and standard deviation of CEA levels in bile

| Control | Group I | Group II |
|---------|---------|---------|
| n       | 18      | 30      | 15      |
| mean    | 4.1     | 14.3    | 154.8   |
| Standard deviation | 2.0 | 18.0    | 193.0   |
| minimum | 1.0     | 0.0     | 14.0    |
| maximum | 8.6     | 93.0    | 534.7   |

RESULTS

CEA levels obtained in peripheral serum were as follows: in group I patients, values ranged from 1.0 to 8.6 ng/ml (mean: 11.4 ng/ml; standard deviation: 24.6 ng/ml); in group II patients, values ranged from 2.1 to 670.0 ng/ml (mean: 66.0 ng/ml; standard deviation: 168.8 ng/ml) and in the control group patients, values ranged from 0.7 to 3.8 ng/ml (mean: 2.0 ng/ml; standard deviation: 0.9 ng/ml). No significant difference was found between values obtained in group I and the control group. However, such values were significantly lower than the ones obtained in group II (P = 0.0002) (Table 1).

CEA levels obtained in bile were as follows: in group I patients, values ranged from zero to 93.0 ng/ml (mean: 14.3 ng/ml; standard deviation: 18.0 ng/ml); in group II patients, values ranged from 14.0 to 534.7 ng/ml (mean: 154.8 ng/ml; standard deviation: 193.0 ng/ml) and in the control group patients, values ranged from 1.0 to 8.6 ng/ml (mean: 4.1 ng/ml; standard deviation: 2.0 ng/ml). No significant differences were found between values obtained in group I and the control group. However, such values were significantly lower than the ones found in group II (P = 0.00000006) (Table 2).

CEA levels found in bile were significantly higher than the ones found in peripheral serum in the three groups studied, with the following values found for groups I, II and the control: P = 0.033, P = 0.001 and P = 0.0001, respectively.

The cutoff point for the CEA level in bile was 7.0 ng/ml, as this CEA level determined the largest area under the curve 0.79 (Figure 1). Sensitivity found for this value was 63.3%, and specificity was 94%. Bile CEA levels tested were those close to the ones

![Image](image_url)
that presented optimal sensitivity and specificity in relation to the presence of colorectal adenocarcinoma in the 48 patients studied in groups I and control.

Two CEA levels in bile determined the largest areas under the curve: 14.0 and 20.0 ng/ml, with an area of 0.87. For the 14.0 ng/ml limiting value, sensitivity found was 100% and specificity was 73.3. For the 20.0 ng/ml cutoff point, sensitivity found was 86.7% and specificity 86.7%. Three CEA values in peripheral serum presented the largest areas under the ROC curve: 2.0, 8.0 and 12.5 ng/ml, with an area of 0.73 (Figure 2). For the 2.0 ng/ml cutoff point, sensitivity found was 100% and specificity 46.7. For the 8.0 ng/ml cutoff point, sensitivity found was 66.7% and specificity 80.6%. For the 12.5 ng/ml cutoff point, sensitivity found was 60% and specificity 86.7%. Comparison between the areas of the ROC curves, drawn to determine the best cutoff points to determine CEA levels in bile and to determine CEA in the peripheral serum, showed a significant difference (P = 0.009) (Figure 2).

**DISCUSSION**

CEA in peripheral serum was found to allow no distinction between patients in the control group from those without liver metastases, i.e. CEA in peripheral blood is not a good diagnosis test. This agrees with other studies in the literature that show CEA in peripheral serum to be of little sensitivity and specificity in cases of early colorectal adenocarcinoma. It was also found that CEA in peripheral serum allowed patients with liver metastases to be distinguished from those without liver metastases. This finding also agrees with data found in the literature showing improved sensitivity in the presence of liver metastases. CEA levels in bile showed the same statistical behavior as CEA in peripheral serum, i.e. they allowed no diagnosis of colorectal adenocarcinoma, but it was possible to distinguish patients with liver metastases from those without liver metastases. The distinction in this latter case had more efficacy, due to increased sensitivity and specificity. Statistical corroboration lies in the significant difference found between the ROC curves areas for both levels. And why is CEA in bile better able to detect liver metastases than CEA in peripheral serum? According to some authors, tumor cell products, with CEA among them, would be more concentrated in smaller amounts of bile than in larger amounts of serum and, furthermore, bile would be more exposed to such tumor products. These are plausible explanations, but there is controversy regarding the origin of CEA in bile, as CEA in bile may arise, at least in part, from the primary tumor. Experimental studies on the production, circulation, liver clearance and release of CEA in bile speak out against such possibility, although there are no studies on the release of CEA in bile in humans. A suggestion for studies that may solve such controversies, and which has already been presented by other authors, is to determine the level of CEA in bile prior to and following resection of the primary tumor.

A further issue which calls for discussion is that of false-positive results regarding CEA levels in bile, i.e. the patients without liver metastases who presented elevated CEA levels in bile. One of the possibilities is again the origin of CEA in the primary tumor, and a further possibility is cross-reactions. The existing methods are known to be adequate for determining CEA in serum, and failures may occur when they are used to determine CEA in bile. However, the most striking possibility for explaining elevated levels of CEA in bile in patients without detected liver metastases may relate to occult liver metastases. The only way to clear up such doubt is to follow up the patients without detected metastases who present high levels of CEA in bile, by performing serial tests to trace the appearance of such lesions. And why would it be important to know whether CEA in bile is predictive of the appearance of liver metastases? Because according to some authors, such a group of patients may benefit from some kind of prophylactic treatment to avoid the development of liver metastases.

**CONCLUSIONS**

The main conclusion of this study is that CEA in bile increases in the presence of liver metastases secondary to colorectal adenocarcinoma. Second, it may be concluded that CEA in bile is better than CEA in peripheral serum for the diagnosis of liver metastases. Two further questions remain to be answered in subsequent studies. One deals with the origin of CEA in bile and the other one concerns the false-positive results.
RESUMO

O objetivo do estudo foi veriﬁcar a correlação entre valores de CEA na bile vesicular e a presença de metástases hepáticas por adenocarcinoma colorretal.

MÉTODOS: Teste de estudo diagnóstico.

LOCAL: Disciplina de Gastroenterologia e Cirurgia do Hospital São Paulo, São Paulo, Brasil.

RESULTADOS: 45 pacientes portadores de adenocarcinoma colorretal, dos quais 30 foram classiﬁcados como não portadores de metástases hepáticas (grupo I) e 15 como portadores de metástases hepáticas (grupo II). O diagnóstico de metástases hepáticas foi feito por tomografia computadorizada, ressonância magnética e porto tomografia computadorizada. Durante a cirurgia, os pacientes foram submetidos à coleta de sangue periférico e bile da vesícula biliar. Um grupo control composto por 18 pacientes doadores.

CONCLUSÃO: O diagnóstico de metástases hepáticas por adenocarcinoma colorretal por métodos invasivos é de uma alta eficácia e sensibilidade. No entanto, a pesquisa de valores de CEA na bile vesicular poderia ser usada como ferramenta complementar no diagnóstico de metástases hepáticas.

PALAVRAS-CHAVE: Antígeno carcino-embriônico, Bile, Metástases Hepáticas, Fígado, Adenocarcinoma.