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Biliary Carcinoembryonic Antigen (CEA) Levels: The Role in Detection of Occult Hepatic Metastases in Colorectal Carcinoma

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ABSTRACT

Objective: Colorectal carcinoma (CRC) is a major public health concern, often complicated by hepatic metastasis. Despite the widespread use of serum Carcinoembryonic Antigen (CEA) for postoperative monitoring, early detection of hepatic metastasis remains elusive. This study aims to evaluate the prognostic significance of CEA levels in both peripheral blood and gallbladder bile for predicting hepatic metastasis in CRC patients, and to explore its potential utility for personalized treatment regimens.

Materials and Methods: A prospective randomized study was conducted over three years, enrolling 31 participants, 21 of whom underwent curative operations for CRC. Preoperative and postoperative CEA levels were assessed with rigorous diagnostic imaging and histological examinations. Patients were stratified into groups based on liver metastasis, postoperative chemotherapy, and CEA levels in both blood and bile.

Results: A statistically significant difference was found in biliary CEA levels between patients with (mean = 129.22 ng/ml) and without intraoperative liver metastasis (mean = 33.16 ng/ml), p-value = 0.01. Serum and biliary CEA levels were robustly correlated, $p > 0.05$. Biliary CEA values differed significantly across Duke's stages, with particular significance between the control group and Duke's stage D ($p < 0.001$). Among patients without intraoperative liver metastasis but with biliary CEA >10 ng/ml, 80% developed liver metastasis postoperatively despite undergoing chemotherapy.

Conclusion: This research highlights the pivotal role of biliary CEA levels in diagnosing latent hepatic metastases in colorectal cancer. Demonstrating superior sensitivity compared to traditional serum tests, biliary CEA presents a potential shift in early detection. Elevated levels suggest expanded therapeutic options, from timely hepatectomies to adopting radiofrequency ablation and anti-CEA monoclonal antibodies, enhancing the likelihood of better patient outcomes. Essentially, these findings enhance our understanding of colorectal cancer, emphasizing the importance of personalized care, early diagnosis, and customized treatments, thereby directing us toward better patient outcomes.

Keywords: Colorectal Cancer, Biliary CEA Levels, Hepatic Metastases, Early Diagnosis, Therapeutic Strategies, Serum Assays, Personalized Treatment, Patient Outcomes, Prospective Research, Neoplastic Lesions.

INTRODUCTION

Colorectal carcinoma (CRC) represents one of the foremost malignancies prevalent in Western nations, ranking notorious as the second most common cancer type (1, 2). Among the multiple complications arising from CRC, hepatic metastasis is predominant, manifesting in 20–25% of patients at the time of primary tumor extirpation (3). Such occurrences emphasize the urgent need for effective monitoring and early detection.

Existing practices for CRC relapse surveillance include periodic assessments of serum carcinoembryonic antigen (CEA) concentrations and hepatic imaging using various techniques, such as ultrasonography, tomography, and magnetic resonance (4, 5). Despite technological advancements, an estimated 10–30% of hepatic metastases remain undiagnosed, curtailing therapeutic success and overall survival rates (6, 7).

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The exploration of CEA as a tumor marker has a rich historical context, with its presence first described in malignant tumors and fetal intestinal tissues in 1965 by Gold and Freedman (8). Since then, the blood CEA assay has become an integral part of preoperative and postoperative monitoring in CRC patients, with the aim of early detection of disease relapse (9).

A pivotal turning point in the application of CEA came in 1989, with Yeatman et al. suggesting that bile CEA concentrations might hold the key to detecting hepatic metastases at an earlier stage (8, 10). This hypothesis was based on the observation that CEA originating from hepatic metastases can be secreted into both bile and blood, with detectable increases occurring earlier in the gallbladder (10). Despite encouraging studies, the use of bile CEA levels remains a subject of ongoing debate and research, with varying results and perspectives in the literature (11, 12).

This study aimed to unravel the prognostic implications of CEA determination in both peripheral blood and gallbladder bile in a series of patients undergoing curative operations for CRC. The relationship between these determinations, morphological characteristics of the neoplasia, and hepatic relapse will be meticulously analyzed. Furthermore, this study aimed to elucidate the potential role of biliary CEA in diagnosing occult hepatic metastases, thereby contributing to personalized therapeutic strategies and improving outcomes.

Unveiling the possible predictive value of biliary CEA levels for metachronous liver metastasis in CRC is a vital step towards a more precise and early diagnosis. If established, this marker could revolutionize the current paradigm of CRC treatment, providing a means to identify patients at a higher risk of hepatic recurrence. Thus, the study not only stands as an inquiry into a scientific hypothesis, but also strives to translate the findings into actionable clinical practices.

Bridging the knowledge gaps in CRC hepatic metastasis detection, this study pioneers an insightful exploration of the potential of biliary CEA as a diagnostic and prognostic tool. By synthesizing the existing literature with rigorous empirical investigation, we set the stage for a profound understanding of the complex interplay between CEA levels in different body fluids and colorectal malignancy. This outcome could pave the way for a paradigm shift in the early detection and management of one of the most enigmatic complications of CRC, promising a brighter horizon in oncological care.

MATERIAL and METHODs

Study Patients

A three-year prospective randomized study was conducted, focusing on 21 colorectal operations. Including the control group, the total number of participants was 31, consisting of 21 patients who underwent colorectal surgeries and a control group of 10 individuals.

Patient demographics were as follows:

- Study Group:12 females (38%) and 9 males (29%), aged between 52 and 94 years, mean age 66.8 years.

- Control Group:8 females (25%) and 2 males, aged between 26 and 58 years, mean age 44.5 years.

Preoperative Assessment: Patients requiring emergency surgery and those diagnosed with colorectal cancer were included in the study. Preoperative examinations for patients with colorectal cancer included anamnesis and physical examination, CEA, and routine biochemical tests, rectoscopy or colonoscopy with biopsy for suspicious lesions, ultrasonography, computerized tomography, lung radiography, and electrocardiogram.

Patients identified as having benign or non-colorectal neoplasms that could elevate CEA levels were excluded from the study. Decisions regarding the necessity of surgery were made after assessing the tumor localization, invasion, and presence of metastases.

The patients received liquid food for at least two days before surgery, and mechanical bowel cleansing was performed. Intraoperative examination of tumor invasion into surrounding organs was performed, with resections targeting the complete removal of tumoral tissue without harming vital organs.

Patients were subsequently divided into four groups for study, considering their intraoperative and postoperative situations, including the presence of liver metastasis, chemotherapy post-surgery, and biliary and serum CEA levels.

Postoperative Patient Assessment and Follow-up Procedure: Postoperative and oncological evaluations were conducted at the Okmeydanı Training Hospital Oncology Clinic considering serum CEA, abdominal CT, and USG measurements.

The follow-up procedure involved the following steps: Quarterly control (anamnesis, physical examination, rectal touché), annual colonoscopy or rectoscopy with biopsies as needed, semi-annual ultrasonography, annual computerized tomography, integrated examination if serum CEA >10 ng/ml, CEA determination at specified intervals, exploration for curative resection if recurrent tumors were detected.

Sample Collection and CEA Assay: This study used biliary and serum Carcinoembryonic Antigen (CEA) measurements. Biliary CEA values and Duke's classification were assessed using the Kruskal–Walli’s test. Serum and biliary CEA levels were examined using the Wilcoxon signed-rank test.

Methodologies for serum and biliary CEA measurements included the use of a radioimmunoassay technique for serum CEA level determination and specific procedures for biliary CEA level detection.

Ethical Consideration: The study was conducted between February 1997 and December 1999, with 21 suitable colorectal surgeries. Ethical committee approval and written informed consent were obtained from all participants.

Statistical Analysis

Given the nature of the samples, nonparametric statistical tests were performed. Quantitative variables are expressed as absolute frequency (n) and relative frequency (%), employing arithmetic mean, standard deviation, Mann-Whitney test, Wilcoxon test, and Kruskal-Walli’s test. Data normality was assessed using the Kolmogorov-Smirnov test, and variance homogeneity was verified using the Levene test. A 95% significance level was maintained throughout the study.

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RESULTs

Localization of Colorectal Cancer in the Studied Patients

Comorbidity, Postoperative Oncological Treatments, and Liver Metastasis Development

The study population demonstrated a comorbidity rate of 14.2%, with specific comorbidities as follows: Hypertension and diabetes: 2 patients (9.5%), diabetes with ischemic coronary heart disease: 1 patient (4.7%)

In the cohort of 21 patients investigated, all patients were diagnosed with colorectal cancer across distinctive anatomical locations. The distribution of cancer localization was delineated as follows: ascending colon (9.5%, two patients), transverse colon (9.5%, two patients), descending colon (14.2%, three patients), rectum (14.2%, three patients), and rectosigmoid junction (52.6%, 11 patients).

Preoperative and Intraoperative Biliary Carcinoembryonic Antigen (CEA) Levels

Among the 21 patients, 76% (16 patients) had preoperative serum CEA levels > 10 ng/ml. A corresponding elevation in biliary CEA levels was observed intraoperatively in the same percentage of the patients. Conversely, in five patients (23.8%), biliary CEA levels were < 4 ng/ml. This bifurcation in CEA level leads to a nuanced classification of patients.

Patient Grouping Based on Intraoperative Findings

Group 1: This group, comprising 10 patients (47.6%), was characterized by the absence of liver metastasis during the operation, with biliary CEA levels exceeding 10 ng/ml.

Group 2: consisted of five patients (23.8%); this group displayed no liver metastasis and had intraoperative biliary CEA levels below 4 ng/ml.

Group 3: This subgroup included six patients (28.5%) who had apparent liver metastasis during the operation, concomitant with biliary CEA levels above 10 ng/ml.

Group 4: Serving as a control group, including patients with non-obstructive biliary system diseases, all exhibiting biliary CEA levels < 2 ng/ml.

The characteristics and biliary CEA levels of the groups are shown in **Table 1**.

All patients underwent postoperative chemotherapy (S-FU, cisplatin combination therapy). Intriguingly, 80% of patients in Group 1 developed liver metastasis despite the absence of intraoperative liver metastasis and post-surgical chemotherapy. The statistical measures of sensitivity, specificity, positive predictive value, and negative predictive value are presented in **Table 2**.

Biliary CEA Levels and Intraoperative Detection of Liver Metastases

In the cohort of patients without intraoperatively detected liver metastases, the mean biliary Carcinoembryonic Antigen (CEA) levels were measured at 33.16 ng/ml, with a range spanning from 0.6 138 ng/ml. Conversely, in the cohort with intraoperatively confirmed liver metastases, the mean biliary CEA levels were substantially higher, registering at 129.22 ng/ml and ranging from 68 to 215 ng/ml. Importantly, the variance between the two groups was statistically significant (p-value = 0.01 (**Figure 1**).

Relationship between Serum CEA and Biliary CEA

A robust correlation was confirmed between serum CEA and biliary CEA levels, as no significant difference was detected ($p > 0.05$), evaluated using the Wilcoxon signed-rank test.

Duke's Classification Comparison with Serum and Biliary CEA

A Kruskal-Wallis Test revealed substantial disparities in biliary CEA values across Duke's stages and in the control group ($p < 0.0001$).

Specific statistical significance was detected between the control group and Duke's stage D ($p < 0.001$).

Multiple comparison tests revealed no significant variance between Duke's stages B and C concerning biliary CEA values ($p > 0.005$), but a trend was observed, with lower biliary CEA values in the control group than in Duke's stages B and C. Duke's stage D did not manifest significant differences singularly from Duke's stages B and C ($p < 0.05$).

These multifaceted relationships are detailed in **Tables 3**, and **4** enhancing a comprehensive understanding of the correlations and disparities among the study variables.

Correlation between Tumor Pathology and Biliary CEA Levels

Poorly differentiated adenocarcinomas predominantly have elevated biliary CEA levels (>10 ng/ml), constituting 19% of such cases. Moderately differentiated tumors displayed elevated levels in 14.2% of the cases. In contrast, well-differentiated tumors exhibited a broader range of biliary CEA levels, with 38% having levels >10 ng/ml, 14.2% within 0-5 ng/ml, and 4.7% between 0-10 ng/ml. Mucinous carcinomas accounted for 4.7% of the tumors with CEA levels >10 ng/ml. Table 5 shows the association between biliary CEA levels and tumor differentiation type.

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Table 1: Biliary CEA Characteristics in Study Patients

Group	N	Biliary CEA Levels (ng/ml)
Group 1	**N**	**Biliary CEA Levels (ng/ml)**
No Liver Metastasis, Biliary CEA >4 ng/ml	1	19,8
	2	22,7
	3	70
	4	138
	5	89,4
	6	45,4
	7	10,6
	8	13
	9	76,4
	10	15,7
Group 2	**N**	**Biliary CEA Levels (ng/ml)**
No Liver Metastasis, Biliary CEA <4 ng/ml	1	0,9
	2	3,7
	3	0
	4	6
	5	1,2
Group 3	**N**	**Biliary CEA Levels (ng/ml)**
Liver Metastasis Present, Biliary CEA >10 ng/ml	1	156
	2	98
	3	215
	4	118
	5	120
	6	68
Group 4 (Control)	**N**	**Biliary CEA Levels (ng/ml)**
Cholelithiasis	1	0,2
	2	1,6
	3	1
	4	0,3
	5	0,5
	6	1
	7	0,4
	8	0,2
Gallbladder Polyp	9	2
	10	2

Table 2: Relationship Between Biliary CEA Levels and Liver Metastases

Biliary CEA Levels	Metastasis Present	Metastasis Absent	Total
Biliary CEA >10 ng/ml	True Positive, N=6	False Positive, N=10	16
Biliary CEA <10 ng/ml	False Negative, N=0	True Negative, N=5	5
Total	6	15	

Table 3: Comparison of Serum and Biliary CEA Levels Across Duke's Staging Classification

Stage	Serum CEA n	Biliary CEA Levels (ng/ml) Median
Duke's Stage A	0	N/A
Duke's Stage B	12	19.50
Duke's Stage C	3	7.00
Duke's Stage D (Liver Metastasis)	6	98.00
Cholelithiasis (Control Group)	10	N/A

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Table 4: Preoperative and Postoperative Serum and Biliary CEA Levels Stratified by Duke's Staging Classification

Patient No	Preoperative			Postoperative	
	Serum CEA Level (ng/ml)	Biliary CEA Level (ng/ml)	Duke's Classification	Biliary CEA Level (ng/ml)	Duke's Classification
1	21	19,8	B2	70	B1
2	38	22,7	B2	19,8	B2
3	72	70	B1	22,7	B2
4	148	138	C	89,4	B2
5	72	89,4	B2	45,4	B2
6	46	45,4	B2	10,6	B2
7	14	10,6	B2	13	B2
8	18	13	B2	19,7	B2
9	7	19,7	B2	76,4	C
10	93	76,4	C	138	C
11	1	0,9	C	1,2	B1
12	1,7	2	B1	3,7	B1
13	4	3,7	B1	2	B1
14	1	0,6	B2	0,6	B2
15	2	1,2	B1	0,9	C
16	94	156	D	156	D
17	100	98	D	98	D
18	193	215	D	215	D
19	120	118	D	118	D
20	96	120	D	120	D
21	35	68	D	68	D

Table 5: Association between Pathological Features of Tumors and Biliary CEA Levels in Study Patients

Tumor Type, Adenocarcinoma	Biliary CEA Level (ng/ml)					
	0-5 ng/ml		0-10 ng/ml		> 10 mg /dl	
	n	%	n	%	n	%
Poorly Differentiated					4	19
Moderately Differentiated	1	4,7			3	14,2
Well Differentiated	3	14,2	1	4,7	8	38
Mucinous Carcinoma					1	4,7

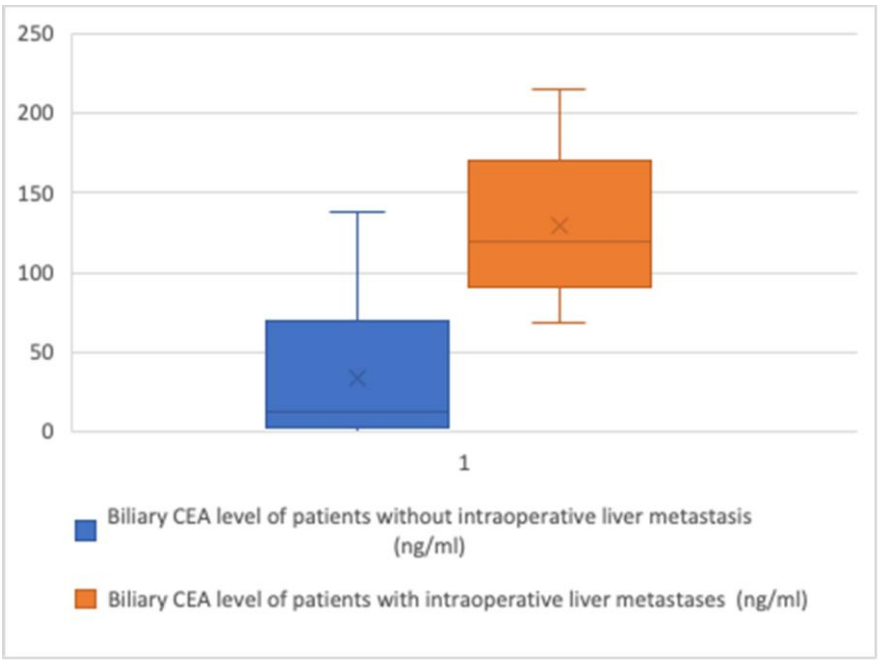

Figure 1: Mean Biliary CEA Levels in Patients with and without Intraoperatively Detected Liver Metastases

DISCUSSION

The ability to predict the emergence of hepatic metastases in patients undergoing colorectal carcinoma surgery with curative intent may profoundly affect medical decisions. This might guide the application of adjuvant chemotherapy and enhance the meticulous monitoring of patients who show signs indicating the need for surgical intervention for removable lesions (6, 13, 14).

One possible way to advance this critical aspect of patient care is to assess bile carcinoembryonic antigen (CEA) concentrations. This approach appears promising for detecting hepatic metastases originating from colorectal carcinoma, especially when hepatic lesions with a volume smaller than 1 cm ^{3} are considered. Such lesions can induce significant elevations in bile CEA concentrations, emphasizing the potential sensitivity of this method (13, 15).

Several studies have further contributed to our understanding of the role of bile and serum CEA in this context. The investigation conducted into Serum and bile CEA levels were measured through preoperative duodenal tube drainage in patients with benign disorders and colorectal carcinoma, both with and without hepatic metastases. Their findings highlighted a significant difference in bile CEA levels between the groups of patients who had undergone surgery for colorectal carcinoma with and without hepatic metastases, thereby corroborating that bile CEA levels can be instrumental in verifying hepatic lesions (16).

Building on this study, Ramphal et al. examined serum and bile CEA levels in patients with colorectal carcinoma (6, 17). Their research implied that determination of bile CEA levels could be an effective tool for uncovering hidden hepatic metastases. These studies collectively demonstrate a potentially transformative direction in the diagnosis and management of hepatic metastases in patients with colorectal carcinoma, although further investigation and validation are required to establish standardized practices.

Elevated preoperative and intraoperative serum CEA levels found in 76% of patients are indicative of an existing trend in colorectal cancer studies. This corroborates the finding that elevated CEA levels are associated with tumor stage and metastatic disease (11). The nuanced classification based on CEA levels may be instrumental in understanding different disease phenotypes and clinical manifestations.

In the examined cohort of 21 patients diagnosed with colorectal cancer, the distribution of the disease across various anatomical locations revealed an understanding of the diversity in tumor sites. With a notable prevalence at the rectosigmoid junction (52.6%), these data may influence targeted diagnostic and treatment protocols.

A significant observation in this cohort was the consistent elevation of preoperative and intraoperative biliary CEA levels (> 10 ng/ml) in 76% of patients. These data align with previous research and have a potential role in refining the risk stratification and management strategies.

The distinction between Groups 1 and 2 (47.6% and 23.8% of the patients, respectively) depends on biliary CEA levels, with or without liver metastasis.

This bifurcation in CEA levels provides nuanced insight into the underlying biological behavior and may guide targeted interventions.

The presence of liver metastasis concomitant with elevated biliary CEA levels in Group 3 (28.5%) indicates a possibly more aggressive disease pattern. This group's characterization aligns with the findings of Waisberg, in which bile CEA levels were instrumental in confirming hepatic lesions (2). The implications of this grouping are far-reaching, potentially influencing diagnostic precision and therapeutic strategies. This group's strong correlation between liver metastasis and biliary CEA levels warrants a comprehensive understanding of the underlying molecular mechanisms.

The grouping of study patients based on intraoperative findings revealed essential dimensions that could shape personalized treatment approaches. In particular, the alarming distribution of liver metastasis in Group 1 and the aggressive disease pattern portrayed in Group 3 elucidate areas requiring further exploration. With continued research into underlying mechanisms, understanding the interplay between biliary CEA levels and tumor behavior could pave the way for more refined and effective management strategies for CRC patients with colorectal cancer.

The relationship between comorbidities, oncological treatments, and liver metastasis development provides a complex scenario for colorectal cancer management. Intriguingly, the high rate of liver metastasis in Group 1 necessitates a close examination of the effectiveness of adjuvant chemotherapy in preventing hepatic recurrence. This finding contrasts with the general efficacy of chemotherapy in reducing metastasis, as highlighted in various studies (5, 14).

The correlation between serum CEA and biliary CEA levels in this study aligns with existing literature, which suggests a direct relationship between these markers (7, 11, 18). This relationship could also reflect the role of the liver in concentrating CEA, thus facilitating its earlier detection in bile (18).

The disparities in biliary CEA values across Duke's stages demonstrate the potential of using this marker in staging and prognosis. This is in line with the study by Li Destri et al. (3), who found a diagnostic accuracy for bile CEA of 91% among patients operated for colorectal carcinoma.

The potential use of bile CEA as a sensitive method for diagnosing hepatic metastases, as reported in previous studies (2, 3, 5), reinforces the clinical utility of this marker. Similarly, the alignment of CEA levels with Duke's stage can further guide treatment decisions.

However, some of the findings, such as the unexpected development of liver metastases in Group 1 and the non-significant differences between biliary and serum CEA levels in predicting hepatic metastases, pose challenges and warrant further research. The prolonged follow-up may reveal more consistent support for bile CEA as a predictive parameter.

CONCLUSION

This research illuminates critical dimensions in colorectal cancer diagnosis, intervention, and prognostic understanding. One of the primary takeaways is the potent utility of biliary CEA levels as a diagnostic marker for latent hepatic metastases. Compared to conventional serum assays, biliary CEA showcases heightened sensitivity, suggesting a paradigm shift in early diagnostic practices.

Elevated biliary CEA levels hint at a broader spectrum of therapeutic strategies that may become available. This could range from timelier hepatectomies to early incorporation of radiofrequency ablation and the proactive use of anti-CEA monoclonal antibodies. It offers a chance at a preemptive strike against potential metastases, thus enhancing patient outcomes.

Furthermore, the study underscores an imperative need for subsequent, meticulously designed prospective research on biliary CEA. Future investigations should ensure consistent sample collection intervals post-neoplastic lesion removal and sustained patient follow-ups, ensuring a comprehensive assessment of bile CEA's clinical efficacy.

In summary, this study enhances our current understanding of the intricate pathology of colorectal cancer, underscoring the potential for personalized treatments, strengthened early detection, and more precise therapeutic targeting. Such revelations epitomize the essence of progressive scientific research, driving us closer to optimal cancer patient care and improved prognostic outcomes.

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Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

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