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RESEARCH ARTICLE

Serum CEA and CA 19-9 along the colorectal Adenoma – Carcinoma sequence

Hayder S. Azzal[1] , Estabraq A. Al-Wasiti[2] (Ph.D) , Ban J. Qasim[3] (ph.D).

1,2 Dept. of Chemistry and Biochemistry- College of Medicine – Al-Nahrain University, Baghdad-Iraq.

3 Dept. of Pathology- College of Medicine – Al-Nahrain University, Baghdad-Iraq.

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Corresponding Author

Hayder S. Azzal

Abstract

Background

Colorectal cancer (CRC) ranks the sixth among the commonest ten cancers in Iraq. It is a major public health problem and there is renewed interest in understanding the basic principles of its molecular biology.

Objective

Assessment of serum CEA and CA19-9 levels in human colorectal tumors and their correlation with different clincopathological parameters

Methods

The study was prospectively designed, sixty serum samples from patients with colorectal tumors (including 30 from patients with colorectal adenoma and 30 from patients with colorectal adenocarcinoma), and 30 serum samples from apparently normal colorectal taken from healthy persons were included in this study. Quantitative measurement of Carcino-embryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) using VIDAS automated instrument was done.

Results

The mean value of CEA was significantly higher in patients with colorectal carcinoma in comparison to colorectal adenoma and healthy controls ($p<0.0005$), and it was not significantly different in colorectal adenomas in comparison to healthy controls. CEA levels was significantly higher in large size adenomas (≥1cm), and those with severe dysplasia. There was significant correlation between CEA and stage C2 in colorectal carcinoma ($p<0.0005$).

The mean value of CA19-9 was higher in patients with colorectal carcinoma in comparison to colorectal adenoma ($p=0.001$) and healthy controls ($p<0.0005$), and it was not significantly different in colorectal adenomas in comparison to healthy controls . CA19-9 levels was significantly higher in large size adenomas (≥1cm), and those with severe dysplasia. CA19-9 levels was significantly higher in stage C2 of colorectal carcinoma

Conclusions

CEA and CA19-9 levels are significantly correlated with size and degree of dysplasia of adenoma and stage of carcinoma. CEA is more sensitive than CA19-9 in adenoma and colorectal carcinoma.

INTRODUCTION

Colorectal cancer (CRC) ranks the sixth among the commonest ten cancers in Iraq[1]. It is a major public health problem and there is renewed interest in understanding the basic principles of its molecular biology[2]. There is growing body of evidence in early detection of this disease with novel screening modalities to reduce compliance and increase specificity of available methods [3].

Carcinoembryonic antigen (CEA), an autoantigen expressed at low levels in normal intestinal epithelia. It is markedly upregulated in most colorectal cancer (CRC) [4]. CEA affects tumorigenesis by enhancing tumor cell survival and by inducing tumor angiogenesis [5] .Carcinoembryonic antigen (CEA) is not recommended for use as a screening test for colorectal cancer, it may be ordered preoperatively in patients with colorectal carcinoma if it would assist in staging and surgical treatment planning. Although elevated preoperative CEA may correlate with poorer prognosis, CEA is the marker of choice for monitoring metastatic colorectal cancer during systemic therapy [6]. Until now, serum CEA level is still frequently used as a marker to monitor recurrence after surgery, but rarely as a marker in predicting the disease [7].

Carbohydrate antigen 19-9 (CA19-9) is a type of glycosphingolipid that is a specific sialyzed derivative of the Lea blood group and shown as Lexa. Recent reports indicated that serum CA19-9 is frequently elevated in subjects with various gastrointestinal malignancies, such as pancreatic, colorectal, gastric, and hepatic carcinomas[8]. CA19-9 has been used as a tumor marker of colorectal cancer in clinical practice, usually accompanied with CEA. Several authors have described the prognostic significance of CA19-9. Some studies have indicated the possible usefulness of CA19-9 in monitoring recurrence, whereas others have shown contradictory results[9]. Carbohydrate antigen 19-9 might be helpful in the management of colorectal carcinoma.

Methods

This study agreed to the terms of ethical considerations according to the form prepared for this purpose by the Iraqi Ministry of Health. It was also approved by the Committee of ethical standards in the Faculty of Medicine, Al-Nahrain University, one of the colleges affiliated to the Ministry of Higher Education and Scientific Research, Iraq

The study was prospectively designed. A total of 90 subjects serum samples were included in the study. Out of the total number of samples, 60 from patients with colorectal tumors (including 30 from patients with colorectal adenoma and 30 from patients with colorectal adenocarcinoma), were collected from Al-Zahra Teaching Hospital in Al-Kut City, Al-Emamayn Al-Khadhimayn Medical City, Oncology Teaching Hospital, Gastroenterology and Hepatology Teaching Hospital and Al-Yarmouk Teaching Hospital, for the period from December 2013 to February 2015. The control group included 30 serum samples of apparently normal colorectal taken from healthy persons, these was quantitative measurement of Carcino-embryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) using VIDAS automated instrument was done.

Venous blood samples, about 3 ml, were collected from each patient and healthy control cases in plain tubes containing no additives. The blood samples were obtained from the patients prior to operation. After allowing the blood to clot at room temperature for 10 minutes blood samples were centrifuged at 5000 rpm for 10 minutes. Sera were separated, divided into aliquots and stored at -200 C prior to the assay.

The quantitative measurement of CEA and CA19-9(tumer markers) had been carried out by VIDAS, which was applied using the ELFA technique (Enzyme linked Fluorescent Assay) .The normal value of the VIDAS CEA assay is up to 3.0 ng/ml . The normal value of the VIDAS CA19-9 assay is up to 37 U/ml.

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Results

Descriptive analysis according to tumor markers in controls, adenomas and carcinomas

The mean value of CEA in patients with colorectal carcinoma was (60.6+55.87)ng/ml, with a range of 2.29 ng/ml to 185.3 ng/ml. The mean value of CEA in patients with colorectal adenoma was (5.8+9.65) ng/ml, ranging from 0.98 ng/ml to 54.28 ng/ml. The mean value of CEA in control group was (1.26+0.64) ng/ml, ranged from 0.42 ng/ml to 3.02 ng/ml. There is significant difference in the mean value of CEA between carcinoma, adenoma, and control groups ($p<0.0005$) (table 1).

The mean value of CA19-9 in patients with colorectal carcinoma was (97.7+139.61)U/ml, with a range of 12.5 U/ml to 464.8 U/ml. The mean value of CA19-9 in patients with colorectal adenoma was (22.39$\pm$32.08)U/ml, ranging from 3.5 U/ml to 180.7 U/ml. The mean value of CA19-9 in control group was (10.29$\pm$7.07)U/ml, ranged from 3.1 U/ml to 35.6 U/ml. There is significant difference in the mean value of CA19-9 between carcinoma, adenoma, and control groups ($p<0.0005$) (table 1).

Table 1. Descriptive analysis according to tumor markers in controls, adenomas and carcinomas

Tumor markers	Groups	N	Mean	Std. Deviation	Std. Error	Minimum	Maximum	P value
CEA (ng/ml)	carcinoma	30	60.6113	55.87919	10.20210	2.29	185.32	p<0.0005
	Adenoma	30	5.8113	9.65677	1.76308	0.98	54.28	
	Control	30	1.2667	0.64966	0.11861	0.42	3.02	
CA19-9 (U/ml)	carcinoma	30	97.7167	139.6137	25.48986	12.50	464.80	p<0.0005
	Adenoma	30	22.3933	32.08390	5.85769	3.50	180.70	
	Control	30	10.2967	7.07446	1.29161	3.10	35.60	

sensitivity and specificity of tumor markers

The majority of cases with colorectal carcinoma (27 out of 30, 90%) had elevated CEA levels (higher than 3.0 ng/ml), while (13 out of 30, 43.3%) patients with adenomas have elevated CEA levels higher than 3.0 ng/ml. All cases of control group had normal CEA levels. The distribution was statistically highly significant (P value < 0.0005) (table 2). In comparison with healthy controls, carcinoma cases have no false positives for CEA, with 10.0% false negatives. Sensitivity and specificity of CEA in detecting colorectal carcinoma were (90% and 100%), respectively. Also in the condition of adenoma, there were no false positives and 56.7% of false negatives, with a sensitivity and specificity accounting (43.3% and 100%), respectively (table 2).

Table 2. Distribution of carcinoma, adenoma and control groups according to CEA levels

			Carcinoma	Adenoma	Control	Total
CEA	Normal ≤ 3.0 ng/ml.	N	False negative (FN) = 3	False negative (FN) = 17	True negative (TN) = 30	50
		%	10.0%	56.7%	100.0%	55.6%
	Elevated > 3.0 ng/ml.	N	True positive (TP) = 27	True positive (TP) = 13	False positive (FP) = 0	40
		%	90.0%	43.3%	0%	44.4%
Total		N	30	30	30	90
		%	100.0%	100.0%	100.0%	100%
Sensitivity			90.0%	43.3%	P. value < 0.0005	
Specificity			100.0%	100.0%		
Positive predictive value (PPV)			100.0%	100.0%		
Negative predictive value (NPV)			99.9%	63.8%		

The majority of cases with colorectal carcinoma (21 out of 30, 70%) had normal CA19-9 levels (up to 37 U/ml). Also the majority of cases with colorectal adenomas had normal CA19-9 levels (27 out of 30, 90 %). All cases of control group had normal CA19-9 levels. The distribution was statistically highly significant (P value = 0.002) (table 3). In comparison with healthy controls, carcinoma cases have no false positives for CA19-9, with 70.0% false negatives. Sensitivity and specificity of CA19-9 in detecting colorectal carcinoma were (30% and 100%), respectively. Also in the condition of adenoma, there were no false positives and 90% of false negatives, with a sensitivity and specificity accounting (10% and 100%), respectively (table 3).

Table 3. Distribution of carcinoma, adenoma and control groups according to CA19-9 levels

			Carcinoma	Adenoma	Control	Total
CA19-9	Normal ≤ 37 U/ml.	N	False negative (FN) = 21	False negative (FN) = 27	True negative (TN) = 30	78
		%	70.0%	90.0%	100.0%	86.7%

	Elevated > 37 U/ml.	N	True positive (TP) = 9	True positive (TP) = 3	False positive (FP) = 0	12
		%	30.0%	10.0%	0%	13.3%
Total		N	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
Sensitivity			30.0%	10.0%	P. value = 0.002	
Specificity			100.0%	100.0%		
Positive predictive value (PPV)			100.0%	100.0%		
Negative predictive value (NPV)			58.8%	52.2%		

Descriptive analysis of tumor markers according to clinicopathological parameters of patients with colorectal adenoma

The mean values of CEA levels of patients groups (under 50, 50-59, and above 59) years were (4.68 ± 1.954, 3.46 ± 2.224,and 8.81 ± 14.903) ng/ml, respectively with no significant difference (p = 0.381). The mean values of CA19-9 levels of patients groups (under 50, 50-59, and above 59) years were (15.96± 8.224, 16.94± 10.673,and 30.97± 49.303) U/ml, respectively with no significant difference (p = 0.504) (table 4).

Table 4. Descriptive analysis of tumor markers of patients with colorectal adenoma according to age

Tumor markers	Age group	Mean	Std. Deviation	Std. Error	P. value
CEA (ng/ml)	<50	4.6880	1.95474	0.87419	0.381
	50-59	3.4669	2.22417	0.61687	
	>59	8.8192	14.90385	4.30237	
CA19-9 (U/ml)	<50	15.9600	8.19805	3.66628	0.504
	50-59	16.9462	10.67377	2.96037	
	>59	30.9750	49.30381	14.23278	

The mean values of CEA levels of adenoma size groups (< 1cm, and ≥ 1cm) were (3.87 ± 2.78, and 12.17 ± 18.98) ng/ml, respectively with significant difference (p = 0. 044) (table 5).

The mean values of CA19-9 levels of adenoma size groups (< 1cm, and ≥ 1cm) were (15.09 ± 9.71, and 46.37 ± 61.62) U/ml, respectively with significant difference (p = 0.021) (table 5).

Table 5. Descriptive analysis of tumor markers of patients with colorectal adenoma according to size of adenoma

Tumor markers	Size group	Mean	Std. Deviation	Std. Error Mean	P. value
CEA ng/ml	<1cm	3.8743	2.78980	0.58171	0.044
	>=1cm	12.1757	18.98810	7.17683	
CA19-9 U/ml	<1cm	15.0957	9.71978	2.02671	0.021
	>=1cm	46.3714	61.26983	23.15782	

The mean values of CEA levels in patients with colorectal adenomas according to degree of dysplasia (mild, moderate, and severe) were (3.62 ± 2.99, 5.15 ± 3.68, and 16.59 ± 25.18) ng/ml, respectively with significant difference (p = 0.046) (table 6).

The mean values of CA19-9 levels in patients with colorectal adenomas according to degree of dysplasia (mild, moderate, and severe) were (13.67 ± 9.11, 19.98 ± 8.87, and 64.87 ± 80.26) U/ml, respectively with significant difference (p=0.010) (table 6).

Table 6. Descriptive analysis of tumor markers of patients with colorectal adenomas according to degree of dysplasia

Tumor markers	Degree of dysplasia	Mean	Std. Deviation	Std. Error	Minimum	Maximum	P. value
CEA (ng/ml)	Mild	3.6224	2.99529	0.72646	0.98	12.32	0.046
	Moderate	5.1556	3.68411	1.22804	1.77	10.93	
	Severe	16.5900	25.18048	12.59024	2.02	54.28	
CA19-9 (U/ml)	Mild	13.6706	9.11138	2.20983	3.50	31.20	0.010
	Moderate	19.9889	8.87897	2.95966	8.50	38.30	
	Severe	64.8750	80.26765	40.13383	4.60	180.70	

Descriptive analysis of tumor markers according to clinicopathological parameters of patients with colorectal carcinoma

The mean values of CEA levels of patients groups (under 60, 60-69, and above 69) years were (77.13 ± 62.81, 63.24 ± 61.78,and 48.48± 46.54) ng/ml, respectively with no significant difference (p = 0. 602) (table 7).

The mean value of CA19.9 levels of patients groups (under 60, 60-69, and above 69) years were (119.8± 156.07, 85.4 ± 132.6, and 100.17± 150.75) U/ml, respectively with no significant difference (p = 0. 888) (table 7).

Table 7. Descriptive analysis of tumor markers of patients group with colorectal carcinoma according to age

Tumor markers	Age group	Mean	Std. Deviation	Std. Error	P. value
CEA (ng/ml)	<60	77.1367	62.81790	25.64530	0.602
	60-69	63.2415	61.78890	17.13716	
	>69	48.4891	46.54276	14.03317	
CA19.9 (U/ml)	<60	119.8000	156.07734	63.71831	0.888
	60-69	85.4462	132.67715	36.79802	
	>69	100.1727	150.75757	45.45512	

The mean value of CEA levels in patients with colorectal carcinoma according to Astler –Coller staging system (B2, C1, and C2) were (10.18 ± 10.46, 51.23 ± 36.64, 122.32 ± 55.43) ng/ml, respectively with highly significant difference (p < 0.0005) (table 8).

The mean value of CA19-9 levels in patients with colorectal carcinoma according to Astler –Coller staging system (B2, C1, and C2) were (24.9 ± 8.41, 50.97 ± 63.02, 249.07 ± 191.26) U/ml, respectively with highly significant difference (p < 0.0005) (table 8).

Table 8. Descriptive analysis of tumor markers according to Astler –Coller staging system in patients with colorectal carcinoma

Tumor markers	stage	Mean	Std. Deviation	Std. Error	Minimum	Maximum	P. value
CEA ng/ml	B2	10.1857	10.46063	3.95375	2.29	31.52	<0.0005
	C1	51.2307	36.64430	9.46152	9.05	106.23	
	C2	122.3225	55.43455	19.59907	25.11	185.32	
CA19.9 u/ml	B2	24.9000	8.41229	3.17955	12.50	36.40	<0.0005
	C1	50.9733	63.02721	16.27356	15.90	230.70	
	C2	249.0750	191.26058	67.62083	25.60	464.80	

Correlation between tumor markers used in adenomas

There was a highly significantly positive correlation between CA19-9 and CEA (r= 0.881, p<0.0005)

Correlation between tumor markers used in carcinomas

There was a significant positive correlation between CEA and CA19-9 (r= 0.485, p=0.007)

Discussion

Carcinoembryonic antigen (CEA) is a classic tumor marker for CRC, and has been used to monitor CRC recurrence and as a prognostic factor for CRC patients. Currently, the serum CEA test is recommended by the American Society of Clinical Oncology and the European Group on Tumor Markers as a prognostic biomarker for recurrent CRC following curative resection. However, the effectiveness of CEA as a preoperative and postoperative marker for CRC remains to be evaluated. In particular, it remains unclear how accurate a negative CEA value is for excluding primary and recurrent CRC, and under what conditions CEA values are inaccurate [(10)].

Reference values of serum CEA for non-smokers are less or equal 3.0 ng/mL, some smokers may have elevated CEA, usually up to 5.0 ng/mL. Serum markers are not specific for malignancy, and values may vary by method[(6)]. Also elevated CEA levels are more common in smokers and in patients with inflammatory conditions but rarely exceed 10 ng/mL. The test can also be elevated in a variety of other carcinomas, including lung, breast, gastrointestinal, and gynecologic cancers[(11)].

In the present study, VIDAS CEA test was highly sensitive in 27 out of 30 carcinomas (i.e. sensitivity = 90%), along with 100% positive predictive value (PPV= 100%) (table 3.6). Elevated CEA levels suppose that VIDAS CEA test is in itself powerful at confirming the colon cancer. Highly elevated carcinoembryonic antigen (CEA) concentrations (>20 ng/mL) in a patient with compatible symptoms are strongly suggestive of the presence of colorectal carcinoma and also suggest metastasis[(6)]. All the controls had normal CEA serum (no false positive) levels, and 3(10%) out of 30 carcinoma cases had falsely normal CEA levels (false negative) (table 3.6). As a screening test, a negative result is not good enough at reassuring that a patient does not have the colon cancer (negative predictive value (NPV) = 90.9%), and at this initial, VIDAS CEA test was highly specific to all those who do not have cancer (i.e. specificity = 100%).

Hence, with large false negative results (17 out of 30), in cases with adenoma a positive CEA test in itself is not good to confirm the colon adenoma (PPV = 100%); it was highly sensitive to only 43.3% of all adenomas (i.e. sensitivity=43.3%). As a screening test, a negative result is not good at reassuring that a patient does not have the colon adenoma (NPV = 63.8%) and further investigations must be undertaken. At this initial, VIDAS CEA test was highly specific to all those who do not have adenoma (i.e. specificity=100%).

In comparison with other studies, the sensitivity of the CEA in colorectal carcinoma is higher in the present study. Li *et al* recorded 33.3% sensitivity, and 96.8% specificity similar to the specificity recorded in the current study. Wu and Sung found in their study a sensitivity of 69% and specificity of 70% of the CEA in colorectal carcinoma mentioned that specificity was 85.7% for CEA, while sensitivity was 58.3% with high positive predictive value of 95.4%. Polat *et al.*, showed 51.9% sensitivity , 90% specificity [(12)].These differences in CEA values are method-dependent [(6)].

The present study showed non-significant correlation between CEA levels with grade of carcinomas, and age, gender, site, histopathological type of both adenomas and carcinomas, which is comparable with other studies [(13,12)].There was a significant correlation between CEA levels and the stage of carcinoma which agrees with a recent study[(12)]. While there was a significant correlation between CEA levels and the dysplasia of adenoma agree with Locker *et al* [(6)].

The carbohydrate antigen (ca) 19-9 test measures a carbohydrate determinant of a circulating antigen. Elevated serum ca 19-9 has been found in patients with various gastrointestinal malignancies, especially pancreatic cancer. Carbohydrate antigen 19-9 might be helpful in the management of colorectal carcinoma. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in ca 19-9 elevations; in those conditions, serum concentrations are usually less than 1000 U/mL [(12)].

In the present study, an elevated CA19-9 results, in the absence of false positives, are powerful in confirming the colorectal carcinoma (PPV = 100%). This initial screen correctly identifies 100% of those who do not have cancer (the specificity). CA19-9 identifies only 30% of all carcinoma cases (the sensitivity). However as a screening test, with large false negatives (70%), a negative result is not good at reassuring that a patient does not have colorectal carcinoma (NPV = 58.8%) and further tests must be done. These results are similar to the results recorded by Park *et al* (sensitivity and specificity were 23.6% and 88.6% , respectively). Polat *et al.*, showed 25.2% sensitivity and 90% specificity [(12)].This variation may reflect variations in methodology.

The current work showed that the sensitivity of CA19-9 was very poor (10%) at confirming adenomas of the colon, while the specificity was (100%). As a screening test for detecting colorectal adenoma, CA19-9 is not useful for this purpose. These results are comparable with other study[(14,8)].

The present study showed non-significant correlation between CA 19-9 levels with grade of carcinomas, and age, gender, site, histopathological type of both adenomas and carcinomas, which is comparable with other study [(8)].There was a significant correlation between CA 19-9 levels and the stage of carcinoma which agrees with a

recent study[12]. While there was a significant correlation between CA 19-9 levels and the dysplasia of adenoma agree with[12].

The correlation between tumor markers used in adenomas was highly significantly positive between CA19-9 and CEA (r=0.881, p<0.0005). In carcinomas, there was a significant positive correlation between CEA and CA19-9 (r=0.485, p=0.007). In carcinomas, the sensitivity and specificity of VIDAS CEA test was (90%,100%),respectively while the sensitivity and specificity of VIDAS CA19-9 test was (30%,100%), respectively. In adenomas, the sensitivity and specificity of VIDAS CEA test was (43.3%,100%),respectively while the sensitivity and specificity of VIDAS CA19-9 test was (10%,100%), respectively.

Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) are well-known tumor markers that are used in the diagnosis of colorectal cancer. They are also used in preoperative staging and postoperative follow-up of patients, especially patients who are treated with chemotherapy [15].

In the current study, there was a significant positive correlation between CA19-9 and CEA in carcinomas (r= 0.485, p=0.007), which is comparable with the results obtained by[12]. The appearance of elevated levels of these markers in the serum is in most cases a sign of recurrence or metastatic lesions in near environment of the tumor as well as remote ones[15].

Conclusion

CEA and CA19-9 are significantly correlated with size and degree of dysplasia of adenoma and stage of carcinoma . CEA is more sensitive than CA19-9 in adenoma and colorectal carcinoma .

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