

## ORIGINAL PAPER

# Cancer Antigens (CEA and CA 19-9) as Markers of Advanced Stage of Colorectal Carcinoma

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**Introduction:** CEA and CA 19-9 are the most common tumor associated antigens used in the staging of patients with rectal cancer and other parts of the colon. **Goal** of this study was to evaluate the value of CEA and CA 19-9 in serum of patients with colon cancer and prove its place in the diagnostic staging. **Material and Methods:** The study was retrospective-prospective performed at the Gastroenterohepatology Clinic, Clinical Center of Sarajevo University. The study included 91 hospitalized patients who had histologically confirmed diagnosis of colon adenocarcinoma in 98% of cases. All patients underwent colonoscopy, targeted biopsy and measurement of CEA and CA 19-9 levels in serum. All of them underwent abdominal CT and MRI of the pelvis in case of rectal cancer. **Results:** The study analyzed 58 men and 33 women, mean age 66.6 years, with the youngest patient at age of 35 and the oldest at age of 89 years. The largest number of patients was aged 56-75 years. According to localization 77 patients had carcinoma located in the area of the rectum and sigma 37.4 and 37.4 in the rectostigmoid area and sigma. Metastases were observed in 37 patients, with predominance in the liver (22 cases) and both liver and lungs (5 cases). CEA and CA 19-9 were determined in all cases but patients with metastases had high values, especially in the two cases of cecoascendent colon cancer where detected values were extremely high (1789ng/ml and 10780U/ml). Values of CA19-9 were significantly higher ( $p<0.05$ ). CEA mean values were highest in patients aged over 75 years. In case of CA 19-9 high mean values have been recorded in patients aged over 75 years with statistically significant differences between the age groups ( $p<0.05$ ). **Conclusion:** CEA and CA19-9 are cancer antigens that are late markers of carcinogenesis, with significantly elevated serum concentrations in case of colon cancer with already developed metastases. Older age group of patient has significantly elevated levels of both antigens. Cancer was twice more common in men than in women. **Key words:** adenocarcinoma of the colon, CEA, CA 19-9, metastases

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## 1. INTRODUCTION

Colon cancer is the human tumor which equally affects both men and women. It belongs to common, solid tumors and is the third most common in men. By mortality it ranks as fourth after lung, stomach and liver. The highest frequency is recorded in the highly industrialized countries, such as countries of North America, Australia and

New Zealand. Mean incidence of this tumor is noticeable in the countries of Europe and it was noted that the population that migrates from regions with lower rates, in a higher percentage is affected in high-risk regions by colorectal cancer (1). Statistical data from our country of Bosnia and Herzegovina does not exist, because we do

not possess unique statistical data at the state level.

Many years of research of the available world data show that carcinogenesis is associated with lifestyle, type of diet, smoking, as well as the influence of the environment in which man lives and works. Sedentary work, inadequate nutrition, low in fiber and vitamins as well as stress, significantly impacting the development of the disease. Carcinogenesis is a long, complex and gradual process. Epithelial cells affected by the abnormal proliferation under genetic influence, leading to the creation of new clones, unrecognized by suppressor genes that probably are so damaged that they are unable to recognize the changes at the level of DNA, so that now new, different cells produce new cells that will be used to form tumor. Histological analysis of the tissue sample from the upper third of the crypt, see enhanced proliferation activity in neoplastic lesions (2).

Thanks to distal endoscopy as gold standard in the diagnosis of colorectal cancer it is diagnosed in time, located, target biopsy is made and histopathological analysis. Endoscopic ultrasound, CT and MRI with complete clinical evaluation, enable abdominal surgeon the choice of therapeutic treatments as surgical as well as oncological.

Carcinoma embryonic antigen (CEA) is an oncofetal tumor marker discovered 1965 by Gold and Freedman. In

70% of cases is significant in the diagnosis of colorectal cancer. According to units of measurement that we use, values up to 5ng/ml are considered as normal antigen concentration in serum. It has been observed that these values in smokers, in case of ulcer colitis, liver cirrhosis and chronic bronchitis can be increased up to 10 ng/ml. Well differentiated adenocarcinoma is accompanied with higher CEA serum concentration. Increase of its concentration for a period of few months after the surgery is speaking in favor of recurrence. Its concentration is also correlated with the tumor size. Thus, tumors of smaller size have normal serum concentrations of CEA antigen. Only tumors greater than 3 cm are accompanied with high concentration of CEA antigen (3).

Carbohydrate antigen (CA19-9) is a cancer antigen whose elevated serum concentration is detected also in case of colorectal cancer. It is a tumor marker that is observed in elevated serum concentration with metastatic colon cancer.

## 2. GOALS

The goal of our study was to determine serum levels of CEA and CA 19-9 in patients with colorectal cancer, to correlate serum levels of antigen with size and location of the tumor., to correlate CEA and CA 19-9 with metastases as well as possible complications, to perform colonoscopy to visualize the tumor lesion and to perform targeted biopsy in order to obtain histopathological confirmation of colon cancer.

## 3. MATERIAL AND METHODS

The study was of prospective – retrospective type and included 91 patients hospitalized at the Clinic of gastroenterohepatology in the period from 2010-2013, with the diagnosis of colon cancer.

All patients underwent colonoscopy, so we visualized tumor infiltrative lesions in a specific segment of the colon. Patients also underwent targeted biopsy.

Histopathologic examination of tissue samples was performed at the Institute of Pathology of the Clinical Center of Sarajevo University. Tissue samples of tumor infiltrate were sent stained

in formalin to Institute for pathology where they were cut, stained and analyzed histologically, so we could get the histological confirmation of our clinical diagnosis.

All patients have determined serum concentrations of CEA and CA19-9 antigen. These analyzes were carried out at the Institute of Biochemistry-CCU Sarajevo.

The data are presented in tables (and charts) by the number of cases, percentage, mean, standard deviation and ranges of values. To test the significance of the differences we used Chi-square test, Student's t-test and one-way analysis of variance ANOVA with a significance level of  $p < 0.05$  which was considered statistically significant or at the 95% confidence level. The analysis was conducted using statistical software for biomedical research Med Calc v12.7.

## 4. RESULTS

The research was conducted at the Clinic of Gastroenterohepatology and the research included 91 patients. Of these, 58 were men and 33 women. By the analysis of gender structure we get that in the total sample were over-represented men with 58 or 63.7% of cases compared to women with 33 or 36.3% of cases.

The average age of the patients was  $66.6 \pm 11.6$  years with a median of 69 years and ranged from 35 years to 89 years in the oldest patients. For ease of comparison according to the levels of tumor markers patients were divided into age groups of 10 years, among which dominated the older age groups 56-65 years (29 or 31.9%) and 66-75 years (33 or 36.3%).

The most common localization was rectally or in 34 or 37.4% of cases, fol-

Localization		
	%	N
Colon ascendants	8	8.8
Colon cecoascendent	2	2.2
Colon descendent	9	9.9
Colon transverse	4	4.4
Rectum	34	37.4
Rectostigmoid	9	9.9
Sigma	25	27.5
Total	91	100.0

Table 1. Tumor localization

Metastases		
	%	N
No	54	59.3
Liver	22	24.2
Liver and lungs	5	5.5
Lymph nodes	9	9.9
Adipose tissue	1	1.1
Total	91	100.0

Table 2. Presence of metastases

lowed by sigma with 25 or 27.5% of cases, while the least was observed localization in cecoascendent colon in only in 2 cases or 2.2%.

According to the type of tumors most present was adenocarcinoma in 89 or 97.8% of the cases followed by one case (1.1%) of intraepithelial and squamous cell carcinoma type.

Within the total sample metastases were observed in 37 cases or 40.7%, of which dominate metastases in lymph nodes in 32 or 35.2% of cases, of which 9 patients had only affected lymph nodes. Followed metastases in the liver in 22 or 24.2% of cases, 5 or 5.5% in the liver and lungs and 1 in adipose tissue.

Analysis of the average value of CEA shows that the it was higher in males ( $1063.4 \pm 2718.2$ ; range 0.24 to 12.0) than women ( $142.2 \pm 446.7$ ; range 0.56 to 2073) but with the extreme values in one case it was not possible to confirm a statistically significant difference ( $p > 0.05$ ). Average values of CA19-9

	Comparison by gender					
	Mean	SD	SEM	Min.	Max.	
CEA F=4.485 p=0.006	Male	1063.4	2718.1	388.3	.24	12000.00
	Female	142.1	446.6	80.2	.56	2073.00
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.077 p=0.782	Male	1865.4	8229.6	1226.8	1.90	54883.90
	Female	2453.2	9663.1	1826.1	1.90	50319.00
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 3. Comparison of mean CEA and CA19-9 values by gender

	Comparison by age					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.186; p=0.945	< 45 yrs.	449.4	1073.0	405.6	.24	2876.39
	46-55 yrs.	.9	.3	.2	.70	1.26
	56-65 yrs.	827.9	1886.2	377.2	1.57	7426.16
	66-75 yrs.	603.2	2257.6	412.2	.34	12000.00
	<75 yrs.	971.5	3081.6	795.6	1.43	11840.34
	Total	706.4	2183.8	244.2	.24	12000.00
CA19-9 F=2.546; p=0.047	< 45 yrs.	13619.1	24544.0	12272.0	2.00	50319.00
	46-55 yrs.	10.6	10.9	6.3	2.39	22.93
	56-65 yrs.	475.9	1531.6	312.6	1.90	7429.18
	66-75 yrs.	980.5	2478.9	460.3	1.90	12000.00
	<75 yrs.	4482.4	15156.3	4203.6	1.90	54883.90
	Total	2090.9	8745.7	1023.6	1.90	54883.90

Table 4. Comparison of mean CEA and CA19-9 values by age groups

	Comparison according to localization					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.627 p=0.708	Colon ascendants	287.1	587.1	239.7	.34	1478.79
	Colon coascendant	1314.8	1857.1	1313.1	1.67	2628.00
	Colon descendants	821.6	1953.7	690.7	1.43	5645.00
	Colon transverse	8.2	14.1	7.0	.56	29.40
	Recti	1225.4	3253.8	594.0	.24	12000.00
	Rectostigmoid	653.6	1257.9	444.7	1.50	3356.90
	Sigma	162.0	627.3	133.7	.60	2960.04
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.118 p=0.994	Colon ascendants	931.3	1306.7	533.4	1.90	3349.00
	Colon coascendant	1070.7	1507.3	1065.8	4.95	2136.60
	Colon descendants	2015.2	4151.6	1467.8	1.90	12000.00
	Colon transverse	184.7	358.8	179.4	1.90	723.00
	Recti	2717.6	10771.1	2112.4	1.90	54883.90
	Rectostigmoid	688.2	1889.8	668.1	1.90	5365.08
	Sigma	2730.4	11526.1	2644.2	1.90	50319.00
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 5. Comparison of mean CEA and CA19-9 values by tumor localization

were higher in women (2453.2±9663.1; range 1.9 to 50319) compared to males (1865.4±8229.7; range 1.9 to 54883.9) without significant difference between genders (p>0.05).

Average values of CEA were highest in patients aged over 75 years (971.5±3081.6) and lowest in patients aged 46-55 years (0.96±0.28) without statistically significant differences between age groups (p>0.05). In case of CA19-9 the highest average values have been reported in patients aged over 75

years (4482.4±15156.3) and lowest in patients aged 46-55 years (10.6±10.9) with statistically significant differences between age groups (p<0.05).

Average values of CEA were highest in tumor process located in cecoascendant colon (1314.8±1857.1) and lowest in the localization in colon transverse (8.3±14.1) without statistical differences between localizations (p>0.05). In the case of CA19-9 the highest average values were observed in the localization at sigma (2730.4±11526.1), and lowest

in the localization in colon transverse (184.7±358.9) with no statistically significant differences between localization (p>0.05).

Analysis of the average value of CEA shows that it has been highest in the case of intraepithelial tumor (1789.4±3945.6) compared to adenocarcinoma (559.6±1810.6), but given the extreme values in one case it was not possible to confirm a statistically significant difference (p>0.05). Average values of CA19-9 were higher in the case of intraepithelial tumor (10779.9±22074.0) compared to adenocarcinoma (2009.8±722.9) with significant differences according to the type of cancer (p<0.05).

Average values of CEA were highest in patients with metastases in the liver and lungs (2098.7±2727.4) and lowest in case of metastases in regional adipose tissue (1.66±0) without statistically significant difference (p>0.05). In the case of CA19-9 the highest average values were observed in case of liver metastases (4061.4±12998.9) and lowest in case of metastasis in adipose tissue (1.9±0) without statistically significant differences (p>0.05).

Analysis of the presence of metastases according to the side shows that the metastases were more frequent in case of tumor process localization in the right hemicolon (8 or 57.1%) compared to the localization at the left hemicolon (29 or 37.7%). Statistical analysis by the Fisher exact test shows that there is no statistically significant difference in the presence of metastases in relation to the side of a tumor process ( $\chi^2=1.863$ ; p=0.143).

## 5. DISCUSSION

Cancer embryonic 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. 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 (1).

Colonoscopy with macroscopic visualization of tumor lesions, followed

	Comparison according to tumor type					
	Mean	SD	SEM	Min.	Max.	
CEA F=1.453 p=0.240	Adenocarcinoma	559.5	1810.6	217.9	.34	12000.00
	Intraepithelial	1789.4	3945.6	1247.7	.24	11840.34
	Squamous	8.9	.	.	8.93	8.93
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=6.615 p=0.002	Adenocarcinoma	722.9	2009.8	255.2	1.90	12000.00
	Intraepithelial	10779.9	22074.0	6980.4	1.90	54883.90
	Squamous	13.5	.	.	13.54	13.54
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 6. Comparison of mean CEA and CA19-9 values by tumor type

	Comparison according to metastases					
	Mean	SD	SEM	Min.	Max.	
CEA F=0.991 p=0.429	No	445.6	2079.5	309.9	.24	12000.00
	Liver	1276.6	2727.4	609.8	1.75	11840.34
	Liver and lungs	2098.2	2311.7	1033.8	13.79	5645.00
	Lymph nodes	53.8	128.6	45.4	.34	371.78
	Adipose tissue	1.6	.	.	1.66	1.66
	Total	706.4	2183.7	244.1	.24	12000.00
CA19-9 F=0.291 p=0.916	No	1658.0	8001.3	1265.1	1.90	50319.00
	Liver	4061.3	12998.9	3063.8	1.90	54883.90
	Liver and lungs	2421.7	2224.7	994.9	78.56	5365.08
	Lymph nodes	136.9	318.2	112.5	1.90	922.02
	Adipose tissue	1.9	.	.	1.90	1.90
	Total	2090.8	8745.7	1023.6	1.90	54883.90

Table 7. Comparison of mean CEA and CA19-9 values by presence of metastases

by targeted biopsy are now considered invasive methods, but we have to admit that these are the methods of choice in the diagnosis of colorectal cancer.

CEA and CA19-9 are used in clinical practice, but we have to accept the reality that they are not specific for early detection of colon cancer, meaning they cannot be used in the diagnosis of carcinoma in situ (1).

Nakatani H. and associates in their research from 2012 provided the data that the colon cancer located in the region of sigma had extremely high concentrations of CEA and CA19-9. CT could not detect metastases. Otherwise it was a case of well differentiated adenocarcinoma or elevated concentrations without metastases (2). When we compare our results we must say that in our study colon cancer had markedly elevated levels of CEA and CA19-9 with metastasis and with the radia-

tion in lymph nodes. Mean CEA values were highest in patients with liver and metastases in the lungs (2098±2727.4) and the lowest in case of metastases in regional adipose tissue (1.66±0) without statistically significant difference ( $p>0.05$ ). In case of CA19-9 the highest average values were observed in case of liver metastases (4061.4±12998.9) and lowest in metastasis in adipose tissue (1.9±0) without statistically significant difference. Average values of CEA and

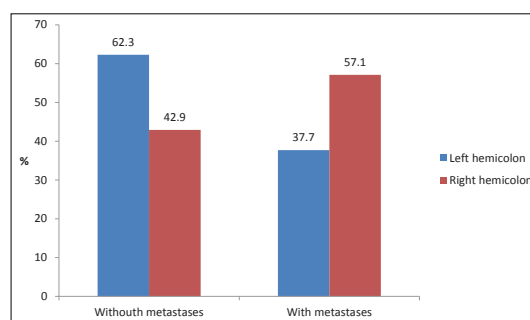


Figure 1. Presence of metastases according to tumor side

CA19-9 were higher in patients without complications. Compared with study by Ochiai H. and associates who in his study did not find significantly higher CEA and CA19-9 levels in patients who had recorded metastases into lymph nodes (4). According to our research, we found in 9 patients (9.9%) metastases in the lymph nodes but without significantly increased levels of these markers. What we found by exploring the colon cancer is that they were extremely higher CEA and CA 19-9 values in patients who have had cancer in the right hemicolon.

According to the localization the largest number of patients had colon cancer in the rectum area 34 (37.4%), followed by sigma in 25 cases (27.5%) and rectostigmoid area 9 cases (9.9%) with the presence in the descending column in 9 cases (9.9%). It means that dominated was localization in right hemicolon in 74% of cases. Bin Jin and associates published that they have found 44 cancers in the rectum region and 68 cancers in other regions of the colon (5). According to our research, we can conclude that there are no major differences between these studies, because it was given that in the largest number of cases cancer was located in the area of the rectum and sigmoid, because we have 91 patients suffering from colon cancer of which 34 cancers was in the area of the rectum and 25 in the region of sigma.

Analysis of the gender structure showed that in the total number of patients with a higher percentage was man 58 or 63.7% compared to women who were present in 33 or 36.3% of cases. According Selcubricik E. and associates in their study was also more present men than women (7).

The population in our sample was older with the average age of patients of 66.6±11.6 years, with a median that ranged from 35 years to 89 years. Otherwise, in our research were most dominant older age groups of 56-65 years (29 or 31.9%) and 66-75 years (33 or 36.3%). Elderly population was observed also in the studies of other authors (6,7).

Analysis of the average value of CEA shows that it was higher

in males (1063.4±2718.2; range 0.24 to 12,000) than women (142.2±446.7; range 0.56 to 2073) but due to the extreme values in one case it was not possible to confirm a statistically significant difference ( $p>0.05$ ).

Average values of CA19-9 were higher in women (2453.2±9663.1; range 1.9 to 50.319) compared to men (1865.4±8229.7; range 1.9 to 54883.9), without statistically significant differences by gender ( $p>0.05$ ) (7).

Average values of CEA were found in patients aged over 75 and the lowest in patients aged 46-55 years. Statistically significant differences were not found between age groups ( $p>0.05$ ).

In the case of CA19-9 the highest average values were recorded in patients aged 75 years and the lowest in patients aged 46-55 years. There is a statistically significant difference between age groups and ( $p<0.05$ ). Other researchers (8), the results were similar to ours.

## 6. CONCLUSION

Insight into the complete study shows that significantly more patients were represented by histological type adenocarcinoma of the colon and the localization of most of them was in the left hemicolon with the highest number in the area of rectum and sigma. Increased serum CEA and CA 19-9 levels

were followed by cancer with metastases: we had only one patient with high value of cancer antigen but without proven metastasis. According to this, these are late markers in the detection of colorectal cancer. Disease that occurs in old age and is more common in men. Metastases were present at the first visit to a doctor and were mostly in the liver and combined both in the liver and lungs. Extremely elevated CA 19-9 concentrations were found in case of cecocolic adenocarcinomas of the colon. According to all of the above, we can conclude this is now a human tumor that dominates human pathology, it is detected late because patients come mostly due to developed complications in form of anemia, malignant stenosis and intestinal obstruction.

**CONFLICT OF INTEREST: NONE DECLARED**

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