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Assessment of the Relation between Serum Carcinoembryonic Antigen and Tumor Node Metastasis Staging of Colorectal Cancer

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ABSTRACT

Background: Although awareness via cancer screenings and the knowledge of therapy modalities has increased, the burden of colorectal cancer (CRC) is much more pronounced in developing countries.

Objective: This study was aimed to estimate serum carcinoembryonic antigen (CEA) levels in preoperative CRC patients and to determine the associations between serum CEA levels and tumor node metastasis (TNM) stage.

Patients and methods: This cross-sectional study included 36 patients with CRC (stages IV) attending at Department of General Surgery, Zagazig University Hospitals. Patients scheduled preoperatively for sigmoidoscopy were prepared by an enema and examined by using standard video endoscopes. The CEA levels were estimated preoperatively for all patients.

Results: CEA level among the studied cases ranged from 0 to 23 ng/dl with mean 6.39 ng/dl and median 4.5ng/ml. Also 58.3% had CEA level ≤ 5 ng/ml. There were no statistical significance relations between the CEA and age or sex distribution. But there was a statistical significance increase in frequency of smoking among cases had CEA level >5 ng/ml. There was no statistical significance relation between site and diameter of lesions and CEA level among the studied cases.

Conclusions: It could be concluded that there is a meaningful link between TNM stage and CEA level. However, normal levels of CEA will not rule out CRC diagnosis, and these patients should be investigated in detail.

Keywords: Carcinoembryonic Antigen, Colorectal Cancer, TNM Stage.

INTRODUCTION

Cancer is a dreadful disease caused to an anomalous growth of cells, which leads to an irregular balance of cell proliferation and death. Cell death is a physiological process where normal cells are regulated by "touch contact-inhibition". However, proliferating tumor cells metastasize to distant sites and invade other tissues, often causing morbidity [(1)]. In recent years, colorectal carcinogenesis (CRC) has imposed a major health burden in developing countries [(2)].

Common symptoms of CRC are rectal bleeding, significant changes in the color of stool (especially dark or black-colored stools), irregular bowel habits, pain or discomfort in the lower abdomen, weakness or fatigue, and certain types of anemias [(3)].

Several risk factors are thought to cause CRC. Age is a major risk factor. About 90% of CRC patients are above the age of 50. The median age of CRC diagnosis is 68 in men and 72 in women. CRC risk also increases due to environmental factors, which include consuming a diet rich in red meat and fat, poor intake of dietary fiber, sedimentary lifestyle, obesity, diabetes mellitus, smoking and consumption of alcohol [(4)]. Malignancy risk has been linked to the site, size, and histological characteristics of polyps. Polyps < 5 mm in diameter are harmless and pose an insignificant risk of malignancy, whereas those with a diameter > 25 mm pose a significant risk [(5)].

The tumor node metastases (TNM) staging system established by the American Joint Committee on Cancer is widely used to predict the prognosis for patients with CRC, to guide adjuvant therapy after potentially curative surgery, and to classify patients for participation in clinical trials. The ideal prognostic system should provide homogeneity within the same stage, good discrimination between different stages, and monotonicity of gradients that predicts survival outcomes that are consistent with the severity of cancer staging [(6)].

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. However, the effectiveness of CEA as a preoperative and postoperative marker for CRC remains to be evaluated. It remains unclear how accurate a negative CEA value is for excluding primary and recurrent CRC, and under what conditions CEA values are inaccurate [(7)].

The aim of the current study was to estimate serum carcinoembryonic antigen (CEA) levels in preoperative CRC patients and to determine the associations between serum CEA levels and tumor node metastasis (TNM) stage.

PATIENTS AND METHODS

This cross-sectional study included a total of 36 cases with CRC, attending at Surgical Oncology Unit, Department of General surgery, Zagazig university hospitals.

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Inclusion criteria: The patients in aged ≥ 18 years of both who have CRC as pathological results of examinations. Patients with early or delayed presentation.

Exclusion criteria: Patients in age <18 years with previous history of surgical or non surgical treatment of CRC, patients with liver disease and patients with other associated tumors.

Preoperative investigations: Full history, clinical examination and laboratory investigations were performed for all patients.

Colonoscopy and biopsy: Colonic preparation was performed. Patients scheduled for sigmoidoscopy were prepared by means of an enema and examinations were performed using standard video endoscopes. Biopsy was taken from site of the lesion and confirmed by histopathology. Site of lesion was classified as: cecum, ascending colon, transverse colon, descending colon and sigmoid colon and rectum.

CT scan abdomen and pelvis: Patients were underwent CT abdomen and pelvis for assessment of preoperative tumor size, node status and presence of metastasis , metastatic lymph nodes tend to be more than 1cm in diameter and have a circular appearance, irregular border or form a collection or group with a tendency to adhere to each other. Patients were classified according to tumor stage

Magnetic resonance imaging (MRI) abdomen and pelvis: MRI more accurate than CT for the evaluation of liver metastases, we use it for CRC staging as it can evaluate the integrity of the rectal wall layers.

Serum CEA measurement: The CEA levels of patients were measured in the preoperative period using double antibody one- step enzyme linked immunosorbent assay (ELISA). The color intensity and human CEA samples were positively correlated. The absorbance (OD value) was measured using a microplate reader at a wavelength of 450 nm to calculate the sample concentration (the normal reference value is 0-5 ng/L). According to the reference range of our hospital's laboratory, values ≤5 ng/mL were accepted as normal, whereas those >5 ng/mL were accepted as positive.

***Ethical Consideration*:**

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from all patients in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analyses using SPSS for Windows version 22 (SPSS Inc., Chicago, IL, United States). Univariate analysis was performed by $\chi 2$ test to analyze pre-CEA levels and clinicopathological parameters. Multivariate survival analysis was performed by the Cox regression model to determine relative risk (RR) and 95% confidence intervals (CI). Statistical significance will be defined as $P < 0.05$.

RESULTS

A total of 36 patients with stages I-IV CRC were admitted to our hospital and underwent surgery, the CEA levels for all patients were determined preoperatively. The age of the studied cases ranged from 29 to 83 years with mean 54.36 years. Regarding sex 63.9% were male. Finally, 38.9% of cases were smoker **(Table 1)**.

CEA level among the studied cases ranged from 0 to 23 ng/dl with mean 6.39 ng/dl and median 4.5 ng/ml. Also 58.3% had CEA level ≤ 5 ng/ml **(Table 2)**. There were no statistical significance relations between the CEA and age or sex distribution. But there was a statistical significance increase in frequency of smoking among cases had CEA level >5 ng/ml **(Table 3)**. There was no statistical significance relation between site and diameter of lesions and CEA level among the studied cases **(Table 4)**.

Table (1): Age and sex of the studied cases:

Variable	(n=36)	
Age: (years)		
Mean ± Sd	54.36 ± 13.85	
Range	29 - 83	
	No	**%**
Sex:		
Female	13	36.1
Male	23	63.9
Smoking:		
No	22	61.1
Yes	14	38.9

SD: Standard deviation

Table (2): CEA level among the studied cases:

Variable	(*n*=36)	
	No	%
CEA: (ng/ml)		
≤5	21	58.3
>5	15	41.7
Mean ± SD	6.39 ± 6.17	
Median	4.5	

Table (3): Relation between CEA level and age and sex of the studied cases:

Variable	CEA ratio				t	P
	≤5 (n=21)		>5 (n=15)			
Age: (years)						
Mean ± Sd	54.76 ± 12.47		53.8 ± 16.03		0.20	0.84 NS
Range	32 - 73		29 - 83			
	No	**%**	**No**	**%**	**χ^2**	**P**
Sex:						
Female	6	28.6	7	46.7	1.24	0.27 NS
Male	15	71.4	8	53.3		
Smoking:						
No	16	76.2	6	40	**4.82**	**0.03***
Yes	5	23.8	9	60		

SD: Standard deviation t: Independent t test χ^2:Chi square test
NS: Nonsignificant (P>0.05) *: Significant (P<0.05)

Table (4): Relation between site and diameter of lesions and CEA level among the studied cases:

Variable	CEA ratio				χ^2	P
	≤5 (*n*=21)		>5 (n=15)			
	No	**%**	**No**	**%**		
Site:						
Cecum	0	0	2	13.3		
Ascending colon	3	14.3	1	6.7		
Transverse colon	1	4.8	1	6.7	3.44	0.63 NS
Descending colon	3	14.3	2	13.3		
Sigmoid colon	4	19	3	20		
Rectum	10	47.6	6	40		
Diameter (cm):						
<3	5	23.8	2	13.3		
3-6	6	28.6	8	53.3	2.3	0.51 NS
7-9	6	28.6	3	20		
>9	4	19	2	13.3		

χ^2:Chi square test NS: Non significant (P>0.05)

DISCUSSION

Colorectal cancer (CRC) is one of the most common malignancies in many regions of the world. It is the third most common cancer in both men and women; also, it is the second most common cause of cancer death in the United States [8]. CRC arises from the accumulation of mutations in a single epithelial cell of the colon and rectum [9]. It has different characteristics based on their location within the colon or rectum; tumors in the proximal, or right, colon are more common among women and older patients whereas distal, or left-sided, tumors are more common among men and younger patients [10].

Serum carcinoembryonic antigen (CEA) can be detected at high levels in breast and lung cancers as well as in the serum levels are detected high at 90% of primary CRC cases. CEA is an important structure regulating promoter functions in intracellular adhesion and aggregation. Therefore, it has been believed that CEA has an important role in tumor invasion and in defining metastasis [11].

A total of 36 patients with stages IV CRC were admitted to our hospital and underwent surgery, the CEA levels for all patients were examined preoperatively for determining the associations between serum CEA levels and tumor node metastasis (TNM) stage.

Most CRC patients are associated with moderately differentiated tumors, whereas high CEA levels are associated with poorly differentiated or undifferentiated CRC that are highly malignant [12]. Further, the differentiation degree of tumors affected the preoperative CEA in CRC patients. CEA is an important risk factor affecting CRC prognosis [13].

In previous studies, preoperative CEA levels were identified as reliable indicators of prognosis and therapeutic efficacy in stage II and III CRC patients [14, 15]. Many studies also reported that pre-CEA levels were an independent risk factor for CRC patients [16, 17].

Our study further confirmed that pre-CEA level was an independent prognostic factor. Preoperative levels of CEA might provide an estimate of lymph node invasion and distant metastasis in colorectal cancer patients [18].

CRC patients with normal serum CEA levels prior to resection maintained these levels during CRC recurrence, especially in cases of local recurrence vs cases of metastasis [7].

Topdagi and Timuroglu [19] revealed the CEA levels of 316 patients could be defined; the CEA levels of samples were within normal limits (CEA= 0-3.4 ng/mL). It was observed that patients were classified according to CEA levels below or about 5 g/mL. Therefore, the second classification was performed in the study and it was defined that 59.5% of cases had CEA ≤5 ng/mL.

The current study shows that there were no statistical significance relations between the CEA and age or sex distribution. But there was a statistically significant increase in frequency of smoking among cases had CEA level >5 ng/ml. There was no statistically significant relation between site and diameter of lesions and CEA level among the studied cases. On the other hand, there was no statistically significant relation between stage and differentiation of lesions and CEA level among the studied cases. According to the correlation between CEA level and age, diameter and TNM stage among the studied cases, the current srudy shows that there was no statistical significance correlation between CEA level and age, diameter and TNM stage of the studied cases. These findings were in accordance with the results in the study of **Lee *et al.*** [11], **Topdagi and Timuroglu** [19] and **Duffy** [20].

However, **Filiz *et al.*** [21] reported in their study on 151 CRC patients in 2009 that 58.8% of patients had normal preoperative CEA levels. No statistically significant correlation was detected between tumor size, localization, and differentiation degree and preoperative CEA levels in that study.

Huh *et al.* [22] investigated the correlation between CEA levels and TNM staging in 474 patients with CRC. Patients were divided into two groups according to CEA levels of above or < 5 ng/mL. However, only patients with non-metastatic CRC were included in the study. As result of the study, a statistically significant correlation between CEA levels and TNM staging of patients was defined. While CEA levels were high in 33.1% of patients preoperatively, they were normal in the rest of patients. No significant correlation was detected between CEA levels, tumor localization, and differentiation degrees of patients.

CONCLUSION

It could be concluded that there was a meaningful link between TNM stage and CEA level. However, normal levels of CEA will not rule out CRC diagnosis, and these patients should be investigated in detail.

Further prospective experimental studies are needed to address the relation of serum CEA pre- and postoperative surgery and TNM staging of CRC.

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