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Relation between Serum Carcinoembryonic Antigen and Tumor Node Metastasis (TNM) Staging of Colorectal Cancer

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ABSTRACT

Background: Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide with steadily increasing mortality rates. The aim of the present study to highlight any relationship between carcinoembryonic antigen (CEA) and tumor node metastasis (TNM) stage in colorectal cancer (CRC) patients that would help in diagnosis and staging of the disease. Patients and methods: A total of 36 patients with stages IV CRC were admitted to department of General surgery, Zagazig university hospitals and underwent surgery. Full medical history, clinical examination, General and specific investigation were performed for all patients preoperatively.The CEA levels for all patients were examined preoperatively. Results: Our study showed the mean 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% were smoker. Most common sites of lesions were rectum, sigmoid colon & descending colon (44.4%, 19.4% & 13.9% respectively). The diameter of lesion among cases ranged from 1 to 15 cm with mean 5.94 cm and 38.9% had diameter from 3 to 6 cm. Regarding differentiations most frequent was moderate and mild (41.7% & 30.6% respectively). 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. Conclusions: There is a meaningful link between TNM stage and CEA level. However, normal levels of CEA will not rule out CRC diagnosis, and it can be concluded that these patients should be investigated in detail.

Keywords: Colorectal Cancer; Carcinoembryonic Antigen; Tumor Node Metastasis,

INTRODUCTION:

Colorectal carcinogenesis (CRC) has imposed a major health burden in developing countries **(1)**. Lifestyle changes including high-fat diet, lack of exercise and mental stress has resulted in a rise in colorectal cancer (CRC) cases **(2)**.

Radical surgery still remains the best therapeutic option for CRC patients. However, high recurrence and metastasis rates have resulted in poor overall survival of

CRC patients **(3)**. Therefore, identification of novel prognostic risk factors is necessary for improving survival rates **(4)**.

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 **(5)**.

Tumor biomarkers have been widely used in clinical diagnosis, post-operative monitoring of tumor recurrence, prognosis and curative therapy of CRC patients **(6)**. The serum carcinoembryonic antigen (CEA) is one of the tumor biomarkers used for predicting recurrence, prognosis and therapeutic efficacy in CRC patients (Das et al., 2017). It is an oncofetal antigen, and its serum levels are increased at a rate of 75% in colorectal cancer recurrence. While CEA levels are highly sensitive in hepatic and retroperitoneal metastases, local recurrences are less sensitive in peritoneal and lung metastases **(7)**. Using this marker, the levels of this marker increase with tumor stage; CEA levels decrease after tumor resection. However, high CEA levels in the blood are not specific for CRC and may be due to other diseases, such as inflammatory bowel disease, liver disease, pancreatitis, and other malignancies **(8,9)**.

The aim of the present study was to highlight any relationship between carcinoembryonic antigen (CEA) and tumor node metastasis (TNM) stage in colorectal cancer (CRC) patients that would help in diagnosis and staging of the disease.

PATIENTS and METHODS:

A Prospective cross-sectional study was conducted on 36 cases with CRC at Surgical oncology unit in department of General surgery, Zagazig university hospital.

Ethics committee approval was received for this study from the ethics committee of Zagazig University. Written informed consent was obtained from patients who participated in this study.

Inclusion criteria:

The patients in aged ≥ 18 years of both who have CRC as pathological results of examinations. Patients come to hospital with early or delayed presentation.

Meanwhile, 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 were excluded from this study.

Full medical history and clinical examination were performed for all patients preoperatively.General preoperative investigation included the estimations of CBC, liver function test, bleeding profile, INR and electrolyte (na, k, cl, urea, creatinine).

Specific preoperative investigations:

(a) CT scan abdomen and pelvis:

All 36 Patients was enrolled in the study 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 as the follow:

- Stage I (tumor without lymph node involvement extending to subserosa)
- Stage II (tumor without lymph node involvement extending beyond subserosa).
- Stage III (tumor with lymph node involvement without metastasis.
- Stage IV (metastatic tumor).

(b) 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.

(C) Bone scan:

Bone scan or scintigraphy performed using phosphate analogues labelled with isotope Technetium-99m has good skeletal localisation in area with osteogenic activity or osteoblastic process. Sclerotic lesions seen as nodular, well circumscribed, uniform radiodense deposits. Bone scan scan detect early metastasis 2-18 months before they are seen on plain film radiographs. Bone metastases from CRC are relatively infrequent.

Specific investigations:

Colonoscopy and biopsy was performed. Patients scheduled for sigmoidoscopy were prepared by means of an enema. Examinations were performed using standard video endoscopes. Biopsy was taken from site of the lesion and confirmed by histopathology laboratory.

Detection of serum CEA:

For each of the selected patients, venous blood was drawn 1 week prior, included s-CEA tumor in three or ten s-CEA tests is utilized by Shanghai Yu- ping biotechnology company kit (Shanghai, China), 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). An s-CEA level of >5 ng/L is considered high, and ≤5 ng/L is considered low.

Carcinoembryonic antigen levels:

The CEA levels of patients were also measured in the preoperative period. 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.

Statistical analysis:

All statistical analyses were carried out 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:

The demographic data of our study showed the mean 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% were smoker **(Figure 1)**.

Most common sites of lesions were rectum, sigmoid colon & descending colon (44.4%, 19.4% & 13.9% respectively). The diameter of lesion among cases ranged from 1 to 15 cm with mean 5.94 cm and 38.9% had diameter from 3 to 6 cm **(Table 1)**.

Our study showed shows that 19.4% were stage II, 36.1% were stage III and 44.4% were stage IV. Regarding differentiations most frequent was moderate and mild (41.7% & 30.6% respectively) **(Table 2)**.

Concerning 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 **(Figure 2)**. In our study, there was no statistical significance relation between stage & differentiation of lesions and CEA level among the studied cases **(Table 3)**. There were no statistical significance correlation between CEA level and age, diameter & TNM stage of the studied cases **(Table 4)**.

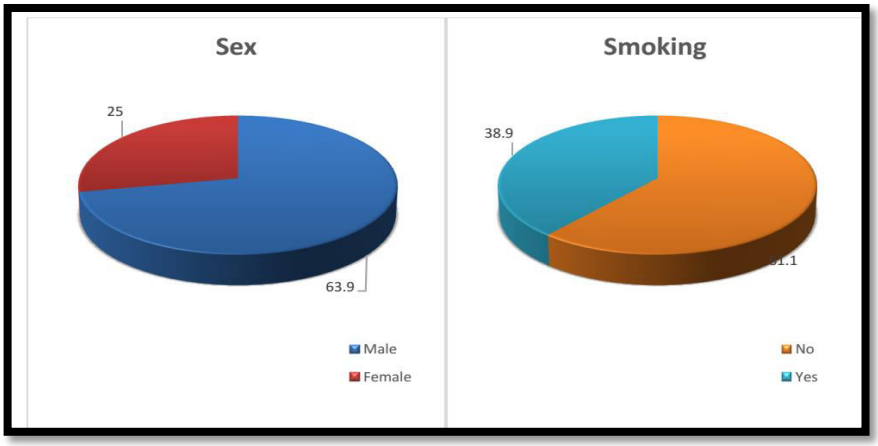

Figure (1): Sex distribution and frequency of smoking among the studied cases.

Table (1): Site &diameterof lesions among the studied cases:

Variable		(n=36)	
		No	%
Site:	Cecum	2	5.6
	Ascending colon	4	11.1
	Transverse colon	2	5.6

	Descending colon	5	13.9
	Sigmoid colon	7	19.4
	Rectum	16	44.4
Diameter: (cm)	<3	7	19.4
	3-6	14	38.9
	7-9	9	25
	>9	6	16.7
	Mean ± Sd	5.94 ± 3.55	
	Median	6	
	Range	1 - 15	

Sd: Standard deviation

Table (2): TNM stage & differentiation of lesions among the studied cases:

Variable		(n=36)	
		No	%
TNM stage:	I	0	0
	II	7	19.4
	III	13	36.1
	IV	16	44.4
Differentiation:	Mild	11	30.6
	Moderate	15	41.7
	Well	9	25
	undifferentiated	1	2.8

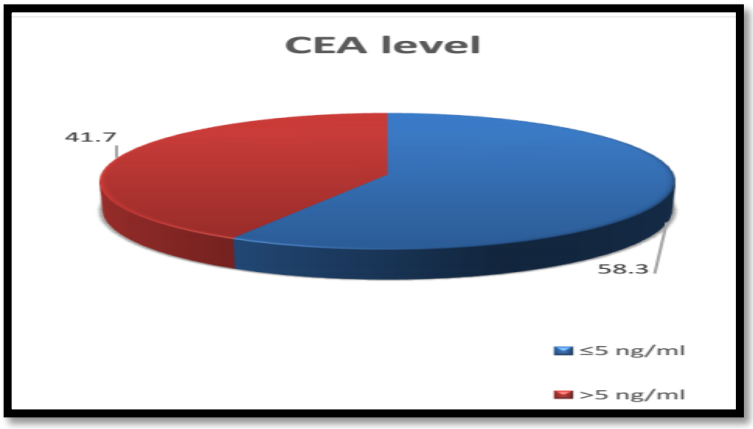

Figure (2): CEA level among the studied case

Table (3): Relation between stage &differentiation of lesions and CEA level among the studied cases:

Variable		≤5 (*n*=21)		>5 (n=15)		χ^2	P
		No	%	No	%		
TNM stage:	II	4	19	3	20		
	III	7	33.3	6	40	0.23	0.89

	IV	10	47.6	6	40		NS
Differentiation	Mild	7	33.3	4	26.7		
	Moderate	7	33.3	8	53.3	1.94	0.59
	Well	6	28.6	3	20		NS
	undifferentiated	1	4.8	0	0		

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

Table (4): Correlation between CEA level and age, diameter & TNM stage among the studied cases:

Variable	CEA (ng/ml) (*n*=36)	
	r	P
Age (years)	-0.24	0.15 NS
Diameter (cm)	0.18	0.28 NS
TNM stage	0.05	0.78 NS

r: Spearman's correlation coefficient, NS: Non significant (P>0.05)

DISCUSSION:

Colorectal cancer (CRC) is an important cause of mortality and morbidity worldwide. It is the fourth cancer type among women and men, and it ranks second among cancer-related deaths **(10)**.

Many studies have suggested that CEA levels can be used for predicting metastasis although few contradictory reports exist (**11**). High CEA levels are observed in cancers, whereas changes are also observed in smoking, inflammation, and hepatitis conditions **(12)**. Furthermore, prognostic potential of preoperative CEA has been reported for CRC patients. **Huh et al., (13)** investigated the correlation between CEA levels and tumor node metastasis (TNM) staging in patients with colorectal cancer. Only patients with non-metastatic colorectal cancer were included in the study. As result of the study, a statistically significant correlation between CEA levels and TNM staging of patients was defined. No significant correlation was detected between CEA levels, tumor localization, and differentiation degrees of patients.

On the other hand, **Lee et al.**, (**14**) accepted a preoperative CEA level of 5 ng/mL as the cut-off value. CEA levels were low among patients with Stage I and II TNM classification (66%), but they were high in patients with more advanced disease; the correlation was statistically significant. Therefore, the current study aimed to highlight any relationship between CEA and TNM stage in CRC patients that would help in diagnoses and staging of the disease.

In the present study, data from 36 patients diagnosed with stages IV CRC during the period study 2020 were evaluated. Of the 36 patients, 23 (63.9%) were males and 13 (36.1%) were females. The mean age was 54.36±13.85 years, and ranged from 29 to 83 years. Regarding there was 38.9% of cases were smoker.

According to site and diameter of mesins, the current study shows that most common sites of lesions were rectum, sigmoid colon and descending colon (44.4%, 19.4% and 13.9% respectively). The diameter of lesion among cases ranged from 1 to 15 cm with mean 5.94 cm and 38.9% had diameter from 3 to 6 cm. These findings in the same line with the study of **Topdagi and Timuroglu** (**15**) who reported in their study on 745 CRC patients that most common sites of lesions were rectum, sigmoid colon and descending colon (55%, 18% and 9% respectively). The diameter of lesion among cases ranged from 1 to 15 cm with mean 6.44 cm and 37.8% had diameter from 3 to 6 cm.

According to the frequencies of TNM stages and differentiation of lesions among the studied cases, the current study that 19.4% were stage II, 36.1% were stage III and 44.4% were stage IV. Regarding differentiations most frequent was moderate and mild (41.7% and 30.6% respectively). These findings were confirmed with the results of **Huh et al. (13)**; **Lee et al. (14)** and **Topdagi and Timuroglu** (**15**).

The current study shows that 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. This finding is go with the study of **Huh et al. (13)**.

Similarly, **Topdagi and Timuroglu** (**15**) demonstrated that, the CEA levels of 316 patients could be defined; the CEA levels of samples were within normal limits (CEA= 0-3.4 ng/mL). When literature was reviewed generally, 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.

In contrast, **Lee et al. (14)** accepted a preoperative CEA level of 5 ng/mL as the cut-off values. CEA levels were low among patients with Stage I and II TNM classification (66%), but they were high in patients with more advanced disease; the correlation was statistically significant. In our study, CEA levels were detected within normal limits in 52.2% of cases; no statistically significant correlation was detected between CEA levels and tumor differentiation degree, tumor diameter, and TNM staging.

Our study was in harmony with the study of **Topdagi and Timuroglu,** (**15**) revealed a clear correlation between CEA levels and TNM staging of patients has not been revealed, clearly indicating that further studies are required about this issue.

In the light of this information, it should be considered that CEA levels may be within normal limits in many patients with colorectal disease; hence, in suspected cases for CRC, normal levels of CEA cannot rule out CRC diagnosis. Moreover, a clear correlation between CEA levels and TNM staging of patients has not been revealed, clearly indicating that further studies are required about this issue.

CONCLUSION:

There is a meaningful link between TNM stage and CEA level. however, normal levels of CEA will not rule out CRC diagnosis, and it can be concluded that 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.

No conflict of interest.

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