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Diagnostic Value of Preoperative Serum Carcinoembryonic Antigen and Carbohydrate Antigen CEA and CA 19-9 in Colorectal Cancer

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Abstract:
Background: *Colorectal cancer is a major common public health problem throughout the world as well as developed countries like ours. Early diagnosis with precise preoperative staging bears great importance by providing more effective treatment and reduced mortality and morbidity in colorectal cancer cases. CEA and CA 19-9 are the most studied serum tumor markers that have been evaluated for the management of gastrointestinal cancers but their usefulness for diagnosis has been a challenging question.* ***Objectives:*** *The objective of this study was to assess whether tumour markers (CEA and CA 19-9) have any diagnostic value as well as distant spread in colorectal cancer patient.* ***Methods:*** *This study was a prospective observational study which was conducted at surgery department of Dhaka Medical College & Hospital, Dhaka, Bangladesh over a period of six months between June 2017 to November 2017. The study prospectively enrolled 73 consecutive patients with a confirmed diagnosis of colorectal carcinoma by histopathology and 73 age and sex matched control subjects with no malignancy. The relationship of the tumor markers (CEA and CA 19-9) with perioperative disease staging (TNM), histological grading, sensitivity, specificity, PPV and NPV were analyzed using SPSS version 22.* ***Result:*** *Gender analysis revealed slightly male predominance (57.53%) over female (42.47%) though that was not statistically significant (p=0.128). Majority age distribution group was 13-30 then 31-40 years revealing tendency to occur malignancy at an earlier age in our patients. Majority of the tumors were located to rectum then sigmoid colon. Sensitivity of CEA and CA 19-9 were found 65.75% and 28.77% respectively. Specificity of CEA and CA 19-9 were 68.49% and 58.90% respectively. Positive predictive value of CEA and CA 19-9 were 67.61% and 41.18% respectively. Whereas negative predictive value of CEA and CA 19-9 were 66.67% and 45.26% respectively. Positive likelihood ratio of CEA and CA 19-9 were 2 and 0.7 which reveals CEA has some diagnostic value though not high but CA 19-9 has no diagnostic value. Negative likelihood ratio of CEA and CA 19-9 were 0.5 and 1.2 which also reveals same result as before. Serum concentrations of CEA were significantly higher in the patient group than in the control group (p = 0.001) but CA 19-9 was not significant (p = 0.086). Serum CEA was also significantly higher in advanced T stage. Serum concentrations of CEA and CA 19-9 were significantly elevated in the patients with spread to lymph nodes. Levels of both tumour markers were significantly elevated in the patients with distant metastasis. CEA and CA 19-9 levels are higher in well differentiated tumor than in those with poorly differentiated tumours.* ***Conclusion:*** *Preoperative levels of CEA and CA 19-9 do not have significant diagnostic value but may provide an estimate of lymph node invasion and distant metastasis in colorectal cancer patients.*

Key Wards: *Colorectal Cancer; CEA; CA 19-9; Carcinoembryonic Antigen*

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I. Introduction

Cancer continues to be an important health problem for both patients and health care workers despite significant advances in medical and technological fields. Colorectal cancers are the common cancers of the gastrointestinal system. Colorectal cancer is the third most common cancer type associated with cancer-related mortality after prostate and lung cancers in men. Cancer incidences vary across the world, indicating that environmental factors play a significant role in many cancer types. Early diagnosis bears great importance by providing more effective treatment and reduced mortality and morbidity in colorectal and gastric cancer cases.

Early diagnosis can be achieved with various screening and laboratory methods. Tumour markers are the substances that are produced by the tumour or secreted by the tissue as a response to the tumour. They may be used in the screening and diagnosis of tumours, as well as in the prognostic assessment and monitoring of recurrence and metastasis in cancer cases [1]. CEA and CA 19-9 are the most studied serum tumour markers that have been evaluated for the management of gastrointestinal cancers. Carcinoembryonic antigen (CEA) is an acknowledged member of immunoglobulin super family, with a role as an intracellular adhesion molecule. Many studies have shown that increased preoperative serum CEA levels are associated with an increased risk of recurrence and a poor prognosis and the prognostic effect of the serum CEA level is independent of the tumor-node-metastasis stage [2,3,4] Carbohydrate antigen 19-9 (CA 19-9) is a ligand for e-selectin that plays an important role in the adhesion of cancer cells to endothelial cells. It has been used as a tumor marker in gastrointestinal cancers. Hang Dong et al. [5] suggested that the CA 19-9 might be a potential valuable indicator for liver metastasis of colorectal carcinoma. Since the first introduction of tumour markers, their usefulness for diagnosis has been a challenging question. Because the use of tumour markers as a diagnostic tool is not well established. We have been routinely using preoperative CEA and CA 19-9 measurements in the management of colorectal cancer patients to obtain more clues about spread of the disease. The data that will be generated from the present study will inform about the relationship of the tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 with disease stage, tumour differentiation (grade), tumor invasion (T stage), lymph node involvement (N stage), distant metastasis (M stage) and also the diagnostic accuracy.

II. Objectives of the study

General:

The present study is planned to assess whether tumour markers (CEA and CA 19-9) have any diagnostic value as well as distant spread in colorectal cancer patient.

Specific:

To diagnose colorectal carcinoma patient by histopathology and age & sex matched patient having no malignancy.

To assess the staging of colorectal carcinoma by clinical, imaging and/or operative findings.

To measure pre-operative serum CEA & CA 19-9 of both groups.

To measure the sensitivity, specificity, positive predictive value & negative predictive value.

III. Literature review

Tumour markers are biologic or biochemical substances that are produced by tumour cells and then secreted into the circulation in detectable amounts. Most tumour markers are greatly limited for screening the asymptomatic population, being neither sensitive enough nor specific enough to detect early disease, small tumours, or the type of tumour present. Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and over expressed in adenocarcinoma, especially colorectal cancer [6]. The sensitivity of CEA in colorectal cancer increases with advancing tumour stage. Serum concentrations of CEA and CA 19-9 are elevated in patients with tumour extension to the lymph nodes and distant metastasis [7]. Nakatani H. and associates in their research from 2012 provided the data that the colon cancer patient had high concentrations of CEA and CA 19-9 [8]. CT could not detect metastases. Otherwise it was a case of well differentiated adenocarcinoma or elevated concentrations without metastases [9]. However, data are insufficient to support the use of CEA to determine whether to treat the patient with adjuvant therapy [10]. Elevation in CEA also occurs in benign conditions such as smoking, peptic ulcer, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction and cirrhosis. The carbohydrate antigen (CA) 19-9 test measures a carbohydrate determinant of a circulating antigen. Carbohydrate antigen 19-9 might be helpful in the management of colorectal carcinoma [7]. In contrast, other publications have reported that the use of CA 19-9 is limited. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations.[11] stated that CEA and CA 19-9 are statistically significantly different in early and metastatic colorectal cancer. Elevated serum CA 19-9 was found to be related to distant metastasis [12]. Preoperative serum CEA and CA 19-9 may suggest when lymph node invasion and distant metastasis are present [7]. This study will inform us about the relationship of the tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 with disease stage (T stage, N stage and M stage), tumour differentiation (grade) and also the diagnostic accuracy.

IV. Materials & Methods

Study design: This is a prospective observational study.

Place of study: This was conducted in Inpatient department of Surgery at Dhaka Medical Collage and Hospital (DMCH), Dhaka, Bangladesh.

Duration of study: The total duration was 6 months. The data was collected from June 2017 to November 2017.
Study population: From the entire admitted patient in the Surgery dept. at DMCH, Dhaka, Bangladesh.
Sample size: Sample size was determined purposively. It is calculated using simple formula (Daniel, 1999)
Sampling method: Purposive sampling was the method of choice to select the sample from the patients admitted in the department of surgery of DMCH.
Equipment: Chemiluminescent immuno- assay by ADVIA Centaur, Immulite 2000XPi SIEMENS
Procedure of collecting data: Information about patient had taken by researcher himself at surgery ward. Record of particulars of the patient and physical examinations was carried out by researcher himself. Details information was collected from investigation reports, operation notes and histopathological examination reports.
Ethical measures: The aims and objectives of the study along with its procedure, methods, risks and benefits of this study was explained to the patients in easily understandable local language and then informed consent was taken from the patient or his/her legal guardian (in case of unconscious patients). Investigations were done as a part of management. Hospital authorities were informed about the study and permission was obtained from Ethical review committee of DMCH. It was assured that all information and records would be kept confidential. Whatsoever, subjects who has given informed consent to participate in the study included as study sample.
Data processing and analysis: All data has been checked and edited after collection. Later on data inserted into the computer and analyzed with the help of software programmer SPSS for windows version 22 and MS Excel work sheet 2010. Some measurements also been done with the help of calculator. Then data presented in the form of tables, graphs, flow charts and cross tabulation.
Statistical significance: Chi-square Test(x^2) and Mann-Whitney U test

V. Result

A total of 146 patients out of which 73 patients with confirmed diagnosis of colorectal malignancy and 73 age & sex matched control subjects were prospectively enrolled between June 2017 to November 2017 admitted in surgery department of DMC&H. 57.53% were male and rests (42.47%) were female which means male were slightly predominant though statistically is not significant ($p > 0.05$) (Table 1). Majorities were in age group 13-30 years (29%) & then in age group 41-50 years 26% meaning tendency to occur in earlier age (Figure 1). 43 (58.90%) patients had malignancy at rectum followed by sigmoid colon (13.70%) and then ascending colon (8.22%), splenic flexure (6.85%), transverse colon (5.48%), caecum & descending colon (2.74%) & finally Hepatic flexure (1.37%) (Table 2). Serum CEA was significantly higher in patient group ($p = 0.001$) but CA 19-9 was not significant ($p = 0.177$) (Table 3). Sensitivity of CEA and CA 19-9 were 65.75% and 28.77% respectively which is not significant. Specificity of CA 19-9 was 68.49% and 58.90% respectively which is also insignificant. Positive predictive value of CEA and CA 19-9 were 67.61% and 41.18% respectively whereas Negative predictive value of CEA and CA19-9 were 66.67% and 45.26% respectively which are not significant. Positive likelihood ratio of CEA and CA 19-9 were 2 and 0.7 respectively. As PLR of CEA > 1 it has diagnostic value but not high as PLR > 10 indicate high diagnostic value. Negative Likelihood Ratio of CEA and CA 19-9 were 0.5 and 1.2 indicates CEA has diagnostic value as NLR < 1 but not high as NLR < 0.1 indicate high diagnostic value (Table 4). ROC curve for serum CEA showed the test is significant as AUC (Area under curve) =0.781 (AUC>0.5 is significant) (Fig. 2). ROC curve for serum CA 19-9 showed the test is not significant as AUC (Area under curve) = 0.418 (AUC>0.5 is significant) (Fig. 3). Serum CEA levels were found significantly higher ($p = 0.013$) in advanced T stages. Patients with more lymph nodes involved showed significantly higher serum CEA ($p=0.001$) and CA 19-9 ($p=0.033$) levels. Patients presenting with distal metastasis showed significantly higher levels of serum CEA ($p=0.006$) and CA 19-9 ($p=0.033$). Patients with well differentiated tumor showed significantly higher serum CEA levels ($p=0.001$) than with moderate and poorly differentiated tumor (Table 5).

Table 1. Distribution of patients by sex (Both case and control)

Sex	Case	Control	Percentage (%)	P value
Male	42	42	57.53	0.128
Female	31	31	42.47	
Total	73	73	100.00	

P value: Chi-Square test

Sex distribution in various age groups (N = 146; 73 in each group)

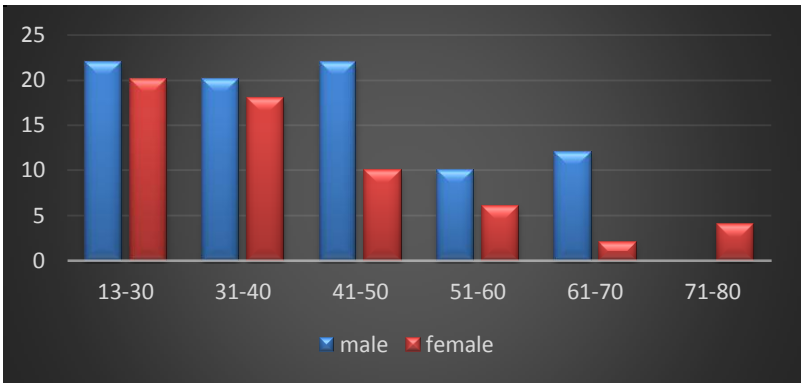

Fig. 1: Cluster bar diagram showing sex distribution in various age groups (P value = 0.001) [P value Chi-Square test]

Table 2: Distribution of patients (case) by tumor site

Tumor site	n=73	Percentage (%)	**p value**
Caecum	2	2.74	0.001
Ascending colon	6	8.22	
Hepatic flexure	1	1.37	
Transverse colon	4	5.48	
Splenic flexure	5	6.85	
Descending colon	2	2.74	
Sigmoid colon	10	13.70	
Rectum	43	58.90	
Total	73	100.00	

P value: Chi-Square test

Table 3. Test results of CEA and CA 19-9 in cases and control

Test results		**Case**	**Control**	**Total**	**p value**
CEA	Positive	48 (65.8%)	23 (31.5%)	71	0.001
	Negative	25 (34.2%)	50 (68.5%)	75	
	Total	73	73	146	
CA 19-9	Positive	21 (28.8%)	30 (41.1%)	51	0.086
	Negative	52 (71.2%)	43 (58.9%)	95	
	Total	73	73	146	

P value: Mann-Whitney U test

Table 4. Statistical measure of CEA and CA 19-9

Statistical Measure	CEA	CA 19-9
Sensitivity	65.75%	28.77%
Specificity	68.49%	58.90%
Positive Predictive Value	67.61%	41.18%
Negative Predictive Value	66.67%	45.26%
Positive Likelihood Ratio	2	0.7
Negative Likelihood Ratio	0.5	1.2

ROC curve for CEA:

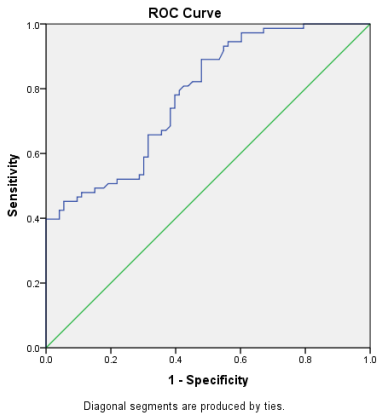

Fig. 2 Receiver Operating Characteristic (ROC) curve for CEA in patients and controls [area under the curve (AUC):0.781]

ROC curve for CA 19-9:

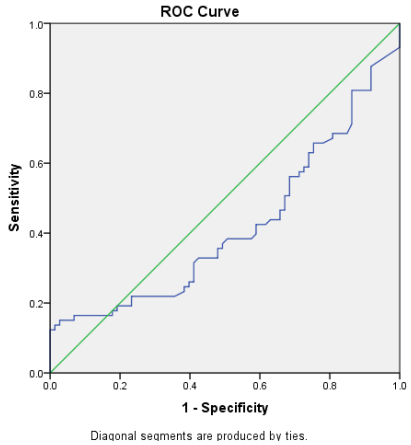

Fig. 3: Receiver Operating Characteristic (ROC) curve for CA 19-9 in patients and controls [area under the curve (AUC):0.418]

Table 5: CEA and CA 19-9 values against grading and staging

Variable		Pts	Antigen level [Median (minimum-maximum)]		p value	
			CEA (ng/ml)	CA 19-9 (U/mi)	CEA	CA 19-9
Grade	1	7	42.60 (7.9-1066.00)	28.20 (1.9-221.00)	0.001	0.007
	2	46	22.85 (0.86-590.52)	8.25 (0.80-201.6)		
	3	20	3.36 (0.53-120.80)	1.90 (0.20-23.16)		
T stage	1	1	0.86	3.30	0.013	0.178
	2	8	7.91 (1.38-42.60)	1.55 (0.80-50.60)		
	3	18	3.07 (0.53-542.80)	6.21 (0.28-201.60)		
	4	46	15.70 (1.08-1066.00)	8.25 (0.20-221.00)		
N stage	0	19	4.2 (0.53-35.40)	2.4 (0.8-201.60)	0.001	0.033
	1	40	13.79 (1.08-128.14)	9.00 (0.20-221.00)		
	2	14	115.80 (2.40-1066.00)	9.00 (1.20-120.00)		
M stage	0	39	7.62 (0.53-128.14)	4.7 (0.28-84.70)	0.006	0.033
	1	34	19.55 (1.86-1066.00)	11 (0.20-221.00)		

P value: Chi-Square test

VI. Discussion

Colon cancer is the tumor that affects equally both men and women. By mortality it ranks as fourth after lung, stomach and liver. The highest frequency is recorded in the highly industrialized country. Since early diagnosis raises the success rate of cancer treatment significantly, it is of utmost importance to investigate tumor markers. Recently, many studies have been performed on the prognostic value of parameters such as lymphatic involvement, preoperative CEA levels, histologic type and grade of the tumor, radial surgical margin and pattern of tumor spread. Most of those parameters have been shown to have a prognostic value, while studies on some are yet to be completed. Nonetheless, pathologic stage is the most important prognostic indicator of colorectal cancer [14]. Preoperative CEA and CA 19-9 measurement have been used routinely in the management of colorectal cancer patients to obtain more clues about spread of the disease. This study therefore aimed to evaluate the feasibility of using preoperative levels of these tumor markers to estimate either local or distant spread of disease. In this study, 73 patients with colorectal malignancy and 73 age and sex matched patients were prospectively included. Analysis of gender structure showed that 42 patients (57.53%) were male and 31 patients (42.47%) were female. Sex distribution was slightly male predominance but not statistically significant which was also reflected in previous studies [5,16]. Majority age distribution group was 13-30 then 31-40 years. So there is a tendency to occur malignancy at an earlier age in our patients. But elderly population was observed in the studies of other authors [15,16,17]. This may be due to socioeconomic and cultural background. Regarding tumor localization, usual distribution of colorectal cancer is rectum 38%, sigmoid colon 21%, caecum 12%, ascending colon 5%, hepatic flexure 2%, transverse colon 5.5% and descending colon 4% [18]. In this study, 43 (58.90%) patients had malignancy at rectum followed by sigmoid colon (13.70%) and then ascending colon (8.22%), splenic flexure (6.85%), transverse colon (5.48%), caecum & descending colon (2.74%) & finally hepatic flexure (1.37%). Bin Jin and associates published that they have found 44 cancers in the rectum region and 68 cancers in other regions of the colon [19]. Another study [15] also reflects similar result. Previous reports showed different overall rates of positivity for tumour markers. In a review that used an upper limit of normal of 2.5 ng/mL for CEA, a sensitivity of 36% and a specificity of 87% was reported in screening for Dukes A and B

colorectal cancer; a more recent study using cut-off values of 3.56 ng/mL for serum CEA and 28 U/mL for ca 19-9 in a limited patient population revealed sensitivities of 56.2% and 36.4% and specificities of 100% and 88.9% respectively for those markers [4,25]. In this study, CEA and CA 19-9 sensitivity were found 65.75% and 28.77% respectively. Whereas specificity of CEA and CA 19-9 were 68.49% and 58.90% respectively. Our ROC curve analysis for CEA in the diagnosis of colorectal patients had 65.8% sensitivity at 90% specificity for a cut-off level of 5 ng/ml whereas in case of CA 19-9, 16.4% sensitivity at 90% specificity for a cut-off level of 18 U/ml. [20] calculated that CEA has a sensitivity ranges from ~19% to 88% in colorectal cancer patient. [21] demonstrated its value as a diagnostic marker, in a cohort of 111 colorectal cancer patients, serum CEA showed a sensitivity of 69% and specificity of 70%. In the same cohort, cancer antigen 19-9 (CA 19-9), a cancer marker more commonly used to detect pancreatic cancer, showed a sensitivity of 36% and a specificity of 97% for colorectal cancer patients. Taking into account these, this study reflects similar results. Positive predictive value of CEA and CA 19-9 were found 67.61% and 41.18% respectively. Whereas negative predictive value of CEA and CA 19-9 were found 66.67% and 45.26% respectively. Yana Bocheva and Pavel Bochev [22] stated higher PPV in both CEA (83%) and CA 19-9 (84%) at their study [25]. Positive likelihood ratio of CEA and CA 19-9 were found 2 and 0.7 respectively. As PLR of CEA > 1 it has diagnostic value but not high as PLR > 10 indicate high diagnostic value. On the other hand CA 19-9 is not diagnostic as PLR < 1. Negative Likelihood Ratio of CEA and CA 19-9 were 0.5 and 1.2 indicates CEA has diagnostic value as NLR < 1 but not high as NLR < 0.1 indicate high diagnostic value. But CA 19-9 has no diagnostic value as its NLR > 1 [26] studied diagnostic accuracy of elevated serum CEA for recurrence and found that PLR > 1 and NLR < 1. In previous study [15], serum CEA was significantly higher in the patient group but CA 19-9 was not significantly different in the patient and control group. This study also reveals similar results as we serum CA 19-9 was not found significantly different in the patient and control group [p = 0.177 (>0.05)]. But CEA was found significantly higher in the patient group [p = 0.002 (<0.05)]. Those results suggest that elevated levels of CEA might signal a need for more complicated diagnostic interventions during preoperative staging. In this study serum CEA levels were found significantly higher in T stages (p=0.013). But CA 19-9 was not found significant (p=0.178) in relation to T staging. Previous study [7] also demonstrated similar results. [11] stated that CEA and CA 19-9 were statistically significantly different in early and metastatic colorectal cancer and elevated serum CA 19-9 was found to be related to distant metastasis[13]. The gene encoding CEA is classified as a member of the immunoglobulin supergene family, which includes intercellular adhesion molecule 1. The structural similarity of CEA to intercellular adhesion molecule 1 might alter cell adhesion, which might in turn have a role in cancer invasion and metastasis. Thus, CEA may play a role in the metastatic process [7]. Preoperative serum CEA and CA 19-9 may suggest when lymph node invasion and distant metastasis are present [7]. In this study, serum CEA and CA 19-9 levels were found higher at more lymph node invasion (p=0.001 & 0.033 respectively) and distant metastasis (p=0.006 & 0.033 respectively) reflecting similar results. These results concerning the relations of preoperative tumour marker levels with T and N stage suggest that a preoperative increase in the serum concentrations of these biomarkers might be a clue to lymphatic invasion as well as distant metastasis. If the results of preoperative imaging studies are negative for lymphatic invasion, but elevated serum concentrations of tumour markers are present in a colorectal cancer patient, the physician might want to manage the patient as suspected for lymphatic invasion. Several studies showed that more CEA per gram of total protein was produced by well-differentiated colorectal cancers than by poorly differentiated specimens [23]. Serum CEA has also been reported to trend higher in patients with well-differentiated tumors than in those with poorly differentiated tumours [24]. A review suggested that a lack of differentiation or poor differentiation may explain why some patients with advanced colorectal cancer don't show increased serum concentrations of CEA [24]. On the other hand, this study also showed that CEA levels are higher in well differentiated tumor than in those with poorly differentiated tumors. Those results have to be confirmed in molecular studies targeting the mechanisms of tumour marker production. Patients with aneuploid colorectal cancers have been shown to have higher serum concentrations of CEA than are seen in patients with tumours having a near diploid pattern[7].

Limitations of the study

Like most of the studies carried out around the world, certain limitations could not be overlooked, as in the study too. The sample size was small and it was selected purposively, so the findings of the study might not necessarily represent the picture of all population of the country. The study was single centered study with a limited catchment area. Most of the patients (case) admitted to DMCH surgery department with advanced stage.

VII. Conclusion

In summary, Given that colorectal cancer is a common cause of death worldwide, an effort either to achieve early diagnosis or to identify patients with poor prognosis in the preoperative period is needed to support patient management. Despite the significant difference found between the patient and control groups in the present study (p = 0.002), tumour markers are known not to be feasible in population screening, and this

study confirmed that understanding, given the low sensitivity and specificity of the markers studied. The main goal in the preoperative management of colorectal cancer patients, after localization of the primary tumour, is to determine lymph node invasion and distant metastasis. According to this study preoperative serum CEA and CA 19-9 might suggest whether lymph node invasion and distant metastasis are present. This study therefore recommends routine preoperative tests to evaluate especially serum CEA in colorectal cancer. Further studies into the molecular basis of tumour biology might contribute the current understanding of the nature of these tumors and tumour markers.

Recommendation: Based on the findings, this study recommends routine preoperative tests to evaluate especially serum CEA in colorectal cancer. This research implies further study to be done in other hospital and in future in a large scale. This research will act as a base line for future research in this field.

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