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CEA and CA19-9 in Recurrence and in Monitoring Response in Gastric Carcinoma

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ABSTRACT
Aim: *To analyze the level of serum Carcinoembryonic antigen (CEA) and CA19-9 before and after treatment.*
Methods: *For the study comprising total 60 cases suffering from gastric carcinoma before and after different cycle of treatment were selected. All patients were clinically and histologically diagnosed. A total of 50 age and sex matched healthy subjects taken as control. The circulating levels of CEA and CA19-9 activity were assayed in the in the serum of control group and in patients with Gastric carcinoma.*
Results: *The activity of CEA and CA19-9 was significantly highly increased found in gastric carcinoma patients compare to normal control. In normal healthy control the CEA and CA 19-9 activity was 1.95 ± 0.45, 23.94 ± 9.17 and in patients group 12.52 ± 4.37, 63.93 ± 16.72 respectively and the sensitivity of CEA in gastric carcinoma patients was 31.94 % and CA 19-9 was 42.56%. The combined detection of CEA and CA19-9 had higher sensitivity and specificity in gastric carcinoma patients. The level of CEA and CA19-9 were related to histological type or staging of malignancy. Compared with preoperative concentration, the level of CEA and CA19-9 significantly decreased 4 weeks after treatment or operation. It shows that the tumor is completely removed or a patient gives response to treatment or it shows disease is not recurrence or metastasized. When metastasis and recurrence occurred, the level of CEA and CA19-9 highly significantly increased found. Increased level of Tumor marker like CEA and CA19-9 indicates poorer survival.*
Conclusion: *CEA is a tumor marker that is measured using a blood test.CEA tumor marker is one of the general type tumor markers. A multiply increased CEA levels in the blood indicate to the presence of a malignant disease in the body, but not to the organ in which the malignant change has occurred. High levels of CEA may indicate that cancer has spread; however, other medical conditions and some treatments, including certain types of chemotherapy, may raise CEA levels. The conclusion of the study was that tumor markers can be useful in monitoring the response to treatment and in estimating the prognosis of disease and the combination of CEA and CA19-9 may be useful in diagnosis and management of patients with gastric carcinoma. The various types of biological behaviors of gastric carcinoma need further studies on molecular basis of tumor cells and tumor markers.*
Keywords: *Gastric carcinoma, CEA, GI tract, CA19-9, DNS, NCRP, Colorectal, Gastric, Esophagus, Liver, Gallbladder and Pancreas, Surgery radiotherapy, Immunotherapy. Chemotherapy*.

INTRODUCTION

Worldwide gastric carcinoma was the fourth most common malignancy till 2002, but recently reported that gastric adenocarcinoma is the second most common malignancy upto 2015 and is leading cause of death [(1)]. In India according to the National Registry programme, esophagus and gastric malignancies are the most common malignancies found in men, while esophagus malignancy ranks third among women there after carcinoma of breast and cervix. Gastric carcinoma is the fourth leading malignancy in the world and the second most common cause of death due to malignancy. Nearly 1 million new cases of gastric carcinoma and 0.7 million gastric carcinoma deaths are reported every year. Age standardized incidence rates are approximately twice as high in men as in women, ranging from 3.9 million in Northern Africa to 42.4 million in Eastern Asia for men and from 2.2 million in southern Africa to 18.3 million in Eastern Asia for women[(2)]. Currently gastric carcinoma is more common in Asia than in United States of America and Europe. The incidence and mortality of GI cancers in India is shown in following table [(3)] .

TABLE1. Shows the incidence rate and mortality of six most common gastrointestinal cancers as per GLOBOCAN 2012

Cancer Type	Colorectal	Gastric	Esophagus	Liver	Gallbladder	Pancreas
Incidence	64,332	63,097	41,774	27,416	18,787	11,936
Mortality	48,603	59,041	38,683	26,763	15,866	10,828

The most common cause is infection by the bacterium Helicobacter pylori, which accounts for more than 60% of cases. Certain types of H. pylori have greater risks than others. Smoking, dietary factors such as pickled vegetables, and obesity are other risk factors. About 10% of cases run in families and between 1% and 3% of cases are due to genetic syndromes inherited from a person's parents such as hereditary diffuse gastric cancer. Most cases of stomach cancers are gastric carcinomas. This type can be divided into a number of subtypes. Lymphomas and mesenchymal tumors may also develop in the stomach. Most of the time, stomach cancer develops in stages over years. Diagnosis is usually by biopsy done during endoscopy.

SIGNS AND SYMPTOMS OF GASTRIC CARCINOMA

Early gastric carcinoma has no associated symptoms; however, some patients with incidental complaints are diagnosed with early gastric cancer. Most symptoms of gastric carcinoma reflect advanced disease. All physical signs in gastric carcinoma are late events. By the time they develop, the disease is almost invariably too far advanced for curative procedures.

- Indigestion
- Nausea or vomiting
- Dysphagia
- Postprandial fullness
- Loss of appetite
- Melena or pallor from anemia
- Hematemesis
- Weight loss
- Palpable enlarged stomach with succussion splash
- Enlarged lymph nodes such as Virchow nodes and Irish node.

Late complications of gastric carcinoma may include the following features:

- Pathologic peritoneal and pleural effusions
- Obstruction of the gastric outlet, gastroesophageal junction, or small bowel
- Bleeding in the stomach from esophageal varices or at the anastomosis after surgery
- Intrahepatic jaundice caused by hepatomegaly
- Extrahepatic jaundice

- Inanition from starvation or cachexia of tumor origin

Through in India, the incidence of gastric carcinoma reported is very low as compared to that of western countries, the number of new gastric carcinoma cases reported is approximately 34,000; with male's predominance, (male to female ratio is 2:1). It was estimated that by the year 2020, approximately 50,000 new cases of gastric carcinoma will be reported annually in India. National survey of malignancy mortality in India reported gastric carcinoma as the second most common cause of malignancy related deaths amongst men and women [4]. Annual incidence rate of gastric carcinoma in India reported 10.6 per 100,000 populations, whereas the incidence rate in male 5.7 per 100,000 men and in female 2.8 per 100,000 women [5]. It is documented that GIT malignancy has high prevalence in southern part of India, however recent data highlights that the incidence rates are higher in the north-eastern part of India also [6]. As per latest reports available from National Cancer Registry Programmed the incidence rate of gastric carcinoma documented as below [7,8].

TABLE2:-Incidence of Gastric carcinoma in India as per National Cancer Registry Programme (NCRP) of India.

Registry Center	Mumbai (Urban)	Bangalore (Urban)	Chennai (Urban)	Thiruvan-anthapuram (Urban)	Delhi (Urban)	Auran-gabad (Urban)	Bhopal (Urban)	Barshi (Rural)
Men	**4.2 %**	**9.1%**	**12.2%**	**4.8%**	**3.4%**	**1.7%**	**1.6%**	**1.6%**
Women	**2.4%**	**5.5%**	**5.2%**	**1.9%**	**1.6%**	**0.8%**	**1.3%**	**1.0%**

CLASSIFICATION OF GASTRIC CARCINOMA

The World Health Organization (WHO) and the Japanese classifications are describe elaboratately several histopathological types of gastric carcinoma and are useful for the prognosis based on the grade of the histological differentiation of early lesion.

a) Adenocarcinoma
   i. Papillary Adenocarcinoma
   ii. Tubular Adenocarcinoma
   iii. Mucinous Adenocarcinoma
   iv. Singet-ring cell carcinoma
b) Adenosquamous carcinoma
c) Squamous cell carcinoma
d) Small cell carcinoma
e) Undifferentiated carcinoma
f) Other carcinoma

RISK FACTORS OF MALIGNANCY

It is usually not possible to know exactly why one person develops cancer and another doesn't. But research has shown that certain risk factors may increase a person's chances of developing cancer. Cancer risk factors include exposure to chemicals or other substances, as well as certain behaviors. They also include things people cannot control, like age and family history. A family history of certain cancers can be a sign of a possible inherited cancer syndrome. Most cancer risk factors are initially identified in epidemiology studies. In these studies, scientists look at large groups of people and compare those who develop cancer with those who don't. These studies may show that the people who develop cancer are more or less likely to behave in certain ways or to be exposed to certain substances than those who do not develop cancer.

The list below includes the most-studied known or suspected risk factors for cancer.

- Age
- Alcohol
- Cancer-Causing Substances
- Chronic Inflammation
- Diet
- Hormones

- Immunosuppression
- Infectious Agents
- Obesity
- Radiation
- Sunlight
- Tobacco

The malignancy causes in India are almost same as in other parts of the world. The chemical, biological and other environmental identities are responsible for uncontrolled and unorganized proliferation of cells i.e. carcinogens. Basically under special circumstances carcinogens interact with DNA of the normal cell resulting into series of complex multistep processes responsible for uncontrolled cell proliferation or tumor. The causes for malignancy can be both either internal factors like inherited mutations, hormones, immune conditions or external factors like environmental factors such as tobacco, diet, alcohol, radiation and infectious agents. There are significant variations in incidence of malignancy due to life style and food habits [9,10]. It is interesting to mention here that the rates of these malignancy incidences increase substantially when Asians migrates to the Western Countries; indicating a clear relationship of carcinogenesis with food habits and life styles. As per NCRP Dietary habit, Smoking or chewing of Tobacco, Alcohol consumption, Age and Sex, Inheritance and H. Pylori infection are the risk factors which Promotes malignancy in India.

Carcinoembryonic antigen (CEA) is glycoprotein consisting of 60% carbohydrate and molecular mass of 180-200kDa, which is present in normal mucosal cells and it is originally described by Gold and Freedman in 1965, is currently classified under the immunoglobulin super family and function as an intracellular adhesion molecules. CEA is a glycosylphosphatidyl-inositol cell surface anchored glycoprotein with specialized sialofucosylated glycoform that act as functional colon carcinoma L-selectin and E-selectin ligands which may significantly affect the metastatic dissemination of colon carcinoma [11, 12]. From immunohistological and immunocytological studies; it is well known that most carcinomas of the GI tract contain tumor markers such as CEA. The CEA consist of large family related cell surface glycoproteins, it is stable protein marker for colorectal, gastrointestinal, lung and breast carcinomas [13].

Science 1990s, CEA, CA19-9 and some other enzymes have been used as tumor marker for monitoring, prognosis and recurrence of gastric carcinoma, but specificities have not been satisfactory [14].

The aim of the present study was to evaluate the pre and post operative level of serum CEA and CA19-9 in gastric carcinoma patients.

MATERIAL AND METHODS

Selection of Patients

For the study total 60 cases of carcinoma of gastric before and after chemotherapy were selected. All patients were clinically and histologically diagnosed. All patients with stage-II received chemotherapy (cisplastin based chemotherapy) or any type of surgical treatment. There are 37 males & 23 female of gastric carcinoma. For control total 50 normal healthy age and sex matched persons were selected. Subjects with gastric carcinoma and those without any evidence of any type of cancer participated in this study as listed in table.

TABLE3: Distribution of control and gastric carcinoma patients

	Number of subjects (male/female)	Age-range (years)
Control	50 (32/18)	25-55
Gastric Carcinoma patients	60(37/23)	25-75
Stage I	60(37/23)	25-60
Stage II	60(37/23)	25-75

Inclusion criteria

1. Histopathologically proven gastric carcinoma; T2 or T3 or T4 tumor based on endoscopic ultrasound.
2. No evidence of distant metastases by endoscopy, tomography and laparoscopy.

3. No prior gastric surgery or therapy.
4.No metachronous carcinoma.
5.Age between 25-75 years

Exclusion criteria

1. Age not more than 75 years or younger than 25 years
2. Hepatic, renal, pulmonary, cardiac dysfunction.
3. Sever postoperative complications such as anastomosis leakage that may cause malnutrition or make the patients intolerant to postoperative therapy.

Collection of samples

Overnight fasting 5 ml blood sample were collected before and after chemotherapy in plain bulb. Serum was separated and used to estimation of CEA and CA19-9. Estimation of serum CEA was carried out by using commercial available kits from accu-bind. On ELISA micro plate Immunoenzymometric assay [(15)] and estimation of CA19-9 was carried out by using commercially solid phase immunoradiometric (Sorin, Saluggia, Italy).

Data Analysis

Data were expressed as mean ±SD. Mean values were assessed for significance by paired and unpaired student –t test. A statistical analysis was performed using the Stastical Package for the Social Science program (SPSS, 23.0). Frequencies and percentages were used for the categorical measures. Probability values $p < 0.0001$ were considered statistically significant.

TABLE4. Control group and gastric carcinoma patient's data.

	Control	Gastric carcinoma
No of Cases	n=50	n=60
Age ± S.D yrs	34.96 ± 6.83	57.26 ± 6.72
Male	31	37
Use of Tobacco / alcohol consumption	23	31
Female	19	23
Use of Tobacco/alcohol consumption	07	09
Stage I (before chemotherapy)	50	60
Stage II (After Chemotherapy)	50	60
Recurrence and Metastasis	-	23

OBSERVATIONS AND RESULTS

TABLE 5: Shows the serum CEA and CA19-9 in normal control and gastric carcinoma patients

Biochemical Parameters	No. of cases	Mean ± SD	" P" Value
CEA Control	50	1.95 ± 0.45	-
CEA in patients (µg/l)	60	12.52 ± 4.37	<0.001
CA19-9 control	50	23.94 ± 9.17	-
CA19-9 in patients (U/ml)	60	63.93 ± 16.72	<0.005

Table 5 shows that the activity of CEA and CA19-9 was significantly highly increased found in gastric carcinoma patients compare to normal control. In normal healthy control the CEA and CA 19-9 activity was 1.95 ± 0.45, 23.94 ± 9.17 and in patients group 12.52 ± 4.37, 63.93 ± 16.72 respectively and the sensitivity of CEA in gastric carcinoma patients was 31.94 % and CA 19-9 was 42.56%. The combined detection of CEA and CA19-9 had higher sensitivity and specificity in gastric carcinoma patients. The level of CEA and CA19-9 were related to histological type or staging of malignancy.

TABLE 6: Shows the serum CEA and CA19-9 in normal control and in gastric carcinoma patients with and without chemotherapy.

Parameters	Control	Before treatment	After 1 week of chemotherapy	After 4 week of chemotherapy
CEA (µg/l)	1.95 ± 0.45	12.52 ± 4.37	1.85 ± 0.59	2.27 ± 0.54
CA19-9 (U/ml)	23.94 ± 9.17	63.93 ± 16.72	19.48 ± 7.29	24.74 ± 9.59
In Recurrence or Metastasis CEA level	_	15.63 ± 6.13	5.49 ± 2.38	19.72 ±11.93
In Recurrence or Metastasis CA19-9 level	_	66.47 ± 19.72	27.93 ± 14.70	79.73 ± 22.82

Table 6 shows the level of CEA and CA19-9 before and after any type of treatment. Before treatment the level of CEA and CA19-9 was significantly increased found in gastric carcinoma patients. Compared with preoperative concentration, the level of CEA and CA19-9 significantly decreased 4 weeks after treatment or operation. It shows that the tumor is completely removed or a patient gives response to treatment or it shows disease is not recurrence or metastasized. When metastasis and recurrence occurred, the level of CEA and CA19-9 highly significantly increased found. Increased level of Tumor marker like CEA and CA19-9 indicates poorer survival.

DISCUSSION

The present study was carried out in the Dept. of Biochemistry in collaboration with Dept. of Pharmacology, Medicine and Surgery at Chandulal Chandrakar Memorial Medical College and Hospital Kachandur, Durg. Serum sample obtained from 60 gastric carcinoma patients admitted for evaluation & treatment were analyzed for the assay of CEA, CA19-9 and routine investigation.

The increased levels of tumor markers such as CEA and CA 19-9 are proposed to be correlated with clinic and pathological features of gastric carcinoma. In clinical practice; the tumor markers CEA and CA 19-9 are used to assess the efficacy of adjuvant treatment as a supplementary evidence for response [16]. Despite numerous reports on the usefulness of preoperative and periodic postoperative CEA measurements to predict stage, tumor progression, recurrence [17-19] and prognosis [20, 21] in patients with gastric carcinoma, already tumor markers have limited clinical utility due to their low sensitivity and specificity.

The positive rate of serum CEA and CA 19-9 at the initial diagnosis of gastric carcinoma has been reported to be 11.8%-37% 33-37 and 18%-45% [16], respectively. As per Erdal Polat et. al serum CA 19-9 levels had showed no significant difference between gastric carcinoma patients and controls, the serum levels of CEA was found to be significantly elevated in patients than controls [22] but our study result shows that the level of serum CEA and CA19-9 were significantly increased found in gastric carcinoma patients than control compared with postoperative the concentration of CEA and CA19-9 significantly decreased after operation or chemotherapy. When Carcinoma already metastasized or recurrence occurred, the levels are significantly increased. Similar Findings reported by Xavier Filella et.al [23]. The available data from previous studies confirm that the conventional tumor markers such as CEA and CA 19-9 don't allow diagnosis of gastric cancer with adequate sensitivity and specificity. CA 19-9 has been used in the diagnosis of digestive tract malignancies.

The serum CA 19-9 concentration increases to the greatest extent in patients with pancreatic cancer or cholangiocarcinoma. CA 19-9 resembles carcinoembryonic antigen in colorectal carcinoma and various different gastrointestinal adenocarcinoma [24]. The expression of CA 19-9 has been studied in normal and malignant gastrointestinal tissues. The antigen was found by immune peroxidase staining in 40–80% of carcinomas from the gallbladder, stomach, pancreas, and colon [25]. The association of elevated CA 19-9 levels with gastric carcinoma has been presented in a case report and in other studies. Elevated serum levels of CA 19-9 have been described in 15–30% of patients with gastric cancers, but these patients had multiple liver metastases. Elevated CA 19-9 levels have been significantly correlated with lymph node metastasis, vascular invasion and liver metastasis [26]. Our patient had an exceptionally elevated CA 19-9 level, with a serum level over 7,000 ng/ml, and a stomach cancer without liver metastasis or peritoneal dissemination as determined by laparotomy; at the time of death, the patient's serum CA 19-9 was over 120,000 ng/ml. A high serum CA 19-9 level in a patient with gastric cancer is extremely rare [27]. Jie-Xian Jing et.al. 2014 [28] studied sensitivity of CEA, CA 19-9, CA

24-2, AFP, SCC, CA 72-4, TPA and TPS were 26.80 %, 36.15%, 42.89%, 20.84%, 25.39%, 34.59% and 30.89% respectively reported in upper GIT carcinoma respectively. The combined detection of all these parameter had higher sensitivity and specificity in gastric carcinoma and cardiac carcinoma for diagnosis. On multivariate analysis high preoperative CA 72-4, CA 24-2 and SCC served prognostic factor for cardiac carcinoma, gastric carcinoma and esophagus carcinoma. A study realized by T. Yamao et al included 26 patients diagnosed with gastric cancer, in an advanced stage, with increased concentrations of CEA, CA 19-9 and CA 125 before systemic chemotherapy. A response to treatment was considered as a ≥50% decrease in the concentration maintained for more than 4 weeks. The results showed a good correlation between the imaging studies and the assessment of response by tumor markers. The patients who responded to treatment were also characterized by longer survival times.

There seems to be many controversial and conflicting reports about the relationship of tumor markers and the clinical properties of gastric carcinoma. On the basis of our result we concluded that CEA is a tumor marker that is measured using a blood test.CEA tumor marker is one of the general type tumor markers. A multiply increased CEA levels in the blood indicate to the presence of a malignant disease in the body, but not to the organ in which the malignant change has occurred. High levels of CEA may indicate that cancer has spread; however, other medical conditions and some treatments, including certain types of chemotherapy, may raise CEA levels. The conclusion of the study was that tumor markers can be useful in monitoring the response to treatment and in estimating the prognosis of disease and the combination of CEA and CA19-9 may be useful in diagnosis and management of patients with gastric carcinoma. The various types of biological behaviors of gastric carcinoma need further studies on molecular basis of tumor cells and tumor markers.

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