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Clinical Utility of GST and CEA in Gastrointestinal Cancer

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Abstract:

Purpose: *- To analyze the level of serum Glutathione-S-Transferase (GST) and Carcinoembryonic antigen (CEA) before and after different Cycles Of chemotherapy in GI carcinoma patients.*

Methods: *- For the study comprising total 58 cases suffering from GI carcinoma stage I, stage II stage III and Stage IV (before and after different cycle of chemotherapy) were selected. All patients were clinically and histologically diagnosed. A total of 42 age and sex matched healthy subjects taken as control. The circulating levels of GST and CEA activity were assayed in the in the serum of control group and in patients with GI carcinoma.*

Results: *- Serum level of GST and CEA were highly significant in GI carcinoma patients as compared to control group ($p<0.001$). After first cycle of chemotherapy (stage II) the activity of GST and CEA were significantly higher than before chemotherapy (stage I). In stage III (after second cycle of chemotherapy) activity was significantly decreased than that of stage II and the activity of GST and CEA was significantly decreased in stage IV (after third cycle of chemotherapy) than stage III (after second cycle of chemotherapy).*

Conclusion: *- On the basis of data from our study, it can be stated that serum GST measurement in plasma may be useful tumor marker in gastrointestinal carcinoma, its activity might helpful to predict the response of chemotherapy in advance stage of cancer.*

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. CEA tests are one way doctors can find out whether the cancer has spread or returned. Cancer that has spread or returned can be treated successfully for many patients. CEA measurement is mainly used to identify recurrences after surgical resection and for staging.

Keywords: - GI carcinoma, GST, CEA, GI tract, Colorectal, Gastric, Esophagus, Liver, Gallbladder and Pancreas

Introduction

Gastrointestinal carcinoma (GI carcinoma) refers to malignant conditions of the gastrointestinal tract (GI tract) and accessory organs of digestion and it includes esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus. The symptoms relate to the organ affected and can include obstruction, abnormal bleeding or other associated problems. The diagnosis often requires blood test, urine test, stool test endoscopy and biopsy of suspicious tissue. The treatment depends on the location of the tumor, as well as the type of malignant cell and whether it has invaded other tissues or spread elsewhere. These factors also determine the prognosis of disease. Overall, the GI tract and the accessory organs i.e. pancreas, liver, and gall bladder are responsible for more malignancies and more deaths from GI carcinoma than any other system in the body. There is significant geographic variation in the rates of different gastrointestinal carcinomas.[1]

GI carcinoma is not only one of the most common carcinomas but also one of the most common causes of carcinoma mortality. A quick look at GLOBOCAN data 2012 showed that out of estimated 1.01 million new cases in the year 2012 in India, 227,000 were located in GI tract. Similarly, out of about 682,000 carcinoma-related deaths, approximately 182,000 deaths were because of GI carcinomas.[2] The six most common GI carcinomas are colorectal carcinoma (CRC), gastric, esophagus, liver, gallbladder, and pancreas. In this issue of the journal,

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authors have tried to summarize and compile important Indian studies involving GI carcinomas. This is a step to showcase what has been the collective contribution of Indian medical and scientific research in this field.[3]. More importantly, this also gives a chance to introspect whether as a community we are happy with this contribution or this is the high time we introspect. In this report, authors have divided various published studies based on organ of involvement. The incidence and mortality of GI cancers in India is shown in following table.[4]

Table 1: 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

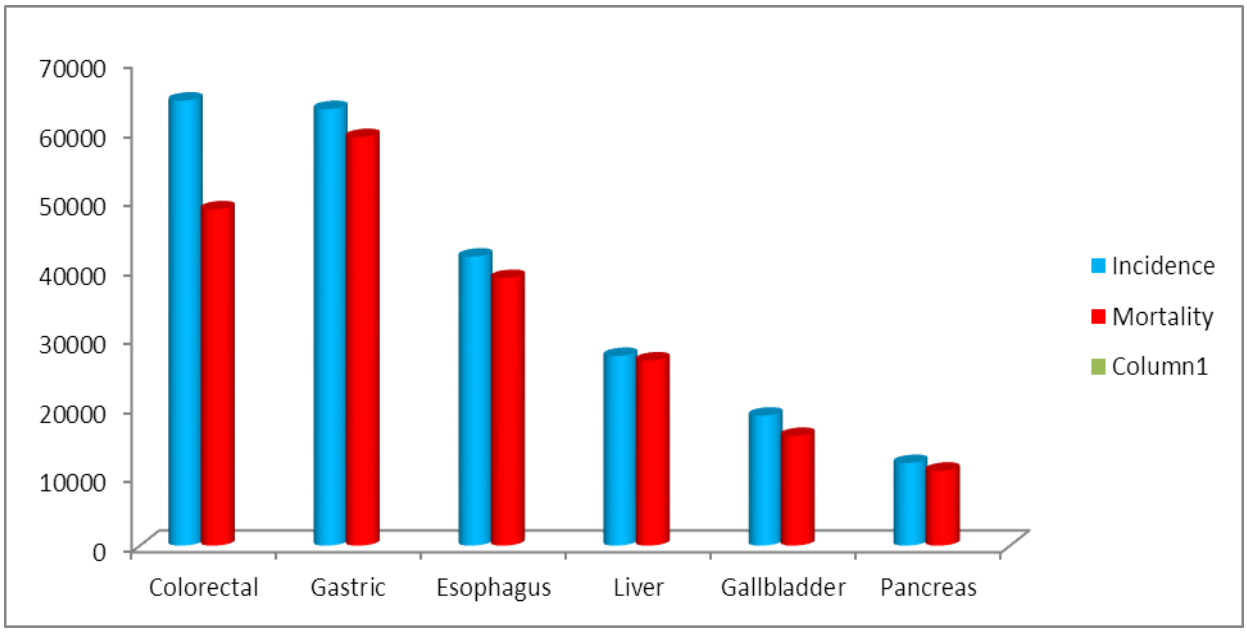
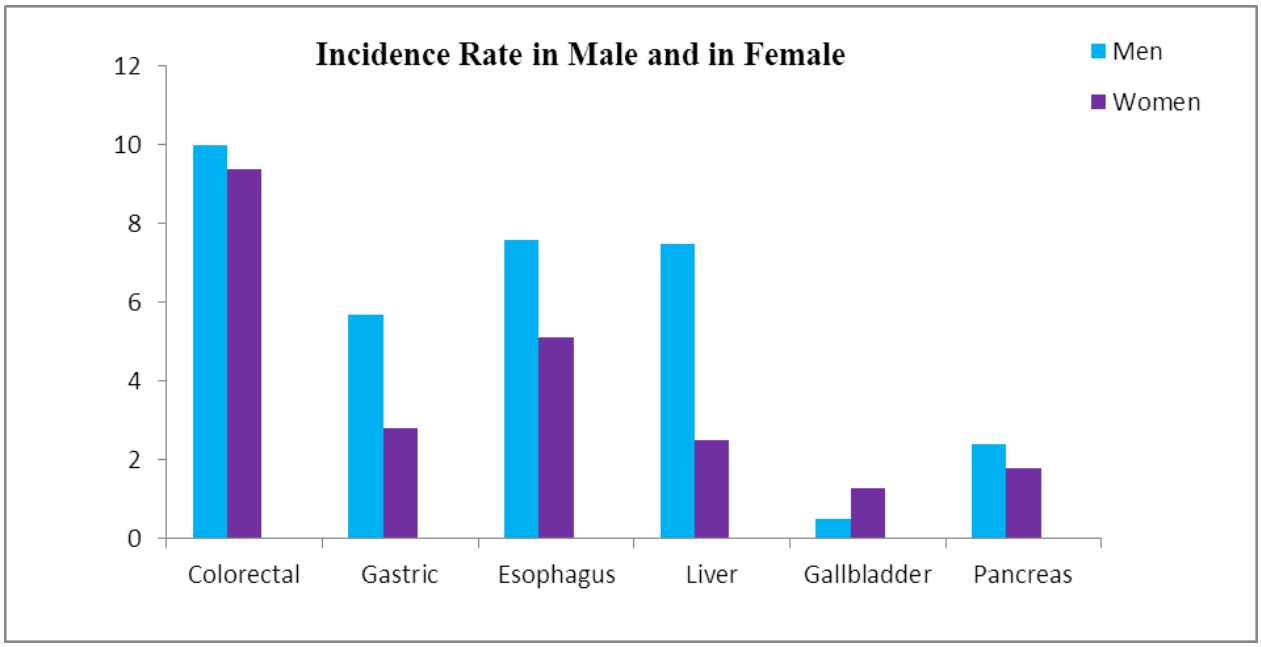


Table 2:- Incidence of Gastrointestinal cancer in male and female per 100,000 in India as per National Cancer Registry Programme (NCRP) of India [5-7].

Cancer Type	Colorectal	Gastric	Esophagus	Liver	Gallbladder	Pancreas
Men	10	5.7	7.6	7.5	0.5	2.4
Women	9.4	2.8	5.1	2.5	1.3	1.8



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Based on clinical observations some substances may increase risk of GI carcinoma like, excessive use of alcohol and tobacco, low socioeconomic status, poor oral health and consumption of hot drinks. The presence of N-nitrosamine in food stuffs, low intake of fresh fruits and vegetables, vitamin and trace mineral deficiency, smoking opium, chewing betel squid, drinking mate and disease affecting the esophagus like achalasia and Plummer Vinson syndrome have been linked to GI carcinoma.[8]

Certain substances in the diet may increase GI carcinoma risk for e.g. there have been suggestions as yet net well proven, that a diet high in processed meat may increase the risk of GI carcinoma. Drinking very hot liquids frequently may increase the risk for esophageal carcinoma. This might be the result of long term damage the liquids do to the cell lining the esophagus. Overeating which leads to obesity, increase the risk of GI carcinoma. On the other hand, a diet high in fruit and vegetables is linked to a lower risk of esophageal carcinoma. The exact reason for this are not clear but fruits and vegetables have a number of vitamins and minerals that may help prevent carcinoma.[9]

Most of the treatments outcomes of patients have been poor because the disease has already progressed to an advanced stage by the time it is diagnosed. Consequently, various tumor markers have been used to detect malignancy at an early stage and monitor malignancies. Recently many researchers and clinical practices indicate that there are some tumors markers including Carcinoembryonic antigen (CEA) and Glutathione-S-Transferase (GSTs) are commonly found in digestive tract or gastrointestinal tract (GIT). Moreover they can be used for the monitoring of tumor recurrence and used as prognostic factor.[10-12]

Individualized chemotherapy administrated taking into account biomarkers expression may improve the response to chemotherapy and clinical outcome of patients. Therefore better understanding of the role of pharmacogenetics could help establishing an individualized chemotherapy and patients may benefit more from chemotherapy to prolong their life, as the gene which influences the clinical response to chemotherapeutics, control drug absorption, distribution, metabolism and excretion.

GSTs are a family of cytosolic enzymes, and they play an important role in the detoxification of various exogenous and endogenous reactive species.[13] They participate in anti-oxidant defense through several mechanisms including reactive oxygen species.[14] GSTs catalyze the binding of large variety of electrophiles to the sulphydryl group of glutathione (GSH) yielding less harmful and more water soluble molecules which can excrete via urine or bile. Since most reactive, ultimate carcinogenic forms of chemicals are generally electrophiles GST takes considerable importance as a mechanism for carcinogen detoxification.[15] GSTs distributed in liver, lung, skin, brain, esophagus, intestine, stomach, and placenta.

GSTs have attracted interest in the field of diagnosis, monitoring of recurrence and prognosis of malignancies. In most of the tumors GSTs expression in response to tumor formation is probably a resistance mechanism by which cell can survive and the source of plasma enzyme is mainly transformed cell with expression of GSTs.[16]

Carcinoembryonic antigen (CEA) is a glycoprotein. It was first identified in 1965 by Gold and Freedman in human colon carcinoma tissue extracts. CEA currently classified under the immunoglobulin super family and functions as an intracellular adhesion molecule. In the recent years CEA has been widely used as a tumor marker in the diagnosis and monitoring of some malignancies.[17] Science the 1990s tumor marker including CEA and other have been widely used to monitor GI carcinoma progression and even to assess the prognosis of GI carcinoma patients although their specificities have not been satisfactory.[18] Therefore, the serum CEA level may be a pertinent index of tumor progression for patients with GI carcinoma.

In trial of chemotherapy for patients with a GI carcinoma and who had undergone a noncurative resection, we determined serum CEA levels before and after different cycles of cisplastin based chemotherapy in GI carcinoma patients. Measurement of CEA in GI carcinoma patients poses a continuing challenge to surgeon. Major predicators of survival are the stage of the tumor at the time of presentation and the extent of the surgical restriction performed.[19] Little emphasis has been given to the value of detection of recurrent disease which has been reliant a crude method such as development of dysphasia or systemic metastases both of which herald the patients' rapid decline. The tumor marker CEA is often elevated in patients with tumor of the gastrointestinal tract.[20] Elevated CEA levels have been used as a marker for recurrent colorectal carcinoma and prognostic marker for second surgery. CEA has been reported to be beneficial in determining the relapse and the follow up of the response to the chemotherapy or treatment of the patients with gastric and esophageal carcinoma.[21]

This shows that change in tumor marker enzyme level of GSTs and CEA have role in carcinoma progression. Also, many clinicians try to predict the effect of chemotherapy by obtaining serial level of tumor markers during chemotherapy. In general a rising tumor marker level means tumor progression in patients who are receiving chemotherapy. In this our study, serum GST and CEA activity has been measured before and after different cycles

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of chemotherapy in patients suffering from GI carcinoma compared with normal healthy control group.

Material and Methods

I. Selection of Patients

For the study total 58 cases of carcinoma of GI before and different cycles of chemotherapy were selected. All patients were clinically and histologically diagnosed. All patients with stage-II (First Cycle), stage-III (Second Cycle) and stage-IV (Third cycle) received chemotherapy including cisplastin, 5-FU capecitabine, cyclophosphamide, Transtuzumab and doxorubicin. There are 28 males & 30 female of stomach cancer. For control total 42 normal healthy age and sex matched persons were selected. Subjects with GI carcinoma and those without any evidence of any type of cancer participated in this study as listed in table.

II. Collection of samples

Overnight fasting 10ml blood sample were collected before and after different cycle of chemotherapy in plain bulb. Serum was separated and used to estimation of glutathione-S-transferase (GSTs) and Carcinoembryonic antigen (CEA). Serum GSTs activity measured by, using 1-chloro-2, 4 dinitrobenzene (purchased from Sigma company) as substrate, was measured according to the procedure described by Habig et al[14] and Estimation of serum CEA was carried out by using commercial available kits from accu-bind. On ELISA micro plate Immunoenzymometric assay.[20]

III. Follow Up

Overall 86 patients were followed up at time of admitted in hospital and after discharge from hospital. Out of 19 patients follow up were lost during the follow up period and 9 patients were dead. The follow up system consisted of measurement of tumor marker GST and CEA level before and after different cycles of chemotherapy countineuly 3 months intervals for first 3 month and at 6 month intervals thereafter. The follow up program included, clinical examination, hematological analysis, tumor marker and enzyme assay at each check-up. Criteria for the establishment of recurrent disease included histological conformation or disease evident radiological with subsequent clinical progression and supportive biochemical data.

IV. 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.

Table 3: Distribution for control and GI cancer patients

	Number of subjects (male/female)	Age-range (years)
Control	42(25/17)	25-55
GI Carcinoma patients	58 (28/30)	25-60
Stage I	58 (28/30)	25-60
Stage II	58 (28/30)	25-60
Stage III	58 (28/30)	25-63
Stage IV	58 (28/30)	25-70

Results

As shown in table 2 mean serum GSTs activity (mean±SD) in control using CDNB as substrate was 5.05±0.51 IU/L. Serum GSTs activity of gastrointestinal carcinomas patients was 9.13 ± 1.71 IU/L. GSTs activity was significantly higher in gastrointestinal carcinomas patients than control ($p<0.001$).

CEA activity (mean±SD) in control using commercial kits from accu-bind on ELISA micro plate Immunoenzymometric assay was 1.55±0.30. Serum CEA activity of gastrointestinal carcinoma patients was 13.7 ± 4.43. CEA activity was significantly higher in gastrointestinal carcinoma patients than control ($p<0.001$).

Table 4: Comparison of serum GST and CEA activity in control with gastrointestinal carcinoma

Tumor Markers	No. of cases	Mean ± SD	" P" Value
GST Control	42	5.05 ± 0.51	-
GST IU/L	58	9.13 ± 1.71	<0.001
CEA Control	42	1.55 ± 0.30	-
CEA ng/ml	58	13.7 ± 4.43	<0.001

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Table 5: Serum GST (IU/L) levels before and after different cycles of chemotherapy comprised with control counterpart.

	No. Of Cases	Mean ±SD	p-value
Control	42	5.05 ± 0.51	-
Before Chemotherapy (Stage I)	58	9.13 ± 1.71	< 0.001*
First Cycle of Chemotherapy (Stage II)	58	12.68 ± 1.05	< 0.001**
Second Cycle of Chemotherapy (Stage III)	58	8.06 ± 1.32	< 0.001$
Third Cycle of Chemotherapy (Stage IV)	58	5.65 ± 0.66	< 0.001$$

*(Values are expressed in IU/L) * Control vs Stage-I, **Stage-I vs Stage-II, $ Stage II vs Stage III and $$ Stage III vs Stage IV.*

Table 6: Shows Comparison between control vs stage I and Control vs Stage IV

	Mean ±SD	Upper Range	Lower Range	p-value
Control	5.05± 0.51	5.18±0.60	4.88±0.39	
Before Chemotherapy (Stage I)	9.13 ± 1.71	11.59±1.71	7.42 ±1.14	< 0.001*
Third Cycle of Chemotherapy (Stage IV)	5.65 ± 0.66	5.83±0.76	5.45±0. 56	< 0.001$

*(Values are expressed in IU/L) * Control vs Stage-I, $Control vs Stage IV*

Table 7: Serum CEA (ng/ml) levels before and after I, II, III, IV comprised with control counterpart.

	No. of Cases	Mean ±SD	p-value
Control	42	1.55 ± 0.30	-
Before Chemotherapy (Stage I)	58	13.7 ± 4.43	< 0.001*
First Cycle of Chemotherapy (Stage II)	58	6.36 ± 2.64	< 0.001**
Second Cycle of Chemotherapy (Stage III)	58	2.46 ± 0.34	< 0.001$
Third Cycle of Chemotherapy (Stage IV)	58	1.55 ± 0..45	< 0.001$$

*(Values are expressed in IU/L) * Control vs Stage-I, **Stage-I vs Stage-II, $ Stage II vs Stage III and $$ Stage III vs Stage IV.*

Table 8: Shows Comparison between control vs stage I and Control vs Stage IV

	Mean ±SD	p-value
Control	1.55 ± 0.30	
Before Chemotherapy (Stage I)	13.7 ± 4.43	< 0.001*
Third Cycle of Chemotherapy (Stage IV)	1.55 ± 0.45	< 0.186$

*(Values are expressed in IU/L) * Control vs Stage-I, $Control vs Stage IV*

All values are given as mean ± S. D.
Stage I- Without any treatment (Surgery, chemotherapy, Radiotherapy)
Stage II- After First Cycle of Chemotherapy
Stage III- After Second Cycle of Chemotherapy
Stage IV- After Third Cycle of Chemotherapy

Discussion

The present study was carried out in the dept. of Biochemistry, Dept. of Surgery and Dept. of Medicine at Chandulal Chandrakar Memorial Medical College Kachandur, Durg in collaboration with Grant Government Medical College and JJ group of byculla Mumbai. Serum sample obtained from 58 gastrointestinal carcinoma patients admitted for evaluation & treatment were analyzed for the assay of Glutathione-S-Transferase (GST), Carcinoembryonic antigen (CEA), and routine investigation.

Changes in tissue enzymatic activity are often reflected in blood. Rapid turnover of malignant cell causes seepage of enzymes into the blood stream. Numbers of enzymes are present on the cell and organelle's membranes. Membrane constituents are shed into surrounding milieu at increasing rate due to uncontrolled cell division. Enzymes present in the nucleus, cytoplasm and mitochondria are also released when cells are destroyed. Also enzymatic changes may reflect the overall changes in metabolism that occur in malignancy. Finally the presence of carcinoma may induce the release of enzymes from surrounding normal cells.

Glutathione-S-transferases are among the catalysts that participate in the process of detoxification. Enzymatic reaction involving conjugation of reduced glutathione with variety of electrophiles by GSTs results in detoxification of variety of electrophiles. The GSTs distributed widely in tissues such as the liver, lung, skin, brain, intestine and placenta etc. These enzymes are implicated in tumor genesis and both μ class GSTs and α class GSTs have been described in human renal cell carcinoma.[22] Levels of enzyme detection in serum are useful for diagnosis and

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prognosis of human diseases. Recently several investigators reported that GSTs may be useful in monitoring pathogenesis of liver disease.[23] Recently GSTs have attracted interest in the fields of diagnosis & monitoring of malignancy. The GSTs has a considerably important role in the detoxification of carcinogens. The GSTs are present in many species and tissues and also in relatively large amounts in the epithelial tissues of the human GIT. GSTs were found to be over expressed in most the tumors. GSTs expression in response to tumor formation is probably a resistance mechanism by which cells can survive and the source of plasma enzyme is mainly transformed cell with over expression of GSTs.[24] A literature reports have suggested that serum GSTs level may be increased in wide range of gastrointestinal and hematological malignancies. GSTs was expressed in high levels in hepatic neoplastic lesions in rat had illicit interest in this enzyme as a potential marker of hepatocellular carcinogenesis.

The CEA molecule has a nominal molecular mass of 180-200 kDa with a protein core that makes up somewhat less than half of the molecule. As deduced from the complete sequence of the cloned CEA gene, the protein consists of a single polypeptide chain, containing 107 amino acid NH-terminal domains followed by three highly homologous domains of 178 amino acids each. The C-terminal domain, consisting 26 amino acids, is processed so that CEA binds to the plasma membrane through a glycophosphatidyl inositol (GPI) anchor. Carbohydrate side-chains comprise the remainder or over half of the molecular mass bound to the protein core via 28 potential Asn-linked glycosylation sites that have been identified on the CEA molecule. The molecule appears as a screw- or cruller-shaped structure with dimensions of approximately 9 x 40 nm when visualized by electron microscopy after appropriate shadow casting.[25]

In the present study serum GST was significantly higher in Stage I (P<0.001), Stage II (P<0.001) and Stage III (P<0.001) in GIT carcinoma patients as compared to those obtained from normal healthy control group but in Stage IV (P< 0.001) the level of GST is normal in range. G.S.Mahammadzadeh et.al[26] observed similar result which is stastically insignificant in which plasma activity was significantly higher in esophagus and gastric carcinoma patients. The GST activity in plasma represents a non invasive biomarker of the cellular protection.

The activity of serum GST was higher in 78.57% patients of GI carcinoma in this study supports the finding of N. R. Hazari et. al.[27] the increased activity of GSTs in tumor tissue can be due to over expression isoenzymes of GSTs in response to metabolic changes in tumor cells. The human GST π class was found to be over expressed in most of cases. GST π expression in response to tumor formation is probably a defence mechanism to aid cells to survive and the source of plasma enzyme is mainly the transformed cells with over expression of GST π. Present study showed a significant increased activity of GST in stage II patients than stage I patients in GI carcinomas, which may due to the progression of disease or carcinoma. GST π expression in malignant tissues and plasma GST π levels in human colorectal and gastric carcinoma are believed to increase depending on the stages of tumor.[28] Several studies also showed progressive increase of GST with advancing carcinoma and has been associated with poor prognosis and development of drug resistance.[29, 30]

Similarly, comparing stage III (P<0.001) and stage II (P<0.001), there was a significant decreased level of GST found in patients of stage III, but stage III patients had significant higher values than control group in GI carcinomas these findings supports study of Kadam Charushila et. al. in breast cancer[31] & Lina Daukantiene[32] in cervical cancer. The decreased activity of GSTs in tumor tissue can be due to drugs, causing depletion, which may be due to higher oxidative stress after chemotherapy.

When stage IV (P<0.001) and stage III (P<0.001) were compared the level of GST decreased significantly in stage IV. Also according to our study no significant association was found between GI carcinoma patients with control group but values are in normal range, which needs further elaborate research work with more number of patients. Elevation of serum GST activity in GI carcinoma is probably a defense mechanism by which cells can survive and source of plasma enzyme is mainly, the transformed cell with over expression of GST.

In the present study the serum GST level in stage II patients (received chemotherapy) of GI carcinoma was significantly elevated than stage I & control group and suggests that enhanced antioxidant made the tumor tissue less susceptible to oxidative stress conferring growth advantage. K. Johansson et.al.[33] reported glutathione-s- transferase protect the cells from lipid peroxidation (which is increased by cisplastin) & from hydrogen peroxide.

The result of our present study show a significant increase in CEA level in GI carcinoma patients compare to normal control subjects. Individual patient's data revealed that total 58 of 58 (100%) patients of GI carcinoma had CEA levels above normal limit. Estimating CEA is useful in diagnosis and prognosis of carcinoma. In carcinoma patients increased level of CEA after chemotherapy may indicate poor response to that treatment or progression of carcinoma. The values of CEA in stage I were 13.7± 4.43 ng/ml in GI carcinoma patients found to be significantly increased in gastrointestinal carcinoma patients than control group 1.55 ± 0.30. The level of CEA in stage II 6.36 ± 2.64 ng/ml in

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carcinoma patients were significantly decreased than stage I. The activity of CEA significantly decreased in stage III 2.46 ± 0.34 ng/ml found in GI carcinoma patients than stage II 6.36 ± 2.64 carcinoma patients. In stage IV 1.55 ± 0.45 in GI carcinoma patients elevated in stage I the level of CEA significantly decreased than stage III 2.46 ± 0.34 ng/ml in GI carcinoma patients.

According to study by Bhawna Bagaria et. al[34] that the mean level of CEA in esophagus carcinoma and gastric carcinoma patients were significantly higher than control group. The mean level of CEA was 5.57 ± 5.98 ng/ml in esophagus carcinoma and 6.23 ± 7.73 ng/ml in gastric carcinoma patients were significantly higher than control group and Hisanao Ohkura et. al[35] showed the remarkable sensitivity of serum tumor marker CEA in 60 patients of oesophagus squamous cell carcinoma and gastric carcinoma. The sensitivity of CEA was reported as 70 % high in both carcinomas. In clinical practice tumor molecules such as a CEA are commonly used for screening of gastrointestinal malignancies.

Yonggoo Kim et.al.[36] reported that the activity of CEA in gastrointestinal tract carcinoma patients was much higher than in controls (44.1 ± 70.1 ng /mg stool Vs 3.7 ± 3.5 ng /mg stool, p<0.001). The activity of CEA in gastric carcinoma patients was much higher than in control group (42.5 ± 57.4 ng /mg stool Vs 3.7 ± 3.5 ng /mg stool, p<0.001); there was no significant difference between early gastric carcinoma patients and those with invasive gastric carcinoma (42.0 ± 89.6 ng /mg stool Vs 42.9 ± 38.8 ng /mg stool, p<0.001). The activity of CEA was not increased in patients with benign gastrointestinal disorder (4.5 ± 8.2 ng / ml). Serum level of CEA in patients with gastrointestinal tract carcinoma (6.43 ± 11.85 ng / ml) was significantly higher than normal controls (1.14 ± 1.01 ng / ml). In this study they showed the CEA assay is superior for detecting gastrointestinal tract carcinoma and Jie-Xian Jing et.al [37] studied 573 patients of upper gastrointestinal carcinoma patients the sensitivity of CEA was 26.80 %. The level of CEA was significantly higher (10.41 ± 3.67 ng/ ml) than control group. Preoperative serum level of CEA was increased found than postoperative (9.58 ± 1.90 ng/ ml Vs 1.01 ± 1.37 ng/ ml).

Conclusion:

On the basis of data from our study, it can be stated that serum GST measurement in plasma may be useful tumor marker in gastrointestinal carcinoma, its activity might helpful to predict the response of chemotherapy in advance stage of cancer.

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. CEA tests are one way doctors can find out whether the cancer has spread or returned. Cancer that has spread or returned can be treated successfully for many patients. CEA measurement is mainly used to identify recurrences after surgical resection and for staging.

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