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Use of Tumor Marker and Enzymes in Recurrence and Monitoring Response to Pre and Post Chemotherapy for Patients with Upper Gastrointestinal Carcinoma

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Abstract:

Aim *- To analyze the level of serum Carcinoembryonic antigen (CEA) Glutathione-S-Transferase (GSTs), Lactate Dehydrogenase (LDH) and Alkaline Phosphatase (ALP) before and after different cycles of chemotherapy in reference to upper gastrointestinal cancer patients.*

Methods *- For the study comprising total 232 cases suffering from gastrointestinal cancer (before and after different cycles of chemotherapy) were selected. All patients were clinically and histopathologically diagnosed. A total of 42 age and sex matched healthy subjects taken as control. The circulating levels of CEA, GSTs, LDH and ALP activity were assayed in the in the serum of control group and in patients with gastrointestinal cancer.*

Results *- Mean CEA, GSTs, LDH and ALP activity in serum were significantly higher in gastrointestinal cancer patients as compared to normal control group ($p<0.001$). After first chemotherapy (stage II) the activity of GSTs, LDH and ALP were significantly higher but the activity of CEA was highly significantly decreased 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 CEA, GSTs, LDH and ALP was significantly decreased in stage IV (after third cycle of chemotherapy) than stage III (after second cycle of chemotherapy) and levels become normal in range.*

Conclusion *- The study highlights serum CEA and GSTs measurement are useful marker for gastrointestinal cancer, its activity helpful to predict the response of treatment in advanced stage of cancer and recurrence of disease. Increased levels of serum LDH and ALP indicates infection or blockage or metastasized or liver damage by treatment. LDH and ALP are good prognostic marker in gastrointestinal cancer treated with chemotherapy. Increased level of ALP indicates advanced disease progression or treatment strategy. Statistically significant changes in CEA, GSTs, LDH and ALP levels during the treatment with positive response and no established disease progression during study period near about 27 months after the treatment, which indicate that GSTs and CEA are important predictive factor.*

Keywords *- **GIT, Cisplastin, capecitabine, gastrointestinal cancer, Stomach cancer, Esophagus cancer, tumor marker, chemotherapy, CEA, Glutathione-s-transferase, LDH, ALP, ROS.***

Introduction

Gastrointestinal tract (GIT) is one of the most essential organ after heart and brain. Though definitely not the most attractive organs in the body, but they are certainly among the most important. A poorly functioning or nonfunctional gastrointestinal tract may be source of chronic diseases problems that can cause the quality of life status. The GIT system is for breakdown and absorption of food and liquid needed to sustain life. Many other different organs have essential role in the process of food digestion. The GI tract initiate from mouth and proceeds to esophagus, stomach, small intestine, large intestine, rectum and ends at the anus.

Human beings and animals have been reported, suffering from cancer. The earliest evidence of cancer is found among fossilized bone tumor, human mummies in Egypt. Bone growth suggests bone cancer known as osteosarcoma, it is found in human mummies in Egypt. Before 3000BC oldest

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description of cancer was discovered in Egypt (cancer word was not used). The Greek physician Hippocrates discovers cancer word in 460-370 BC. Hippocrates used the term carcinos and carcinoma to describe ulcer and non-ulcer forming tumors. In the beginning of 15th century, scientists developed greater understanding of the human body.

In 1915, scientist from Tokyo University, first time induced cancer in experimental animals by coating coal tar to rabbit skin. There after a London based clinician, John Hill recognized tobacco as a carcinogen. Today scientist recognized many substances that cause cancer like Benzene, Hydrocarbons, substances used for making dyes, asbestos, ionizing radiation, sun radiation and many others. In 2014 as per World Health Organizations (WHO), International Agency for Research on Cancer (IARC) has discovered more than 100 chemical, physical and biological carcinogens. Cancer has major impact on society across the world.[1]

Cancer refered as a group of diseases characterized with uncontrolled growth with increase of abnormal cells. If the growth is uncontrolled, this can be result in death. The development of cancer is promoted by an internal as well as external factor. Furthermore these external and internal factors may act upon to initiate carcinogenesis. The promotion of most cancers requires multiple steps that occur over many years. There are types of category of cancers which can be blocked by abstinence of tobacco and other factors that promotes the development of cancer.

Potential malignancies can be detected before cells become cancerous or at an early stage, when the disease is most treatable. Multipurpose therapy for diagnostic, prognostic purposes being excised for ill pated cancer disease. Worldwide prevalence of cancer reported as one in eight; more deaths are due to cancer causes than AIDs, tuberculosis and malaria combined. Cancer is the main cause of death in all worlds after heart diseases. According to WHO projections, cancer will replace ischemic heart disease as the overall leading cause of death worldwide 2010.[2]

A large proportion of human cancers are claimed to be caused by lifestyle or dietary factors. Our diet contains many toxic or potentially carcinogenic compounds, which are absorbed and metabolized in the GIT. Upper GIT is a common site for neoplasm, especially malignant tumors. However there are variations in incidence among the component site from esophagus to anus; furthermore number of histologically confirmed types of tumors at these sites differs in their incidence and prognosis.[3] The GI cancer includes malignant condition of the GIT and accessory organs of digestion inclusive digester organs and anus. The disease symptoms pertaining to the tissue affected may include abnormality in functioning or other disease conditions. The conditions for prognosis often require endoscopy followed by biopsy of suspected organ. The GIT and other digestive organs are responsible for cause of cancer.[4,5]

The worldwide cancers of the lung, stomach, colon, rectum, liver and esophagus are associated with higher incidence whereas cancer of the lung, liver and esophagus are associated with the highest mortality and are indicative of poor survival.[6] The lung, colorectal, stomach and breast cancers account for nearly all cancer deaths.[7]

Causes and Risk Factors for Gastrointestinal Cancer:

- Smoking
- Excessive alcohol consumption
- Increasing age
- Diet high in animal fat
- Diet containing high amounts of salted, cured, or poorly preserved foods
- Chronic pancreatitis
- Obesity

Symptoms of Gastrointestinal Cancer:

- Abdominal pain, tenderness, or discomfort
- Change in bowel habits, such as frequency or consistency or shape
- Rectal bleeding or blood in stool
- Bloating
- Loss of appetite
- Nausea/vomiting
- Unintentional weight loss
- Fatigue

Gastrointestinal Cancers includes:

1. Anal Cancer
2. Colorectal Cancer
3. Esophageal Cancer
4. Gallbladder Cancer
5. Gastric Cancer
6. Liver Cancer
7. Pancreatic Cancer
8. Small Intestine Cancers

According to, National Cancer Institute incidence rate of cancer in the year 2008-2012 was 454.8 per 100,000 men and women per year, and in same period the mortality was 171.2 per 100,000 both men and women per year. Cancer mortality is higher in men than women, mortality in men is 207.9 per 100,000 men and mortality in women is 145.4 per 100,000 women. The literature report documented that highest in African men i.e. 261.5 per 100,000 and lowest in Asian women i.e. 91.2 per 100,000. In 2016 1,685,210 new cancer cases were estimated and predicted that 595,690 people will die by cancer in USA. In India according to the International Agency for Research on cancer (IARC)

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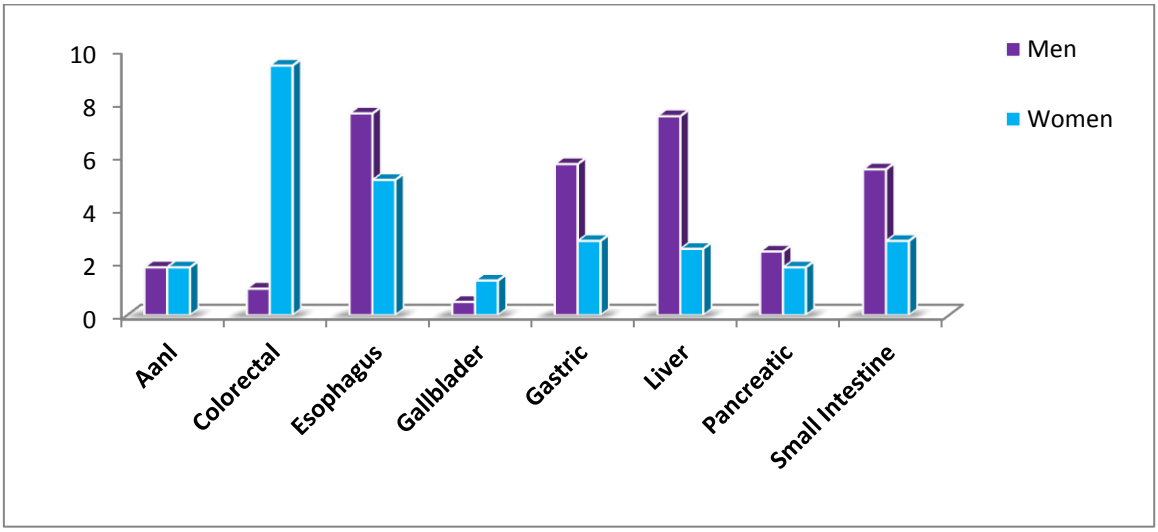
GLOBOCAN project predict the burden will nearly double in next 20 years. These documented findings highlights that number of cancer deaths will be elevated from 680,000 to 1.2 million in the same period.[2]

Table 1: Incidence of Gastrointestinal cancer per 100,000 in India as per National Cancer Registry Programme (NCRP) of India.[8,10]

Cancer Type	Anal	Colorectal	Esophagus	Gallbladder	Gastric	Liver	Pancreatic	Small Intestine
Men	1.8	10	7.6	0.5	5.7	7.5	2.4	5.5
Women	1.8	9.4	5.1	1.3	2.8	2.5	1.8	2.8

Comparative incidence rate of gastrointestinal cancer per 100,000 in INDIA as per NCRP



Carcinoembryonic Antigen (CEA) is high molecular weight glycoprotein present in colonic adenocarcinoma and fetal gut. An increased level of CEA has been observed in cancer of colon, rectum, lung, breast, liver, pancreas, prostate, stomach, esophagus and ovaries. It is also increased in benign liver, gastric, intestinal and breast disease, pulmonary infection emphysema and renal failure.[11] The CEA measurement in patients with carcinoma of the GI is of great benefit in the diagnosis and prognosis. The serum tumor marker CEA was measured in 60 patients who had oesophagus squamous cell carcinoma or gastric carcinoma. The sensitivity of CEA in both carcinomas reported as 70 %. In clinical practice tumor molecules such as a CEA are commonly used for screening of gastrointestinal malignancies.[12]

Recent past years Glutathione-S-Transferase (GSTs) attracted interest in the field of cancer because due to its activity increases chemically induced tumors. The GSTs catalyze the conjugation of GSH to a variety of reactive compounds indeed GSTs are one of the enzyme system induces by anti-carcinogens and thus can prevent tumor formation. GSTs and CEA has also been suggested to play an important role in multiple drug resistance in cancer chemotherapy agents.[13,14]

LDH and ALP have been used earlier to aid in diagnosis of various malignancies. The Lactate Dehydrogenase (LDH) is an enzyme in the glycolytic pathway that is released as the result of cell damage. An elevation of LDH has been used earlier to aid in the diagnosis of various malignancies. It has been demonstrated in a variety of cancers such as Liver, non-Hodgkin's lymphoma, acute leukemia, non seminomatous germ cell, testicular cancer, seminomas, neuroblastoma, breast, colon, stomach, esophagus and lung cancer.[15] Serum LDH has been shown to correlate with tumor mass in solid tumors and provides a prognostic indicator for disease progression. The increased level of LDH is responsible for tissue injury, necrosis, hypoxia, hemolysis, multiple cancers and myocardial infarction.

Alkaline Phosphatase (ALP) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate. Like other enzymes, LDH has many isoenzymes. In healthy adults, this enzyme is mainly derived from the liver, bone and lesser amounts from intestines, placenta, kidneys and leukocytes. Liver, Bone, and Placenta are primary sources of ALP. An ALP in normal adult serum is primarily derived from the liver or biliary tract. Elevation of ALP is seen in primary or secondary liver cancer. Quantifications are helpful in evaluating metastatic cancer with bone or liver involvement. Placental alkaline phosphatase (PALP) is synthesized by the trophoblast and is elevated circulation of pregnant mothers. It is elevated in variety of malignancies including ovarian cancer, lung cancer trophoblastic cancer, GIT cancer, seminoma and Hodgkin's disease.[15] Clinicians 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

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chemotherapy. In anticipation of this present study was undertaken to assess, the clinical utility i.e. diagnostic prognostic importance of CEA, GSTs, LDH and ALP in upper gastrointestinal cancer patients.

Material and Methods

The present study was carried out at Department of Biochemistry, Medicine, Surgery and Community Medicine at **Subharti Medical College and Chatrapati Shivaji Subharti Hospital Meerut**. Investigations carried out in 104 established patients of upper GIT cancer (47 patients of gastric cancer & 57 patients of esophageal cancer) from Dec 2013to March 2017.

I. Patients Selection Criteria

Present study comprising total 47 cases of carcinoma of stomach and 57 cases of carcinoma of Oesophagus (Stage I, Stage II, Stage III and Stage IV). All patients were clinically and histopathologically diagnosed. All patients with Stage-II, Stage-III and Stage-IV received chemotherapy including cisplastin, capecitabine, cyclophosphamide, Transtuzumab, 5-FU and doxorubicin. There are 31 male & 16 female established cases of stomach cancer and 24 male & 33 female of oesophagus cancer. For control total 42 normal healthy aged (35.40 ± 5.72) yrs and sex matched persons were selected. Subjects with stomach cancer, oesophagus cancer and those without any evidence of any other type of cancer participated in present study as listed in table-I.

Table-2: Control and gastrointestinal cancer patient's data

	Control	Stomach	Esophagus
No of Cases	n=42	n=47	n=57
Age ± S.D yrs	35.40 ± 5.72	55.42 ± 4.67	52.76 ± 8.36
Male	25	31	24
Female	17	16	33
Stage I	42	47	57
Stage II	42	47	57
Stage III	42	47	57
Stage IV	42	47	57

II. Collection of samples

Overnight fasting 5ml venous blood samples were collected before and after different cycles of chemotherapy in plain bulb. Serum was separated and stored at -20^0 till analysis of GSTs, CEA, LDH and ALP. 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.[16] For Estimation of serum LDH was processed by using commercial kits from AGAPPE diagnosis on semi auto analyzer (Transasia ERBA CHEM-5 plus) by kinetic method based on SCE recommended method.[17] For quantitative estimation of ALP in serum kinetic method (pNPP) is used,[18] and Estimation of serum CEA carried out by using commercial available kits from accu-bind USA, using ELISA micro plate Immunoenzymometric assay.[19]

III. Treatment

According to the protocol, 59.57% (28 out of 47) of the patients of stomach cancer completed one cycle of preoperative and three cycle of postoperative chemotherapy included the cisplastin, capecitabine, cyclophosphamide, transtuzumab and doxorubicin and 52.63% (30 patients out of 57) of the patients of oesophagus cancer completed three cycle of chemotherapy included the cisplastin, 5-FU. All the chemotherapy regimens were used under standard protocol.

IV. Follow Up

Overall 47 patients of stomach cancer and 57 patients of oesophagus cancer were followed up in hospital and after discharge. Out of 14 patients of stomach cancer and 18 oesophagus cancer patients could not be follow up during the follow up period and some patients are dead in study period. The follow up system includes measurement of serum CEA, GSTs, LDH and ALP level after chemotherapy continuously 3 months intervals for first 3 months and at 6 months intervals thereafter. The follow up program included, clinical examination, hematological analysis, tumor marker and enzyme assessed at every checkup, abdominal ultrasound were scheduled came for treatment.

All estimated results were expressed as mean ±SD. Mean values were assessed for significance by unpaired student - t test for control and gastrointestinal cancer patients and GIT cancer stages were assessed for significance by paired student - t test. A statistical analysis was performed using the Statistical Package for the Social Science program (SPSS, 23.0). Frequencies and percentages were used for the categorical measures. Probability values $p < 0.001$ were considered statistically significant.

Control Group

Total 42 normal healthy subjects (25 Male and 17 Female), age & sex matched subjects from study area was selected. Study was cleared from Ethical clearance committee of both SMC and CCMMC, respectively.

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Table 3: Distribution of control and cancer cases according to their age

Age wise Distribution (Yrs)	Control [n= 42]				Stomach Cancer patients (n=28)				Esophagus Cancer Patients (n=30)			
	Male	Female	Total	%	Male	Female	Total	%	Male	Female	Total	%
25-35 yrs	12	5	17	40.5	1	1	2	7.2	1	1	2	6.7
36-45 yrs	8	9	17	40.5	4	0	4	14.3	1	4	5	16.7
46-55 yrs	4	3	7	16.7	7	6	13	46.4	6	6	12	40
56-65 yrs	1	0	1	2.4	3	6	9	32.1	5	6	11	36.7
Total	25	17	42	100	15	13	28	100	13	17	30	100

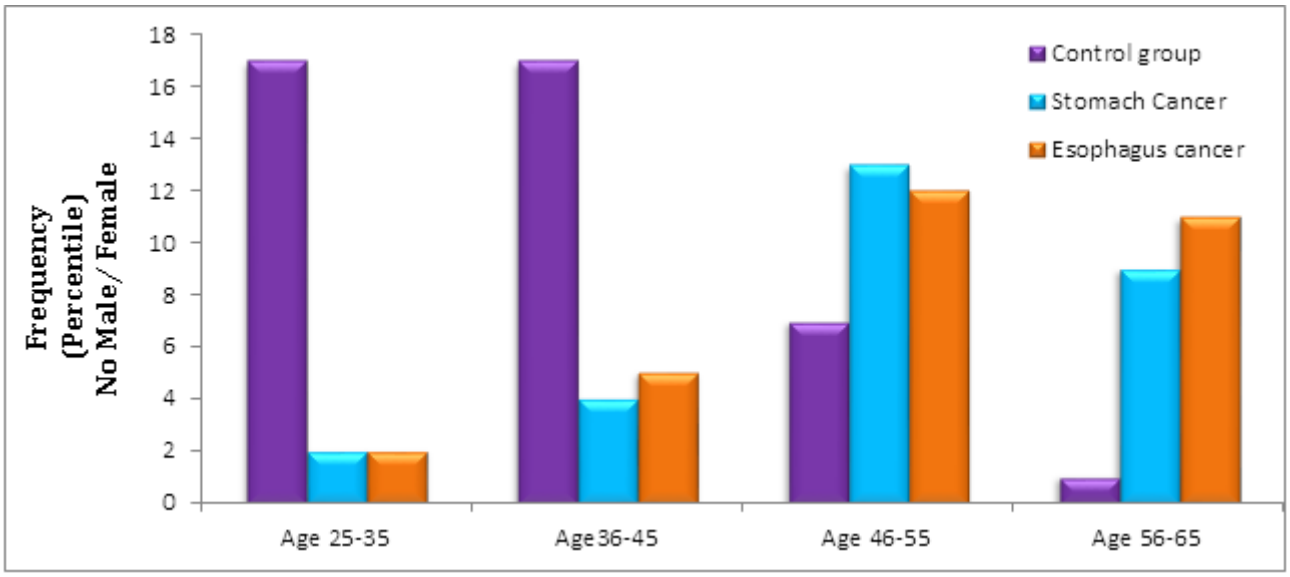
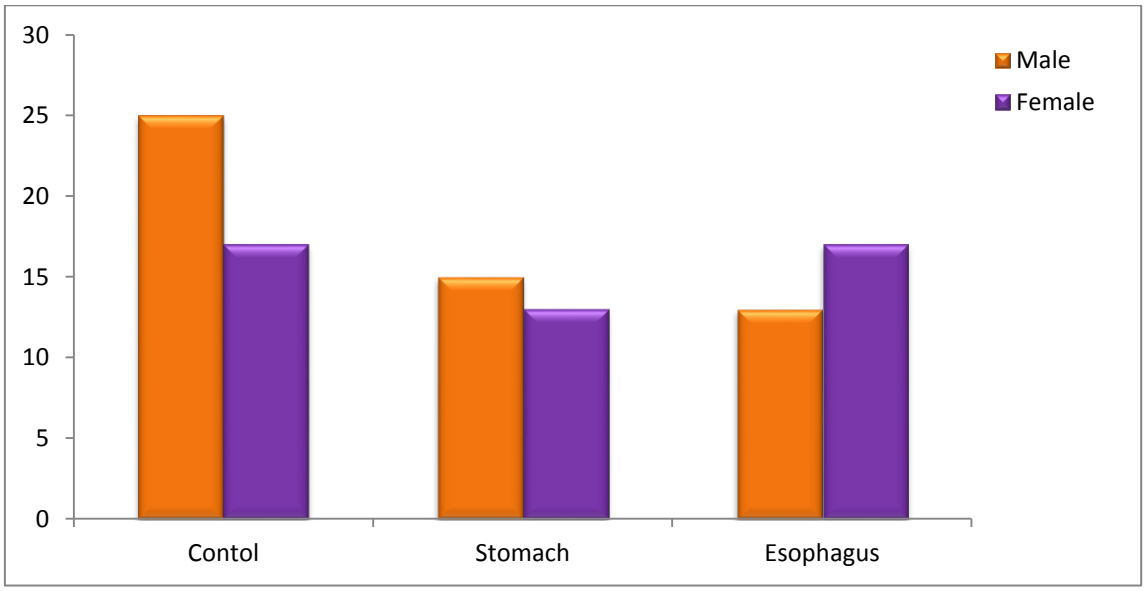


Table 4: Distribution of genders in study subjects and control group

Sex	Control (n=42)		Stomach Cancer Patients (n=28)		Esophagus Cancer Patients (n= 30)	
	Frequency	%	Frequency	%	Frequency	%
Male	25	59.52	15	53.57	13	43.33
Female	17	40.47	13	46.42	17	56.66
Total	42	100	28	100	30	100



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Observations and Results

Table 5: Comparison of serum CEA, GST, ALP and LDH activity in control with stomach cancer

	Control and Stomach Cancer		Control and Esophagus Cancer		" P" Value
	No. Of cases	Mean ± SD	No. of cases	Mean ± SD	
CEA Control	42	1.55 ± 0.30	42	1.55 ± 0.30	-
CEA ng/ml	28	9.90 ± 2.30	30	17.33 ± 2.41	<0.001
GST Control	42	5.06 ± 0.515	42	5.06 ± 0.515	-
GST IU/L	28	8.80 ± 2.11	30	9.45 ± 1.12	<0.001
ALP Control	42	82.54 ± 15.66	42	82.54 ± 15.66	-
ALP IU/L	28	179.82 ± 38.11	30	255.27 ± 100.79	<0.001
LDH Control	42	293.47 ± 39.83	42	293.47 ± 39.83	-
LDH IU/ L	28	526.50 ± 62.56	30	538.83 ± 61.92	<0.001

Table 5 shows the mean serum level of CEA, GSTs, LDH and ALP were significantly higher in upper gastrointestinal cancer patients (In stomach cancer patients it was 9.90 ± 2.30 ng/ml, 8.80 ± 2.11 IU/L, 526.50 ± 62.56 IU/l and 179.82 ± 38.11 and in esophagus cancer it was 17.33 ± 2.41ng/ml, 9.45 ± 1.12 IU/l, 538.83 ± 61.92 IU/l and 255.27 ± 100.79 IU/l respectively) than control group and it was 5.05±0.51 IU/L (p<0.001).

Table 6: Serum CEA (ng/ml) levels before and after different cycles of chemotherapy in gastrointestinal cancer patients compared with control group

	No. Of Cases	Stomach	p-value	No. of Cases	Esophagus	p-value
		Mean ±SD			Mean ±SD	
Control	42	1.55 ± 0.30	-	42	1.55 ± 0.30	-
Stage I	28	9.90 ± 2.34	< 0.001*	30	17.33 ± 2.41	< 0.001*
Stage II	28	4.60 ± 0.97	< 0.001**	30	8.01 ± 2.60	< 0.001**
Stage III	28	2.35 ± 0.41	< 0.001$	30	2.57 ±0.23	< 0.001$
Stage IV	28	1.66 ± 0.45	< 0.001$$	30	1.44 ± 0.43	< 0.001$$

(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 7: Serum GST (IU/L) levels before and after different cycles of chemotherapy in gastrointestinal cancer patients compared with control group

	No. Of Cases	Stomach	No. of Cases	Esophagus	'p-value'
		Mean ±SD		Mean ±SD	
Control	42	5.06 ± 0.51	42	5.06 ± 0.51	-
Stage I	28	8.79 ± 2.15	30	9.45 ± 1.12	< 0.001*
Stage II	28	12.28 ± 1.01	30	13.06 ± 0.95	< 0.001**
Stage III	28	7.05 ± 1.11	30	9.01 ± 0.58	< 0.001$
Stage IV	28	5.22 ± 0.59	30	6.06 ± 0.42	< 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: Serum LDH (IU/L) levels before and after different cycles of chemotherapy in gastrointestinal cancer patients comprised with control group

	No. of Cases	Stomach	No. of Cases	Esophagus	'p-value'
		Mean ±SD		Mean ±SD	
Control	42	293.47 ± 39.83	42	293.48 ± 39.36	-
Stage I	28	526.50 ± 63.70	30	538.83 ± 61.92	< 0.001*
Stage II	28	811.43 ± 313.48	30	1076.40 ± 320.98	< 0.001**
Stage III	28	669.18 ± 168.87	30	798.53 ± 175.27	< 0.001$
Stage IV	28	409.14 ± 40.09	30	413.67 ± 49.29	< 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.

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Table 9: Serum ALP (IU/L) levels before and after different cycles of chemotherapy in gastrointestinal cancer patients comprised with control group

	No. of Cases	Stomach	'p-value'	No. of Cases	Esophagus	'p-value'
		Mean ±SD			Mean ±SD	
Control	42	96.54 ± 15.66	-	42	96.54 ± 15.66	-
Stage I	28	179.82 ± 38.11	< 0.001*	30	255.27 ± 100.79	< 0.001*
Stage II	28	375.39 ± 107.71	< 0.001**	30	532.00 ± 237.79	< 0.001**
Stage III	28	183.86 ± 53.07	< 0.001$	30	238.97 ± 32.37	< 0.001$
Stage IV	28	126.96 ± 35.48	< 0.001$$	30	115.93 ± 20.91	< 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.

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

Carcinoma is a group of disease that can cause some signs or symptoms. The signs and symptoms depends upon carcinoma type or where the location of carcinoma. After metastasis or after growth of carcinoma it pushes to near organs, blood vessels and nerves. It causes some signs and symptoms of carcinoma, but in critical area of body such as brain, the smallest tumor can cause symptoms of carcinoma.

Knowledge of diagnostic and prognostic factors are essential for the diagnosis, prognosis and management of treatment and these factors should be taken into account in the design of randomized trials and in interpreting the result of such trials. Serum tumor markers and some enzymes have been used in aiding the diagnosis of gastrointestinal carcinomas for a long time. Previous studies reported that the elevated serum values reflect the increased secretion of tumor antigens by tumor itself.[20] However mild elevation of serum tumor marker levels in early-stages of carcinoma has been always difficult to justify as many benign pathologies may frequently cause such changes. The clinical use of tumor markers is much more beneficial in determination of prognosis assessing response to treatment and detection of early recurrence.[21,22]

Generally, tumor markers are made by malignant as well as normal cell. Its activity reported elevated in all type of malignancies, i.e. in blood, urine and stool. Many tumor markers are used in clinical practice. There is no universal tumor marker which may detect any single type of carcinoma. Tumor markers help to diagnosis and manage of carcinoma. Increased level of tumor marker may indicate the presence of carcinoma but this signal is not enough for diagnosis of carcinoma. Therefore, for diagnosis of carcinoma detection is to measure the activity of tumor marker, enzymes with other test like blood test, urine test, biopsies. Measurement of tumor marker and enzyme activity may be helpful to physician for proper treatment and exact treatment.

The result of our present study show significant increase in CEA, GSTs, LDH and ALP concentrations in esophagus and gastric carcinoma patients compare to normal control subjects. Individual patient's data revealed that total 100% patients of esophagus and gastric carcinoma had CEA levels above normal limit. The activity of GST was higher in 100% & 93% in esophagus and gastric carcinoma patients respectively. On the basis of result, conclude that GST is useful tumor marker for gastrointestinal carcinoma. In present study it was observed that 96.66% of esophagus carcinoma and 85.71% of gastric carcinoma patients had LDH activity greater than 500 IU/Liter. Significant increase in ALP activity in esophagus and gastric carcinoma patients compares to normal control subjects. Individual patient's data revealed that 23 of 30 (76.66%) patients of esophagus and 22 of 28 (78.57%) patients of gastric carcinoma had ALP activity above normal limit shown in above table no 5. Similar findings reported by N.R. Hazari et. al, G.S. Mahammadzadeh et. al. and in my last study.[22,25]

In our study Table no 6, Table no 7, Table no 8 and Table no 9 shows that the activity of serum CEA, GSTs, LDH and ALP significantly increased ($p<0.001$) in stage I (before chemotherapy) and stage II (After cycle of chemotherapy) than control group similar findings reported by N. R. Hazari but the activity of CEA in stage II (after first cycle of chemotherapy) significantly decreased and it shows tumor is completely removed similar findings reported in my previous studies.[25,26] But after second cycle of chemotherapy means in stage III level of CEA, GSTs, LDH and ALP significantly decreased ($p<0.001$) observed in present study than stage II (after first cycle). This result indicates that patients were responded to the treatment, status of tumor and may in the direction of recovery. Similarly in stage IV after third cycle of chemotherapy the activity of GST, LDH, ALP and GST decreased than stage III (after second cycle), and activity become in normal range. This shows that patients were responding and totally recovered by cisplastin based treatment.

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According to study by Bhawna Bagaria et. Al[27] 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[28] showed that the 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.

N.R. Hazari et.al.[22] In their study reported that serum GST significantly higher (P<0.001) in patients with esophagus and gastric carcinoma. The GST level in serum represents a noninvasive biomarker of the cellular protection. The activity of GST was higher in 100% & 93% in esophagus and gastric carcinoma patients respectively. On the basis of result they conclude GST is useful as tumor marker for gastrointestinal carcinoma.

The several studies[29,30] reported that serum LDH activity rise in gastrointestinal carcinoma and stated that LDH has positive correlation with stages of malignancy. Our present observations are in accordance with these reports. Scartozzi et. al.[31] reported that increased level of LDH has been found in advanced type of malignancies and relationship of LDH level and tumor growth has been assessed. The preoperative level of LDH was good predictive factor for assessing chemotherapy. In our study the level of LDH after second cycle of chemotherapy was decreased than first cycle of chemotherapy but after third cycle of chemotherapy was in normal in range.

Nishio H. et. al.[32] observed, that rise in ALP level in 73% of esophageal and 59% in gastric concluded that the total ALP activity increased due to placental alkaline phosphatase isoenzymes which is probably originates from malignancy itself and M. Wasif Saif et.al[33] Studied 105 patients of colorectal carcinoma (mean age 59 yrs, 53% male and 47% female), out of 43 stage II patients, 31 stage III patients and 32 stage IV patients. The activity of ALP was in stage II 116 IU/L, in stage III 219 IU/L and stage IV 302 IU/L. It means level of ALP correlate with stages. They showed increased level of ALP over four to six weeks indicate disease progression.

The concentration of tumor markers and enzymes reflect the stages and prognosis of malignancy. After treatment the increased levels are returns to normal level of tumor markers and enzymes indicate that the response of treatment or it is use to check for recurrence of malignancy and increased value indicates the patient not responding to treatment or carcinoma cell is not responding to given treatment.

Conclusion:

1. Increased levels of CEA during initial diagnosis provide diagnostic and prognostic significance and it is benefited for clinical practice. The CEA play an important role in diagnosis and success of treatment procedure. Its levels facilitate the management of gastrointestinal cancer patients for postoperative treatment. Postoperative increased level of CEA predicts the recurrence of disease.
2. Elevation of serum GST activity is probably a resistance mechanism by which cells can survive and source of circulatory levels of enzyme is mainly transformed cell with over expression of GST. Depletion of GST level after administration of chemotherapeutic drug due to higher oxidative stress after chemotherapy.
3. LDH level raised with progression of disease hence it is good indicator of stages of disease and bulk of tumors. Increased levels of serum LDH used as independent diagnostic marker in preoperative gastrointestinal cancer patients and postoperative decreased levels of serum LDH showed as prognostic marker. Variation of serum LDH during chemotherapy suggests treatment strategy, reinforcing chemotherapy.
4. ALP activity was three times greater than normal limits which indicate that it probably originates from cancer itself. Increased levels of ALP before treatment can be used as prognostic factor. Also it is used for detecting liver damage or dysfunction, infection and blockage caused by chemotherapy. Increased level of ALP provides the evidences of liver and bone damage.

On the basis of present study results conclude that.

GST and CEA exhibit highest sensitivity for gastrointestinal cancer compare to ALP and LDH.

LDH, ALP are good indicator of stages and bulk of tumor, LDH is also good prognostic factor in advanced GIT cancer treated with chemotherapy.

GST measurement in plasma may be useful tumor marker in gastrointestinal cancer. Alterations in serum GST levels may be helpful to predict the response of chemotherapy.

The measurement of GST CEA ALP and LDH may be useful in monitoring of response and prediction and prognosis in patients received chemotherapy. Monitoring of GST, LDH and ALP are simple, low cost and relatively sensitive screening tool for upper gastrointestinal cancer.

Available literature data show that the discovery of new tumor markers and the combinations of tumor markers are

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the best solutions for the improvement of patients' management still needs further research in depth.

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