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Original article

A study of Free radical, Enzymatic, Non Enzymatic Antioxidant levels and immunohistochemical expression CD34 in different stages of gastric cancer patients in tertiary care hospital

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Abstract

Aim and objectives: *The main investigation of this study is to assess the free radicals, enzymatic, non enzymatic antioxidant levels and Immunohistochemical expression of CD34 in different stages of gastric cancer patients. Oxidative stress occurs when there is an imbalance between the production of free radical species and the antioxidant ability to neutralize their harmful effects. Oxidative stress could be both a potential cause and a consequence of Gastric function alteration, since the primary effect of proper redox regulation is to keep the balance of electrolytes and physiological buffer systems. Free radicals scavenged by antioxidants. CD34 is a hematopoietic stem cell marker. It is mostly used as an angiogenic marker.*

Materials and Methods: *This is a descriptive, cross sectional comparative study. 150 patients were included in the study. The patients were selected from department of Gastroenterology, Meenakshi Medical College Hospital and Research Institute, Kanchipuram. Patients were divided into five groups based on the histopathological analysis. Each group consists of thirty patients. Who selected for the study and informed written consent was obtained.*

Results: *Free radicals of OH, O_2^-, and H_2O_2 levels on stage 5 gastric cancer patients were significantly increased ($P<0.001$) when compared with group I control and Group-II stage I Gastric carcinoma patients.In Stage 5 gastric carcinoma patients serumenzymatic antioxidants (Super oxide dismutase, Catalase and Glutathione Reductase) and Non Enzymatic (Vitamin C, Vitamin E and Reduced Glutathione) levels were significantly decreased when compared with control and stage I gastric cancer patients.CD34 expression is noted only in advanced gastric adenocarcinoma of diffuse histological type while there is no expression seen in intestinal type and early gastric adenocarcinoma.*

Conclusion: *In the Present study we conclude that the both enzymatic, non enzymatic antioxidants level and expression of CD34 was significantly associated with advanced gastric adenocarcinoma of diffuse type thus this is used as a differentiation marker.*

Key Words: *Gastric Cancer, Enzymatic, Non Enzymatic antioxidants, CD34*

Introduction

Globally, gastric cancer is the one of the third leading cancer cause of death of all malignancies and is fifth most commonly diagnosed malignancy (1033701 new cases in 2018)[1][2]. Universally, the disease has male preponderance with two to four times higher rates as compared to females[3]. Incidence of gastric cancer is very low below 30yrs of age group and is high in 60-80yrs age group[4]. Incidence in South India related to age group is 35-55years whereas in North India it is 45-55years[5].

Etiology of the disease is complex with multiple risk factors among which Helicobacter Pylori infection is the most commonly attributed risk factor [7]. Endoscopic biopsy and histopathological examination is routinely done for diagnosing gastric cancer. Majority of patients in early stages present nonspecific symptoms because of which disease is diagnosed in advanced stages in spite of modern diagnostic techniques. In cells, these radicals can act as oxidants or reductants by losing or accepting a single electron, and they are continuously produced by the organism's normal use of oxygen. Free radicals include reactive radical and nonradical derivatives of oxygen (ROS) and nitrogen (RNS) that are collectively called reactive oxygen nitrogen species (RONS). The generation of RONS is a physiological process and, at moderate or low levels, RONS are important molecules involved in a number of cellular signaling pathways, in the extraction of energy from organic molecules, in immune defense, in mitogenic response, and in redox regulation. An excess production or a decreased scavenging of RONS has been implicated in aging and age-related diseases. Both endogenous and exogenous sources of RONS have been described. The endogenous sources of RONS include different subcellular organelles, such as mitochondria, peroxisomes, and endoplasmic reticulum, where oxygen consumption is high. NADPH oxidase (nicotinamide adenine dinucleotide phosphate oxidase) is a prevalent source of the superoxide radical ($\bullet O^{2-}$), which is formed by the addition of one electron leak from the electron transport system during cellular respiration to the molecular oxygen. Most of the superoxide dismutates into hydrogen peroxide (H_2O_2) through superoxide dismutase (SOD). H^2O^2 is a neutral molecule because it has no unpaired electrons, but it is able to form the most reactive and dangerous radical, the hydroxyl radical (•OH), through a Fenton or Haber–Weiss reaction. Hydroxyl radicals mainly react with phospholipids in cell membranes and proteins. In activated neutrophils, in the presence of chloride and myeloperoxidase, H^2O^2 can be converted into hypochlorous acid that can react with DNA and produce pyrimidine oxidation products and add chloride to DNA bases.

Oxidative stress arises between the production of free radical and antioxidant defense against the free radicals. At the end of the result, certain biomolecules were oxidized, leading to structural and functional modifications of these molecules. Oxidation mechanism mainly involved in mitochondria with the help of mitochondrial cytochrome oxidase enzymes of cytochrome P450. The free radical products from these processes mainly contribute to the progression of gastric cancer. The primary Reactive oxygen species responsible for oxidative stress are superoxides (•O2). The major source of superoxides is the production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytes and endothelial cells. Superoxides are removed by superoxide dismutase (SOD) by conversion to hydrogen peroxide (H2O2). Studies have shown significant decrease in gastric function[6]. . In our laboratory, we focused on human studies regarding an evaluation of the overall redox/inflammatory state in a significant gastric cancer population and also discussed about the antioxidant levels in different stages of gastric cancer patients.

Gastric adenocarcinoma is the most common histological type comprising 90% of all gastric carcinomas. Lauren classified gastric adenocarcinoma by the dominant histologic appearance of the tumor into intestinal and diffuse however these types not only differ in histology but also in epidemiology, clinical picture, genetics and progression pattern. WHO classifies gastric carcinomas based on pure histomorphological appearance.

Gastric cancer has a very poor prognosis with a very low 5-year survival rate of 30% [9]. Many studies were there on tumor cells of gastric carcinoma, but very few studies were done on the stromal components which have a significant role in tumor metastasis. CD34 is a hematopoietic stem cell marker. It is mostly used as an angiogenic marker. In our present study CD34 stromal cells are studied in gastric adenocarcinomas and are correlated with histological types, grades and depth of invasion. Chemotherapy is of limited value in advanced stages of disease, surgery is considered as the main stay in the treatment of gastric cancer [10].

Materials and Methods

This is a descriptive, cross sectional comparative study and conducted during the period of January 2024 to November 2025 in the department of Gastroenterology, Meenakshi Medical College Hospital and Research Institute, Kanchipuram. 150 newly diagnosed gastric adenocarcinomaspatients were selected in the study after getting an informed consent. The study parameters were estimated in the patients and compared with 150 gastric adenocarcinomas patients based on the stage. Ethical clearance was obtained from Institutional Ethical Committee before collection of the samples. All the patients were categorized based on the histopathological report and after conformation draw the blood for further biochemical analysis.

Biochemical analysis:

OH^- were analyzed by the method of Gutteridge et al (1981),H_2O_2Concentration was estimated by the method of Wolff (1994) and O_2^-Concentration were analyzed by the method of Nishikimi *et al.* (1972). Serum total protein concentration was estimated by Lowry et al method. The activity of serum enzymatic antioxidants like Superoxide dismutase, catalase and glutathione peroxidase was analyzed by Marklund and Marklund, Sinhaand Rotruck respectively. Serum Reduced Glutathione concentration was analyzed by the method of Ellman (1959) with small modification (Beutler*et al*., 1963).

Experimental Setup

This is a Descriptive, cross sectional and comparative study. 150 patients were included in the study. The patients were selected from department of Surgery and Gastroenterology, Meenakshi Medical College Hospital and Research Institute. Patients were classified into five groups based on the histopathological changes. Each experimental group consists of thirty gastricadenocarcinoma patients. Who selected for the study and informed written consent was obtained. Human ethical clearancealso obtained from Institutional ethical committee.

The gastric adenocarcinoma patients were divided into fivegroups. Each group consist of 30 patients

Group-1: Stage O gastric adenocarcinoma patients

Group-II: Stage I gastric adenocarcinoma patients

Group-III: Stage II gastric adenocarcinoma patients

Group-IV: Stage III gastric adenocarcinoma patients

Group-V: Stage IV gastric adenocarcinoma patients

Blood and urine samples were collected and biochemical parameters were done.

Results:

Free radical concentration in different stages of gastric adenocarcinoma patients

Table 1 observed the free radicals concentration in control and Gastric adenocarcinoma patients. Free radicals likeH_2O_2, $O_2^-$and OH, concentration on group VIGastric adenocarcinoma patients were significantly increased ($P<0.001$) when compared with group I control and Group- II Gastric adenocarcinoma patients. Group III, IV, V and VI Gastric adenocarcinoma patientswere significantly decreased ($P<0.05$) the activities of free radicals when compared with group VIGastric adenocarcinoma patients.

Table 1. Free radical concentration in different stages of gastric adenocarcinoma patients

Particulars	Group I (Control)	Group II Stage-O	Group III Stage-I	Group IV Stage-II	Group V Stage-III	Group VI Stage-IV
H_2O_2 µmoles/10^{12} cells	66.35±6.05	70.17±7.01	77.17±6.92	89.42±8.07	115.7±10.8	144.44±14.8
O_2^- µmoles NBT reduced/10mm/10^{12} cells	53.16±4.31	57.55±5.63	62.16±6.10	70.12±7.03	95.4±9.8	106.16±9.9

OH MDA a nmol/10^{12}cells	13.18±1.2	18.42±1.9	20.88±2.1	23.72±2.5	25.44±2.8	26.24±2.6

Each value is expressed as mean ±SD for thirty humans in each group.
Units: H_2O_2-µmoles/10^{12} cells; O_2^--µmoles NBT reduced/10mm/10^{12} cells
OH-MDA a nmol/10^{12}cells
a: as compared with Group I, **b:** as compared with Group II
Statistical significance: $^*p<0.001$

Enzymatic antioxidant levels in different stages of Gastric Adenocarcinoma patients in serum

Table.2 shows that the enzymatic antioxidant levels in different stages of Gastric adenocarcinoma patients. Serum enzymatic antioxidant (SOD, Catalase and GPx) levels were significantly decreased in group –VI stage 4Gastric adenocarcinoma patientswere compared with control and different Stages of Gastric adenocarcinoma patients.

Particulars	**Group I (Control)**	**Group II Stage-O**	**Group III Stage-I**	**Group IV Stage-II**	**Group V Stage-III**	**Group VI Stage-IV**
SOD	118.23±11.8	112.56±10.08	104.26±10.5	81.88±8.07	70.5±7.23	63.66±6.5
CAT	109.06±10.5	93.08±9.52	81.25±8.32	70.12±7.03	67.54±6.8	54.66±5.5
Gpx	85.6±8.6	78.23±1.9	69.36±6.5	60.23±6.8	56.42±5.55	48.5±4.6

Each value is expressed as mean ± SD for thirty patients in each group
SOD - units/min/mg protein; GPx - mmoles of H_2O_2 liberated/min/mg protein; CAT - mmoles of H_2O_2 liberated/min/mg protein
a : as compared with Group I ; b : as compared with Group II
Statistical significance - $^{\#}p<0.001$, $^{@}p<0.01$, $^*p<0.05$.

Non Enzymatic antioxidant levels in different stages of CKD patients in serum

Table.3. shows that the non enzymatic antioxidant levels (Vitamin C, Vitamin E and Reduced Glutathione) in different stages of Gastric adenocarcinoma patients. Serum non enzymatic antioxidant levels were significantly decreased in group –VI stage 4Gastric adenocarcinoma patientswere compared with control, acute renal disease and Stage one Gastric adenocarcinoma patients.

	Group I (Control)	**Group II Stage-O**	**Group III Stage-I**	**Group IV Stage-II**	**Group V Stage-III**	**Group VI Stage-IV**
Vitamin C (mg/dL)	0.89± 0.08	0.66± 0.06	0.52± 0.05	0.46± 0.04	0.41± 0.04	0.35± 0.03
Vitamin E(mg/dL)	6.06± 0.61	6.24± 0.62	6.07± 0.61	5.29± 0.5	5.02± 0.51	4.88± 0.47
Reduced Glutathione (mM)	455.5± 45.5	440.5± 40.5	426.01± 40.8	374.5±38.6	348.5± 33.9	330.6± 30.5

Each value is expressed as mean ±SD for thirty humans in each group.
Units: H_2O_2-µmoles/10^{12} cells; O_2^--µmoles NBT reduced/10mm/10^{12} cells
OH-MDA a nmol/10^{12}cells
a: as compared with Group I, **b:** as compared with Group II
Statistical significance: $^*p<0.001$

Interpretation of CD34 based on histological grade of tumor

Table.4 Results from our study revealed a significant correlation with p value 0.0001, the CD34 expression were seen in 40 cases out of 68 (45%) poorly differentiated carcinomas, and no expression in 75 (42%) well differentiated carcinomas and 7 (4.6%) moderately differentiated carcinomas.

Table.4 . CD34 interpretation based on histological grade of tumor

Grade	No	Percentage	Immunohistochemistry interpretation for CD34 expression				P-Value
			Positive Staining		Negative Staining		
			No	Percentage	No	Percentage	
CD34 interpretation based on histological grade of tumor	75	50%	0	0	63	42%	
Moderately differentiated	7	4.6%	0	0	7	4.6%	0.001
Poorly differentiated	68	45%	28	100	40	58.8%	

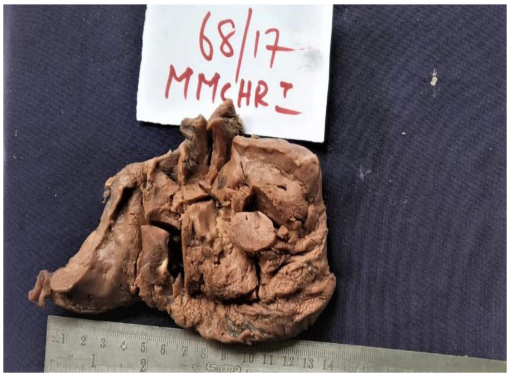
Correlation of CD34 based on type of tumor and depth of invasion

Based on Lauren's classification intestinal type carcinomas are 96 cases in total and diffuse type carcinomas are 64 cases. Among 64 cases of diffuse type tumors, advanced tumors invading muscularis propria and subserosa (24) expressed positivity for CD34 which is statistically significant with p value 0.04.

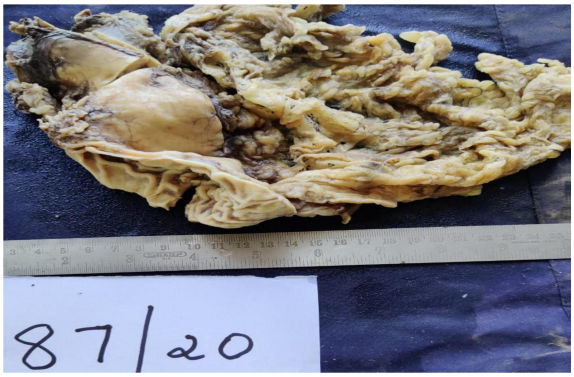
Depth of tumor invasion	Intestinal type			Diffuse type			Chi-Square test (P)
	No. of cases	CD34 Expression		No. of cases	CD34 Expression		
	N=96	Positive Staining	Negative Staining	N= 64	Positive Staining	Negative Staining	
Early tumor (Submucosal invasion)	45	0	45	40	0	40	0.04
Advanced tumor (Muscularis propria and subserosal	51	0	51	24	24	0	

invasion)							

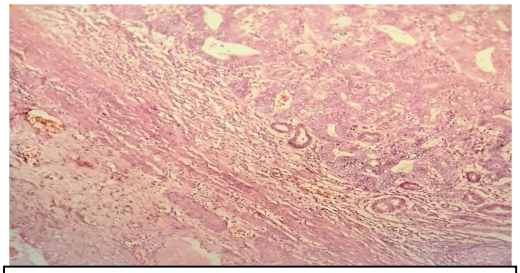
Gastrectomy and CD34 expression in stromal cells



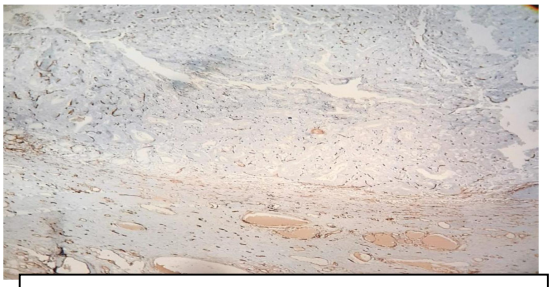
Photograph of a gross specimen of partial gastrectomy showing an ill-defined grey white tumor in the body of stomach



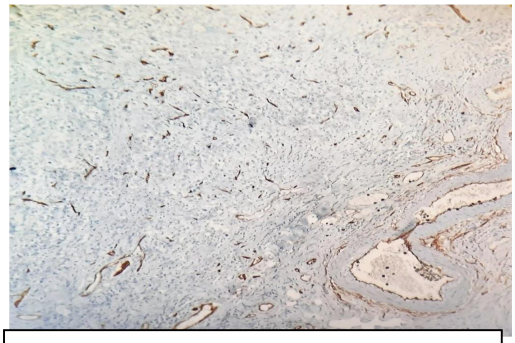
Photograph of a gross specimen of subtotal gastrectomy showing an ill-defined grey white tumor in the pyloric end of stomach and surrounding mucosa showing loss of rugosity.



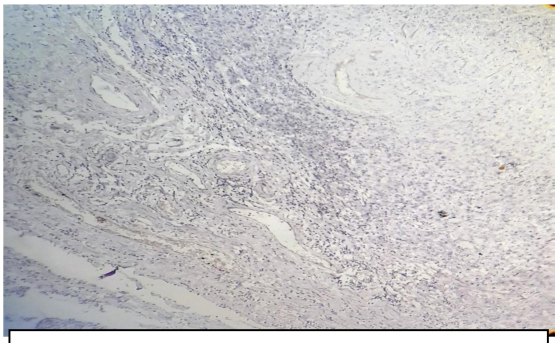
Well differentiated adenocarcinoma showing well-formed glands confined to submucosa



Well differentiated adenocarcinoma with negative CD34 expression in the tumor stromal cells confined to submucosa



Poorly differentiated adenocarcinoma with negative CD34 expression in the tumor stromal cells confined to submucosa



Poorly differentiated adenocarcinoma with positive CD34 expression in the endothelial cells of blood vessels

Discussion

Several authors have reported a profound imbalance between oxidants and antioxidants in Gastric adenocarcinoma patients, though studies on plasmatic oxidative balance have shown conflicting results[7]. In this study, we evaluated oxidative stress through concentration of hydroxyl (‘OH), alkoxyl (RO.’), or peroxyl (ROO:) radical GSH, a nonenzymatic antioxidant, catalase and SOD activity in the serum of gastric adenocarcinoma patients, their first-degree relatives and controls.

The free radicals are termed as ROS which undergoes a series of reactions that ultimately lead to the generation of short-lived diffusible entities such as hydroxyl (‘OH), alkoxyl (RO.’), or peroxyl (ROO:) radical and for some of free radicals species of medium lifetime such as superoxide anion (O2–) or nitroxyl radical (NO’) and also includes the non-radicals H2O2, organic hydroperoxides (ROOH), and hypochlorous acid (HOCl). The ROS produced through electron transport chain causes serious damage to mitochondrial DNA, protein, and lipids. The ROS causes deleterious effects by initiating LPO directly or by acting as a second messenger to initiate LPO.

Moreover, it is unclear at which stage of gastric adenocarcinoma patientsthe redox imbalance becomes more intense and if chemotherapy treatment increases redox imbalance[7]. Our results showed that the oxidative disequilibrium in gastric adenocarcinoma patients was represented by an enhancement of the plasmatic antioxidant barrier effectiveness, which was significantly higher compared to the healthy controls. Although all gastric adenocarcinoma patients possessed good plasmatic redox status, we detected a strong correlation between the oxidative index and C-reactive protein blood levels. This result was not surprising, sincegastric adenocarcinoma patients is characterized by chronic inflammation and oxidative stress is one of the key factors in triggering the inflammatory process. In addition, this constant inflammatory status in gastric adenocarcinoma patients is related to several comorbidities, mainly cardiovascular events.

Antioxidants are molecules that inhibit or quench free radical reactions and delay or inhibit cellular damage.though the antioxidant defenses are different from species to species; the presence of the antioxidant defense is universal. Antioxidants exist both in enzymatic and non-enzymatic forms in the intracellular and extracellular environment[8].

Normal biochemical reactions, increased exposure to the environment, and higher levels of dietary xenobiotics result in the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS).**2** ROS and RNS are responsible for oxidative stress in different pathophysiological conditions[9]. Cellular constituents of our body are altered in oxidative stress conditions, resulting in various disease states. Oxidative stress can be effectively neutralized by enhancing cellular defenses in the form of antioxidants[10].Certain compounds act as in vivo antioxidants by raising the levels of endogenous antioxidant defenses. Expression of genes encoding the enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx) increases the level of endogenous antioxidants.

Thestomach has an effective mechanism to prevent and neutralize free radical-induced tissue damage. This mechanism is accomplished by some endogenous antioxidant enzymes, such as SOD, CAT, GPX, and GSH. There is a balance between a free radical (FR)/ ROS formation and antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress results, which through a series of events deregulates the cellular functions leading to various pathological conditions. Antioxidant enzymes act against toxic oxygen-free radicals such as superoxide and hydroxyl ions in the biological system[11]. It is reported that antioxidant enzymes, such as SOD, CAT, and the glutathione system, have been known to play important role in alleviating oxidative damage since they are involved in the direct elimination of reactive oxygen species[12]. The lower activities of these antioxidant enzymes are indicative of cellular damage and loss of the functional integrity of the cell membranes in the stomach which is always associated with oxidative stress[14].

Oxidative stress may play a causative role in elevated inflammation from the toxic effects of reactive oxygen species which may contribute to the pathogenesis of gastric adenocarcinoma.Given that oxidative stress and inflammation are important factors in the progression of gastric adenocarcinoma, antioxidant therapy to address these factors, particularly in those among whom these are more pronounced, remains a promising option. Antioxidant therapy assists in reducing serum free radicals levels and improving antoxidants in relatively short periods. Hence, there remains possibility that benefits may be conferred for gastric adenocarcinoma, a hypothesis which needs to be tested in sufficiently powered studies specifically involving this population.

CD 34 is initially recognized as a marker of hematopoietic stem and progenitor cells. It is also expressed on hematopoietic tissues such as embryonic fibroblasts, vascular endothelial cells. Many articles discussed its role in the inflammatory and healing process in tissue damage. These CD34 stromal cells are elongated having dendritic processes with inconspicuous nuclei. CD34 reactivity was seen only in stromal cells in the tumor stroma and endothelial cells lining blood vessels in the stroma whereas no reactivity was seen in epithelial cells.

CD31 a platelet endothelial cell adhesion molecule is primarily used to demonstrate endothelial cells lining vessels in stroma of tissue sections. It is used to differentiate CD34 positive cells as CD34 has the same degree of immunoreactive staining for stromal fibrocytes and endothelial cells lining vessels. Endothelial cells show positivity for both CD34 and CD31 but stromal cells in advanced poorly differentiated cells express only CD34.

Fractions of tumor according to WHO classification based on their histological appearance were tubular type 50%, signet ring cell type 20%, mucinous type 14% and undifferentiated 16%. These were comparable with studies done by Roessler K et al [130] in 2005 with 42.1% tubular type, 44.7% signet ring cell type, 11% undifferentiated type and 2.1% mucinous type. Based on Lauren's classification, 32 cases were intestinal type of gastric adenocarcinomas and 18 were diffuse type of gastric adenocarcinomas. CD34 expression in stromal cells of all advanced diffuse type of gastric adenocarcinomas (8 cases) showed a significant correlation with p-value of 0.0008 whereas it is not expressed in intestinal type of gastric carcinomas and early type of diffuse gastric carcinomas. An equivalent CD34 expression was observed in 74 patients by Rosai et al in 2011and Nakayama et al in 2002.

CD34 studies on colorectal carcinoma showed loss of CD34 expression in stromal cells of the well differentiated carcinoma and moderately differentiated carcinoma. Positive expression of CD34 was seen only when the stromal cells were in submucosa, subserosa and muscularis propria. In contrast to the results of our study, Kuroda et al. cited that CD34 positive cells in sub mucosal and subserosal layers of intestinal type carcinomas infiltrated further layers of stomach during invasion . Outcome from our study showed significant association with differentiation of tumor histologically which were comparable to studies done by Tenderenda et al . 44% of poorly differentiated carcinomas (8cases) demonstrated positive for CD34 where as all well differentiated and moderately differentiated carcinomas showed no expression. Statistically analyzed through Fisher's exact probability test, the p value is 0.0001.

Conclusion

In the Present study we conclude that the both enzymatic, non enzymatic antioxidants level and expression of CD34 was significantly associated with advanced gastric adenocarcinoma of diffuse type thus this is used as a differentiation marker.In the course of time, researches in anticancer therapy targeting CD34 stromal fibrocytes along with cancer cells will increase curative potential of therapy strategy thus improving patient's prognosis.

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