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A Clinicopathological Study of Gastric Malignancy in Endoscopic Biopsy

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Abstract: *Gastric carcinoma is common worldwide and also in India. The diagnosis of gastric carcinoma depends on clinical, radiological, biochemical and pathological parameters [1,2],. 52 cases of endoscopic biopsy and histopathology positive patients were studied on the aforesaid parameters and clinical records were correlated with histopathology. Age range was 30 to 90 years, predominantly males. Main age group affected for male was 5th and 6th decades, and women affected mostly in the age range 36 to 45 years. Clinically dyspepsia and weight loss were commonest symptoms. History of smoking was fairly common(53.86%). 38.46% patients had history of using H2 blocker or proton pump inhibitors.Barium meal xray and ultrasonography results correlated well with histopathology.Most of the cancers occurred in the prepylorus and antrum. Adenocarcinoma was the commonest type (92.3%), followed by lymphoma (3.84%) and leiomyosarcoma (1.92%). The increased incidence of Intestinal type of adenocarcinoma in this region of India indicates this is a high risk area and environmental factors play a major role in causing such type of stomach carcinoma . Proper care, early detection ands long-term follow up may reduce incidence of stomach malignancy in this area.*

Key words: *carcinoma, lymphoma, leiomyosarcoma, immunostaining.*

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I. Introduction

Gastric carcinoma is the second most common tumor in the world. In India, malignancy of stomach ranks 7th in males (5.67 per 1 lakh population), Gastric carcinoma is the 5th cause of death in male and 6th cause of death in female due to the cancer causing death in India[3,4]. Approximately 90% of gastric cancers are adenocarcinomas, and rest 10% are lymphoma, leiomyosarcoma etc. Diagnosis of gastric malignancy is based on clinical, biochemical, radiological and pathological parameters. A good number of cases of stomach malignancy are asymptomatic. There are few studies in our country till date which cover up all the regions of India, relating the food habits, blood groups etc. with varying incidences of stomach malignancy in different regions[3,4,5]. The rational approach for a clinicopathological correlation of gastric malignancy should be the proper combination of all regional datas, related with basic clinicopathological longitudinal studies of gastric malignancy done on people from different ethnic groups and geographic region of this vast country for prolonged period, so that the picture of gastric malignancy may be clear in this country.

II. Material And Methods

The work was done in S.S.K.M Hospital, a Govt. Hospital affiliated to I.P.G.M.E & R Kolkata in collaboration with the Department of Pathology and Department of Gastroenterology.
Study design : Retrospective open label observational study.
Study Location : This is a tertiary care teaching Hospital affiliated to West Bengal Health University. The Institute of Post Graduate Medical Education & Research (IPGME&R) with attached hospital SSKM , is also an important referral hospital in eastern India.
Study Duration : February 2011 to January 2012 (one year).
Sample size : 52 cases.

Subjects & selection method : Patient in the age group of 30 to 90 years were selected from the outdoors of the Gastroenterology Departments restrospectively. They were selected on the basis of clinical and pathological pictures they produced. At outpatients' department, patients coming with symptoms of dyspepsia, anorexia, weight loss, abdominal pain and discomfort, lump abdomen, nausea, vomiting, epigastric tenderness or any other gastrointestinal symptoms are thoroughly examined clinically.

Inclusion criteria :
1. Patients with endoscopic biopsy positive gastric malignancy and available clinical records including relevant investigations.
2. Age group 30 to 90 years.

Exclusion criteria :
1. Cases with ambiguous reports of gastric malignancy.
2. Endoscopy done outside the Institute.
3. Follow up and collection of clinical data not avalable.

Procedure methology :
After obtaining written consent from patients and following obtaining clearance from Institutrion Ethics committee, detailed history, clinical examination and relevant investigation reports were taken. History of presenting complaints including pain abdomen, anorexia, weight loss, vomitting etc. were taken. History of habits inmcluding smoking and alcohol intake; drug history including H2 blockers, antacids, proton pump inhibitors; socio-economic history including occupation, family income etc. were taken.

Upper Gastro-intestinal endoscopy : This was performed with the Olympus model of GIF GIO endoscope by an expert endoscopist who in no way was involved in the histologic interpretation of the biopsy obtained from the suspected patient to avoid observers and selection bias. The light source used was CLE 10.

Endoscopic biopsy : In patients showing mucosal abnormality, biopsy was done with FB-25K biopsy forceps.Thus, number of endoscopic cases suspected of malignancy was 56, out of which 52 were proved to be malignant histologically.

LIght Microscopy : Was done to grade histological types of malignancy.

The endoscopic appearance of advanced carcinoma (applying Bormann's classification) described below:

Type 1 **:** well demarcated polypoid / fungating mass growing into the lumen.The surface is irregular, grayish may be friable and can bleed.

Type-2 **:** uncreated , circumscribed mass with a sharp raised margin. Base is necrotic tumor. Tumor nodule may be present. Surrounding mucosa may be abnormal and erythematous.

Type-3 **:** Uncrated lesion limited in part by a wall but elsewhere blending into apparently normal mucosa.The base is infiltrated by carcinoma and infiltration of wall causes heavy fold to appear.

Type-4 **:**Diffuse infiltrating mass, may be ulcerated in part, with poor distensibility and less peristalsis(especially in linitis plastic).The mucosa may mimic gastritis.Visible nodules may be present covered with normal with normal or erythematous mucosa. Tumor break – through areas look rough and red.

Endoscopic appearance of lymphoma:

Infiltrating lesions of mucosa

- Polypoid/nodular bulky growth
- Often as linitis plastic growth
- Single or multiple ulcer
- Volcano type ulcer which is deep with raised margin
- Infiltrative lesion giving rise to rigid, thickened or giant fold.

Patients showing mucosal abnormalities as above were biopsied.Depending on the lesion the number of biopsy varies from 3 to 6

Endoscopic Biopsy handling: A) Before fixation: Biopsy samples were taken gently (by testing with needle) from the biopsy forceps. Then they were placed with proper orientation (submucosa downword) on a square shaped small bit of filter paper.

B) Fixative and fixation: Next, they were put slowly into the vial containing 10% formol saline as fixative and kept for 24 hours for proper fixation

C) Processing to obtain paraffin blocks- the tissue was processed by automatic tissue processor and paraffin blocks were made.

D) Sectioning - multiple sections were made of 0.5-0.6 mm. thickness at different levels to get adequetly oriented material in the deeper cuts

E) Staining **:** the sections were stained with hematoxylin and eosin (Harri's), Special stain such as periodic acid shiff (Schiff 1868,McManus 1946), Immunohistochemical stain like CD-20 were considered when necessary.

Immunohistochemistry : Reagents Required:

- Standard solvents used in immunohistochemistry
- 50 mM tris buffered saline (TBS) pH 73.
- Antigen retrieval solutions
- Enzyme retrieval solutions

- Antibody diluents
- Primary antibody (CD-20)
- Mounting medium

Equipment required:

- Equipment required for antigen retrieval if recommended for the primary antibody

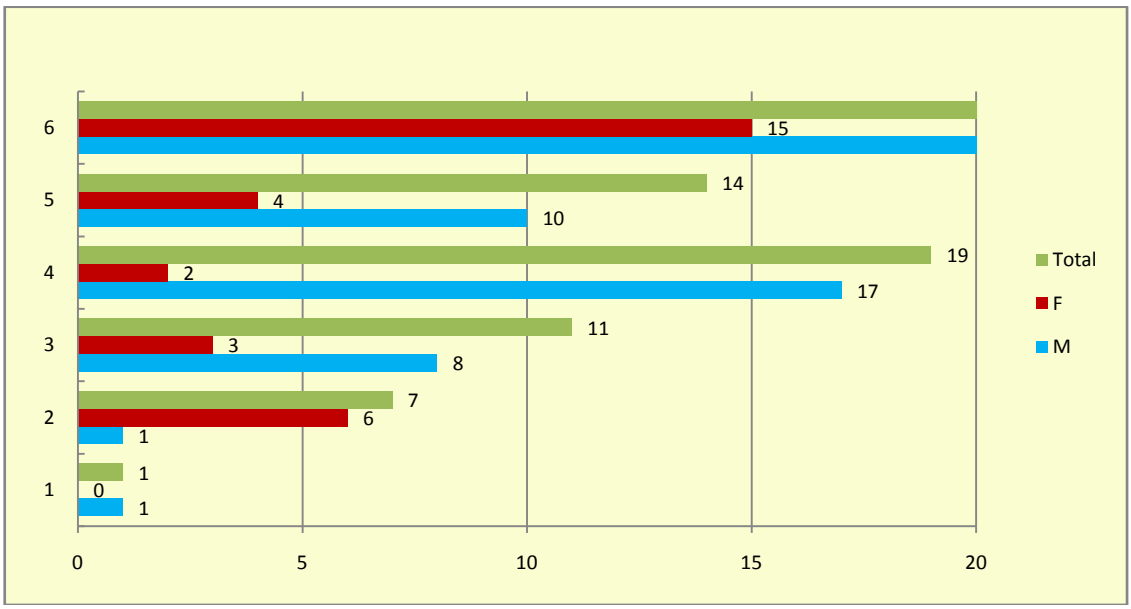
General immunohistochemistry laboratory equipment.

Statistical Analysis : . Data was analysed by entering in Microsoft excel 2007 data sheets. Statistical softwares such as GraphPad Prism5 were used to calculate significance and other variables. P value < 0.05 was considered significant. Fisher's exact test was to used to analyse data. Total number of cases were 52. (n= 52)

III. Result

Table 1: Correlation of age and sex of patients with gastric malignancy

Age(yrs)	M	F	Total
<36	1	0	1
36-45	1	6	7
46-55	8	3	11
56-65	17	2	19
>65	10	4	14
	37	15	52



Out of total 52 cases, 37 were males (71.15%), 15 were females (28.85%).The male: female ratio was 2.5:1

AGE :The peak age incidence for gastric cancer was 5th (36.53%) and 6th (29.92%) decade (table 1).Among patients with gastric cancer the youngest patient was 32 yrs and oldest was 88 yrs.

Table 2 : Correlation between Socio-economic status with different types of malignancy

Income(Rs)	Intestinal CA	Diffuse CA	Signet ring CA	Lymphoma	Carcinoid	GIST	Total
<5000	14	12	1	1	1	0	29(55.77%)
5000-10000	8	3	4	1	0	0	16(30.77%)
>10000	5	0	1	0	0	1	7(13.46%)
Total	27	15	6	2	1	1	52(100%)

Socio-economic status of the patients were judged on three scales of monthly income, 1. Less than Rs 5000, (poor) , 2. .more than Rs 5000, but less than Rs 10000 (middle), 3..more than Rs 10000 (rich) , A total of 29 patients (55.77%) were from low income group, 16 patients (30.77) were of middle income group, .7 patients were from high income group (13.46%) .

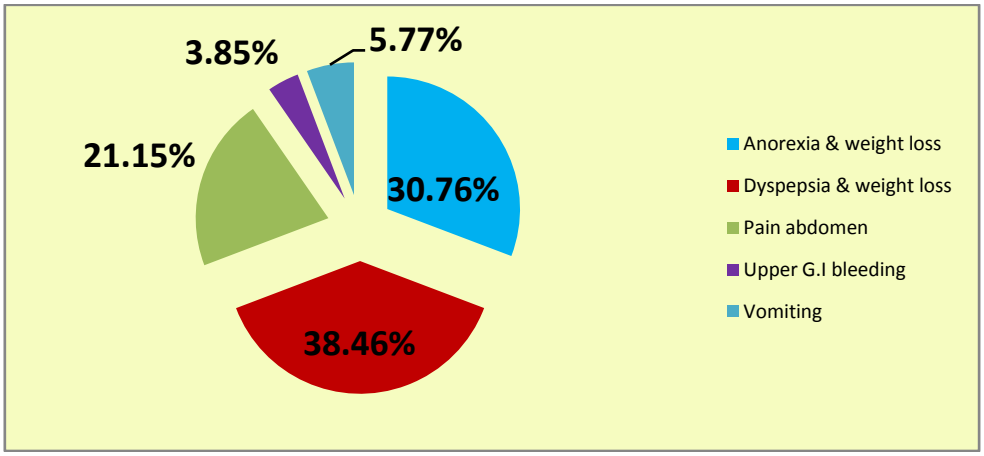
Drinking habit : Out of 52 (37 males and 15 females) patients with gastric neoplasms 28 (53.86%) were smokers and 18 (34.61%) consumed alcohol . Out of the smokers, 25 patients (48.07%) were adenocarcinoma patients, 2 cases were lymphoma patients and 1 was the carcinoid patients. The Leiomyosarcoma patient had no history of smoking or alcohol intake.

Drug history :5 patients (9.6%) had history of H2 blocker therapy. 15 patients (28.84 %) had history of intake of Proton Pump Inhibitors (PPI).

Symptomatology : The most common presenting complaint for patients with gastric carcinoma was dyspepsia and weight loss (38.46%), followed by anorexia and weight loss (30.76%), pain abdomen (21.15), ,vomiting (5.77%) and upper G.I bleeding (3.85%) .

Table 3 :Chronology of symptoms of patients of different types of stomach malignancies

PRESENTING COMPLAINTS	Adenocarcinoma	Lymphoma	GIST	Carcinoid	Total
Anorexia & weight loss	15(31.25%)	1(50%)	0	0	16(30.76%)
Dyspepsia & weight loss	19(39.58%)	1(50%)	0	0	20(38.46%)
Pain abdomen	10(20.83%)	0	0	1	11(21.15%)
Upper G.I bleeding	2(4.16%)	0	0	0	2(3.85%)
Vomiting	2(4.16%)	0	1	0	3(5.77%)



In gastric adenocarcinomas , most of the patients had epigastric pain (80%) (table 6), and of the duration of pain is also important as most of our cancer patients (50%), had duration of pain less than 6 months (table 7).

Ultrasonography (USG) Profile : 19 patients had ultrasonography examination. Out of these 19 patients, 14 cases showed positive findings in ultrasonography (74%). All false negative cases were adenocarcinomas. One case each from lymphoma and Gastrointestinal Stromal Tumour (GIST) had positive findings of USG.

Bareium meal xray of gastric malignancies : 30 patients had barium meal xray, of whiuch 22 (73%) were positive for malignancy. 20 of positive cases were adenocarcinoma, one each of lymphoma and leiomyosarcoma.

Table 4 : Sub-sites of gastric malignancies

SUB – SITE	ADENO CA	OTHERS	TOTAL
Prepylorus & Antrum	32	2	34(65.38%)
Fundus	9	1	10(19.23%)
Body	5	1	6(11.53%)
Entire Stomach	2	0	2(3.84%)

Site of presentation of malignancy : The commonest site of presentation of the gastric malignancies was the antrum and prepylorus (65.38%), followed by the funds (19.23%), and then the body (11.53%) One case (3.84%) involved the entire stomach.

Most of the adenocarcinoma occurred at prepylorus and antrum (66.67%), followed by at fundus(18.75%), at body (10.41%) and entire stomach was least involved(4.16%).

Table 5 : Endoscopic presentation and histological diagnosis of different malignancies

ENDOSCOPIC PRESENTATION	ADENO CA	OTHERS	TOTAL
Ulcerative	23	2	25(48.07%)
Infiltrative	16	1	17(32.69%)
Polypoid	9	1	10(19.23%)

Total	48	4	52(100%)

Endoscopic Presentation : Most common presentation was ulcerative type (48.07%), followed by Infiltrative type (32.69%) and Polypoid type (19.23%).

Types of Adenocarcinoma : Resent study included 48 cases of gastric adenocarcinoma.The most common histopathological type of the gastric adenocarcinoma was intestinal (56.25%) followed by diffuse (31.25%) and signet ring carcinomas (12.50%).

The intestinal adenocarcinomas were mostly moderately differentiated (77.78%) with the remaining being poorly differentiated (14.81%) and well differentiated (7.41%)

Lauren's classification could be applied to 42 cases out of total 48 cancer (87.50%).In opur study Lauren's intestinal type was 64.29% (27 cases) and diffuse type was 35.71% (15 cases) (table 13).All of lymphomas were MALT type of lymphoma and showed CD-20 positivity(Fig 3).

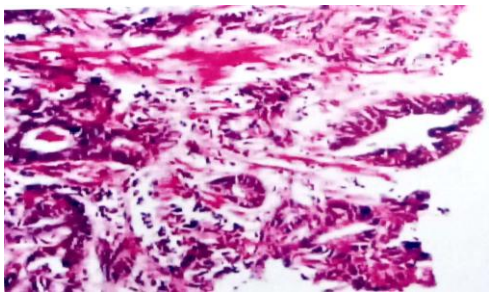


Fig 1 :Moderately differentiated adenocarcinoma stomach (100x)

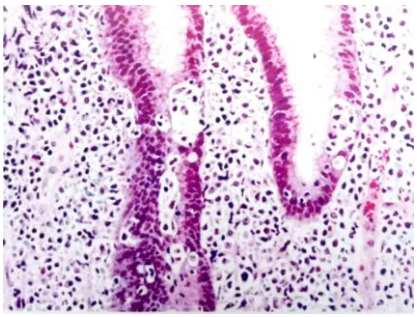


FIG 2 : PAS stain positivity for signet ring adenocarcinoma of stomach (H & E,100X)

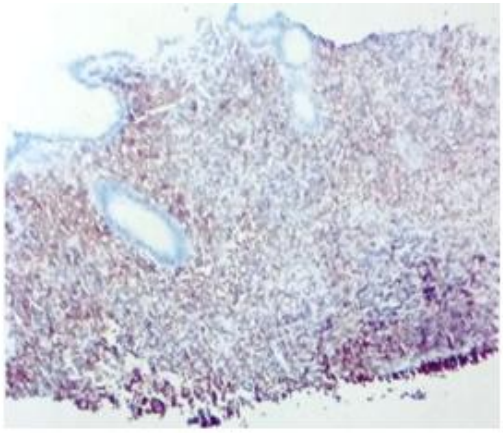


Fig3:MALT Lymphoma Showing CD-20 Positivity lesions (H & E, x100)

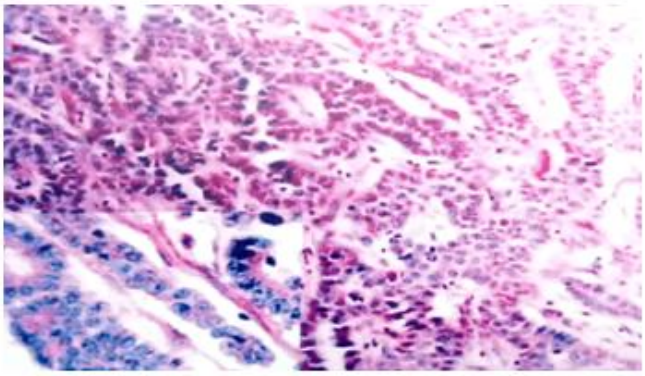


Fig 4 :GIST – Stomach (H & E,100x) with inset showing elongated spindle cells with plemorphic nuclei (H & E,400x)

IV. Discussion

Sex Incidence : In the present study, out of total 52 patients, 37 patients were male (71.15%) and 15 patients were female (28.85%) [table 1].There is a male preponderance of gastric adenocarcinoma through the world. We have found a male : female ratio of 2.5 : 1,which is at par with other studies .

Table 6 : Male : female ratio in different other studies

STUDIES	MALE:FEMALE
Our present study	2.5:1
Remine et al,1966[6]	2.5:1
P.R.Howley ET AL,1970[7]	2.2:1
Lundh G et al.1974[8]	1.8:1
Jose et al [9]	4.1:1

A study group from Trivandrum and study by Bazaz et al[10] also show a steady decline after the 5th and 6th decade – the age group of highest incidence in males according to their observations.

Lymphoma in our study occurred 100% in males. In a follow – up study of 153 cases by M.S Hockey et al[11] , the percentage of male patients with lymphoma was 66.7% with high grade and 60.6% in low grade Non-Hodgkin's lymphoma. In our study , most patients were at the age group og 65 years or more.
The GIST patient was 50 year female. Most patients present between the ages of 50 and 80[12].
The carcinoid patient was 49 year male.The common age group presentedby this malignant lesion is usually 5th and 6th decade[13].
Presenting Complaints : Clinically dyspepsia and weight loss was the commonest symptom found.In this regard,lymphoma,carcinoma,GIST and carcinoid patients presented nearly same high incidence .In gastric adeno carcinomas, most of the patient had epigastric pain (80%). and the duration of pain is also important as most of our cancer patients (50%),had duration of pain less than 6 months.
Vomiting was present in 2 cancer patient (4.16%) and in 1 GIST patient.
Relationship of habits with Gastric Malignancy : Out of 52 (37 males and 15 females) patients with gastric neoplasms 28 (53.86%) were smokers and 18 (34.61%) consumed alcohol (graph 4) out of the smokers,25 patients (48.07%) were adenocarcinoma patients,2 cases were lymphoma patients and I was the carcinoid patient. The GIST patient had neither the history of smoking nor the history of alcohol intake. The relationship between smoking and gastric carcinoma is still unclear with some studies showing a weak to moderate association while some have found none, while others have found a relative risk of less than two fold[143].There was little evidence to support any association between alcohol and gastric cancer.
Drug History : Indiscriminate use of H2 blockers and/ or proton pump inhibitor may give rise to gastric cancer [7,144].In our study, ,out of total 52 patients,20 patients (38.46%) had history of use of such drugs.
Socio-economic Status : A total of 29 patients (55.77%) were from low socio economic status,.In some other studies, socio-economic status shows same trends.

Table 7 : Socio-economic status of gastric malignancy in different studies

STUDIES	Percentage of lower socio economic class
Josie et al[9]	100%
Leena devi et al	855
Swaroop et al11	90%

Diagnostic accuracy of Barium meal xray and Ultrasonography : The diagnostic accuracy of barium meal x-ray in our study was 73.33%. .In some studies [147,148] the accuracy is found to be nearly 90%.USG examination is also diagnostic (diagnostic accuracy – 73.68%) in our study. .In a study the accuracy was found to be up to 80% [12]
Site of Presentation : The commonest site of presentation of the gastric malignancies was the antrum and prepylours (65.38%). Followed by at fundus (18.75%), at body (10.41%) and entire stomach was least involved (4.16%).A comparative analysis is given in table 8.

Table 8 : Site of presemtation of Gastric malignancies in different studies

STUDIES	Pylorus and antrum
PWJ Houghton et al13	48.6%
Paul L TSO et al14	36.9%
Suvanra & Sasidharan15	52.85%
W.H.ALLUM et al16	39.9%

Out of 2 lymphoma cases, 1(50%) was found in the body of stomach. The tumor location sites as per other studies are given in table 9.

Table 9 : Tumour location of lymphoma in different studies

Studies	**Body**
Azra Shah et al 1995 17	73%
Isaacon PG ET AL 1983 18	64%
m.s. Hockey et al 1987 19	49.6%

Endoscopic Presentation : The commonest type of presentation of gastric malignancies observed was an ulcerative growth (48.07%) , followed by infiltrative (32.69%) and polypoidal growth (19.23%). The commonest pattern of presentation of the gastric adenocarcinomas was an ulcerative growth (47.91%) followed by infiltrative (33.33%) and polypoidal growth (9%) .
Types of Gastric Malignancies : In the present study, out of total 52 patients, 48 were adenocarcinomas (92.30%), 2 were lymphomas, (3.84%) 1 was GIST (1.92%) , 1 was carcinoid(1.92%) [vide graph 16]. The percentage of adenocarcinoma in different studies is around 95% . The correlated with the present study where adenocarcinomas constituted 92.30% of all gastric cancer.

For one of the cases reported as 'negative for dysplasia' a subtotal gastrctomy specimen was received later on in the laboratory. On gross examination the mucosa showed a polypoid growth measuring 8 cms across, with the cut surface appearing gray white and showing areas of necrosis, hemorrhage and cystic change. Microscopic examination revealed, a submucosal llesion comprising of fascicles of spindle cells with pale eosinophilic cytoplasm and spindle shaped nuclei. Focal areas of nuclear palisading were seen (Fig 10) A diagnosis of Malignant GIST was given. The reason for missing the diagnosis in the endoscopic biopsy sent earlier could be related to the difficulty in sampling of submucosal lesions by endoscopy.

Types of Adenocarcinoma : Preent study included 48 cases of gastric adenocarcinoma. The most common histopathological type of the gastric adenocarcinoma was intestinal(56.25%) following by diffuse(31.25%) and signet ring carcinomas(12.5%)..

Intestinal type carcinomas have a glandular pattern, usally accompanied by papillary formation or solid components, are made of rather large, pleomorphic The cells with large, hyperchomatic nuclei often showing mitoses. The diffuse adenocarcinomas were characterized histologically by the presence of poorly cohesive small round cells diffusely infiltrating the gastric wall either singly or in a reticular fashion. There was little or no gland formation.

Lauren's classification could be applied to 42 cases cancers out of total 48 cancer cases(87.50%). In our study, Lauren's intestinal type was 64.29% and diffuse type was 35.71% which are almost similar to the other studies given in table 10.

Table 10 : Lauren's Classification of Gastric Adenocarcinoma in different studies

STUDIES	Intestinal	Diffuse
Our study	64.29%	35.71%
Ming SC, 1977[20]	67%	33%
Jose et al , 1995[9]	86%	14%
Lauren, 1965[21]	74%	26%

The signet ring adenocarcinomas were characterized histologically by the presence of groups of round cells, with clear cytoplasm and an eccentric hyperchromatic nucleus which was stretched out long the cell membrane . PAS stain was performed for confirmation of the diagnosis .

Differentiation of Gastric Adenocarcinoma: The cases were mostly moderately differentiated (77.78%) with the remaining being poorly differentiated (14.81%) and well differentiated (7.41%).

Well-defferentiated adenocarcinoma stomach showed irregular atypical glands lined by pleomorphic cells(Fig 1). Moderately differentiated adenocarcinoma- stomach showed irregular atypical glands and cords of pleomorphic cells infiltrating the muscularis In JOSE study, 90% of the lesion was poorly differentiated. Through the world it is commonest, though a lot of observer variations remain.

Carcinoid tumour : In the present study, we encountered one case(1.92%) of gstric carcinoid in a 49 year old male patient who presented with a small polypoid growth in the fundus . It was characterized histologically by the presence of cells were arranged jin acinar and trabecular pattern. The cells were small, uniform with finely granular eosinophilic cytoplasm and oval nuclei with stippled chromatin.. Other studies have observed that gastric carcinoids make up < 1% of all gastric neoplasms and that they are almost always located in the fundus and body.

Gastrointestinal Stromal Tumours (GIST) : The case of GIST (1.92%) in our study was seen in a 50 year old lady who presented with submucosal polypoidal growth in the body. The microscopy showed fascicles of spindle shaped cells, with ple eosinophilic cytoplasm and spindle to ovoid nuclei with fine chromatin (Fig 9, Fig 10). Similar finding s were observed in other studies where GISTs account for 2.2 % of malignant gastric tumors, affecting adults between 6th nd 8th decade and presenting commonly as serosal (Fig 8), submucosal or intramural nodules.

Gastric Lymphoma : We encountered a 2 casea (3.84%) case of MALT type gastric lymphoma in a 68 year male, and in a 65 years male who had an ulcerated growth in the body and an infiltrative growth in the perpylorus and antrum respectively.

Microscopically, MALT lymphoma showed lymphoepithelial lesions (Infiltration of glandular epithelium by lymphocytes) . MALT lymphoma also showed CD-20 positivity (Fig 3) .

Limitation of the Study :

1. Occasionlly , the site and depth of the biopsy were not representative and included necrotic tissue or mucosa alone. Hence, in the former case though there was a strong clinical suspicion of malignancy, a false negative diagnosis was given on the biopsy. In the latter case, it led to missing the diagnosis of submucosal lesions like GIST.

2. Immunohistochemical studies which were necessary in certain cases(i.e. carcinoid tumor and GIST) could not be carried out due to lack kof facilities and financial constraints. Only in case of lymphoma, we did immunohistochemical stain like CD-20.
3. Follow-up was lost in most of the cases as the patients were referred to regional cancer institute for further management.

V. Conclusion

The increased incidence of intestinal type of adenocarcinoma in this region indicates that this is a high risk are and environmental factors play an important role in causing such type of carcinoma.
Proper care, early detection and long term follow up of cases may improve the present status and decrease the mortality rate of gastric cancers in this area.

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