A STUDY ON ROLE OF HER 2/NEU OVER EXPRESSION IN GASTRIC CARCINOMA IN SOUTH INDIAN POPULATION

Dissertation
Submitted in partial fulfillment of the regulations of

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Department of General Surgery

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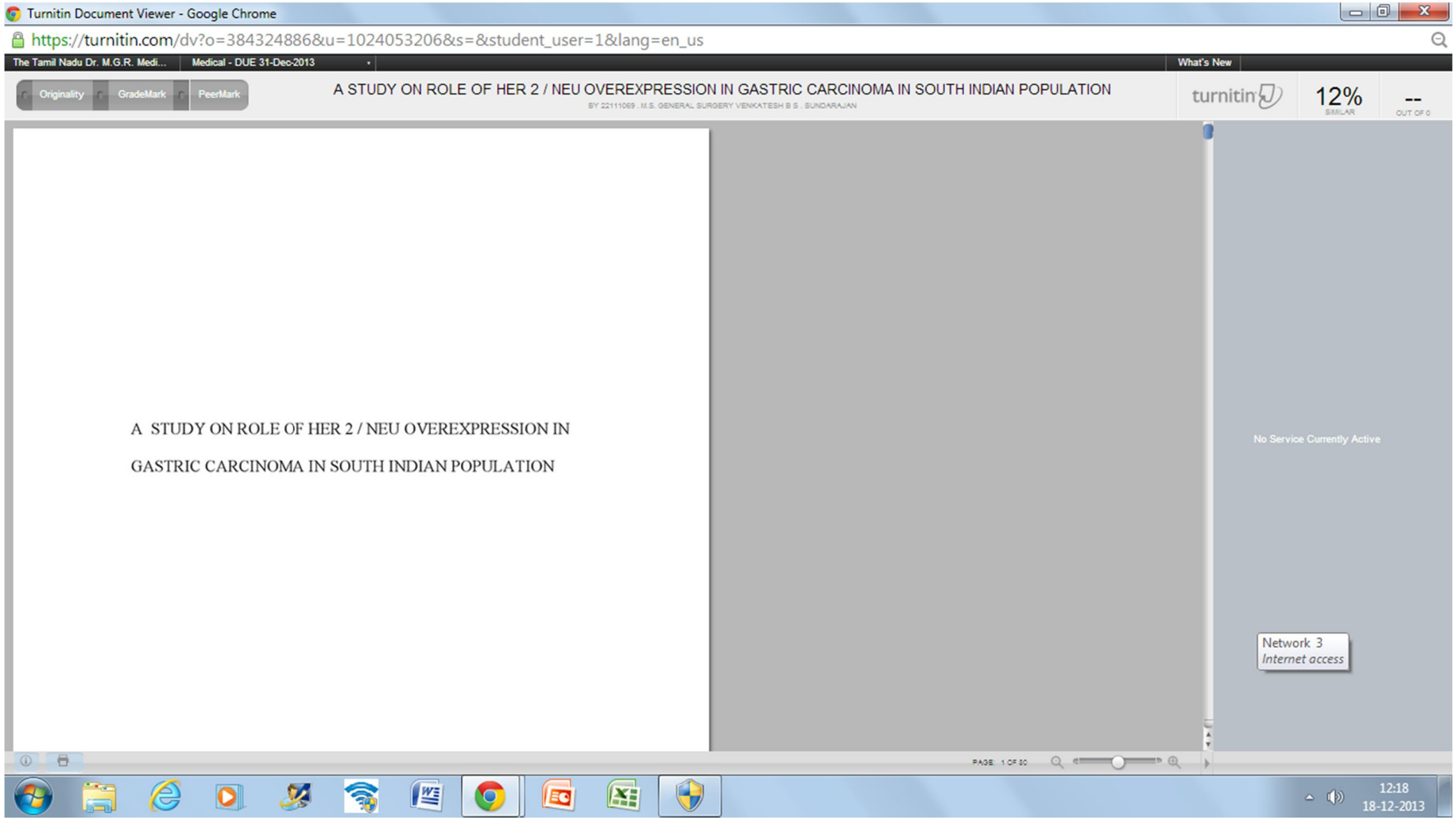
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is the bonafide work done by **Dr. Venkatesh B.S.,** Post Graduate student (2011 – 2014) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamil Nadu Dr. M.G.R Medical University, Chennai for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

Prof.S.VISWANATHAN, M.S.,
Professor of Surgery,
Dept. of General Surgery,
Stanley Medical College,
Chennai-600001.

Prof. K. KAMARAJ,M.S.,
Professor and Head of surgery,
Dept. of General Surgery,
Stanley Medical College,
Chennai-600001.

PROF. S. GEETHA LAKSHMI, M.D., PhD,
The Dean**,**
Stanley Medical College,
Chennai-600001.

DECLARATION

I, **DR. B.S.VENKATESH** solemnly declare that this dissertation titled **"A STUDY ON ROLE OF HER 2/NEU OVER EXPRESSION IN GASTRIC CARCINOMA IN SOUTH INDIAN POPULATION**" is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief.

Prof. S.VISWANATHAN, M.S.,
Professor of Surgery

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2014.

Place: Chennai.
Date: December 2013. **DR.B.S.VENKATESH**

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TABLE OF CONTENTS

INTRODUCTION

Adenocarcinoma of stomach , so called “Captain of men of death” was the leading cause of cancer related deaths through the most of the 20 th century and as on now ranking second only next to lung cancer.

Even though surgical resection is the mainstay treatment for early gastric cancer, most of the patients present to us in advanced stages where adjuvant chemoradiation comes into play.

Survival of patients with advanced resectable/non resectable gastric cancer treated with chemotherapy still remains poor. So the role of novel therapies is warranted.

Her 2/neu (human epidermal growth factor receptor 2) also called as erbB2 /cd340/p185 is a protein encoded by gene ERBB2, a member of EFGR/erbB family. Amplification or over expression of HER 2/NEU which acts as a proto oncogene has been demonstrated to play an important role as a bio marker and target of therapy in breast cancer .

It has been demonstrated in recent western clinical trials , over expression of the same in gastric cancer too. But the frequency of expression differs in each geographical area and incidence of her 2 /neu in gastric cancer in south Indian population is not clear. Western studies

indicate poor prognosis and poor response to chemotherapy in HER2/NEU over expressed cases of gastric cancer, but as on now, no study is clear in India.

Trastuzumab is a monoclonal antibody which specifically targets HER2 protein by directly binding to extracellular domain of receptor and successfully used for breast cancer patients ,but not yet been tried in India for gastric cancer patients. This study may pave way for the introduction of trastuzumab in treating patients with advanced gastric malignancies and thereby enhance survival rates and improve the quality of life of those patients justifying the cost benefits.

Since most of the patients coming to our hospital are poor and cannot afford costly drugs, the justification to start a treatment is warranted and this study may provide a justification.

AIMS AND OBJECTIVES

1. To know the incidence of HER2/NEU over expression in gastric cancer in our locality.
2. To study the staging , operability and prognosis of gastric cancer in relation to HER2/NEU expression
3. To study the aggressiveness and histology of gastric cancer in relation to HER2/NEU expression.
4. To study the HER2/NEU expression based on locality of tumours.

HISTORY OF GASTRIC CANCER

The long history of gastric cancer begins with the mentioning in 1600 BC according to ebers papyrus and also in the Hipprocrates reports around second century AD.

Around 980 AD, Avicenna of Arabia, mentioned about stomach cancer in his encyclopedia. After that during the medieval period, there was no progress in the knowledge of gastric cancer except for the purgatives and blood letting according to the black bile theory of Hippocratic period, till in 1835, Cruvelheir described benign and malignant gastric ulcer.

GASTRIC CANCER AND NAPOLEAN BONAPARTE:

History says that the French emperor Napoleon Bonaparte could have suffered a schirrous carcinoma of stomach following a familial history as reported by Dr.Antonmarchi, his family physician. he exiled to St. Helena, an island in Atlantic Ocean, following defeat in the war of waterloo. During his St. Helena exile,In 1819 he began to suffer from Repeated episodes of fever, abdomen ache, hiccoughs, and vomiting. His treatment was frequent large doses of purgatives and blood letting and his symptoms worsened around September 1820: he vomited daily and altered bowel habits

epigastric pain, fatigue and fever. In 1821, he vomited coffee-ground-vomitus, and had severe hiccoughs and tachycardia and was in delirium . .During then he told Dr. Antonmarchi, " . . . I desire you operate me and examine my stomach and make a detailed report and you should give to my son." He knew he had a gastric problem because it was the cause of death of his father and family relatives. In 1821, may 5, in the early morning he died following a bout of haematemesis and melena and hypovolemic shock.

FIG.NAPOLEAN BONAPARTE AND HIS EPIGASTRIC PAIN.

Eight physicians attended the autopsy. Dr. Francesco Antonmarchi was his friend rest other seven were British. The most

detailed report by Antonmarchi, an anatomopathologist of University of Pisa:

". .. the gastric volume was smaller, its anterior surface is normal and on the right side there is a close adhesion with the inferior left liver and perforated in the center. The perforation was sealed by the liver adhesion. On opening stomach,over Greater curvature its capacity appeared filled with a Coffee coloured liquid. The interiorof the stomach was a cancerous ulcer whose center was near the lesser curve and the induration spread from the cardiac to pylorus, with a scirrhous thickening of the wall."

Since tissue microscopy was not developed by then, autopsy diagnosis relied upon The morphology. Nevertheless the reports clearly show that Napoleon had scirrhous gastric carcinoma probably with gastric outlet obstruction which manifested clinically as intractable vomiting and hiccoughs Previously, for many years, the emperor had suffered vague abdominal symptoms, perhaps due to chronic gastritis which preceded his familial gastric cancer.

In the year 1874-76, Billroth described distal gastric resection with anastamosis of stomach and duodenum type 1 and to the jejunum

type 2. In 1879, Pean was the first do gastric resection for malignancy, even though the patient died on the fifth post operative day.

In 1881, Billroth did a successful resection. In 1881, Wolfler & Nicolodani did antecolic gastrojejunostomy. In 1883, Courvoisier performed retrocolic gastrojejunostomy. In 1893he advised jejunojeunostomy along with GJ. In 1898 Schlatter for the first time performed total gastrectomy. In 1907 wendel resected oesophagus & stomach for malignancy.

In 1930, Polya performed anastamosis of entire opening of stomach with jejunum(santorio 2005)

In 1981, Longmire did radical treatment for stomach cancer. After that there has been immense progress recently, though total/subtotal gastrectomy with D 2 lymphadenectomy stillremains the standard of care.

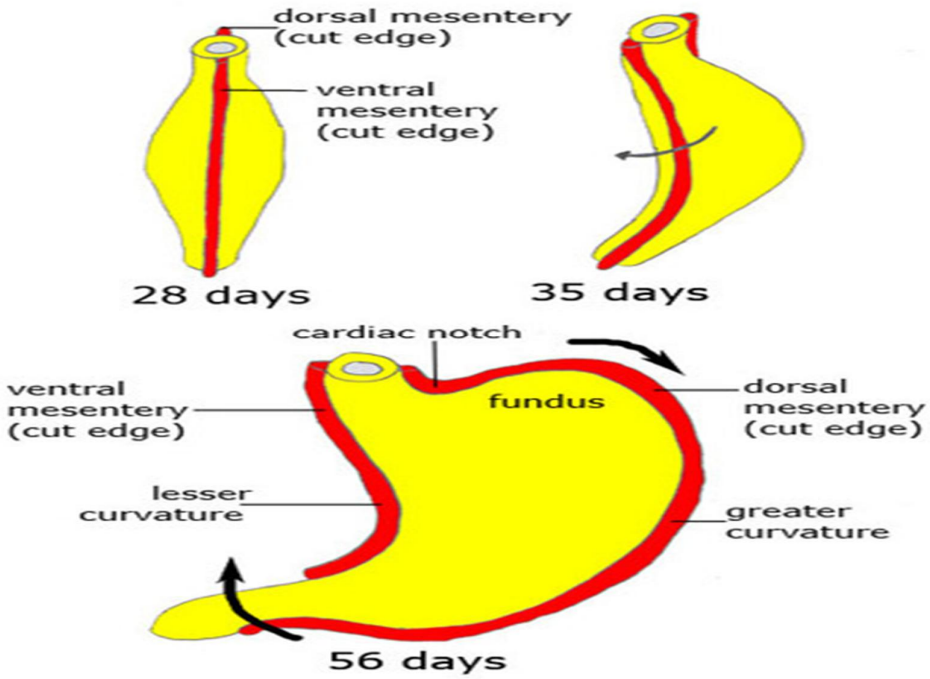
In1982, Robin warren and Barry Marshall found H.pylori was responsible for benign and malignant gastric ulcers. In 1978, Stanley cohen discovered Epidermal growth factor, the first receptor tyrosine kinase and neu oncogene was discovered @ the Massachusetts institute of technology in 1882-84.

In 1998, therapy targeted against HER2/NEU was approved for breast carcinoma, only in the recent years, link between HER 2/neu over expression & gastric cancer has been studied.

EMBRYOLOGY OF STOMACH

Stomach, esophagus and duodenum are developed by the elongation of the foregut, embryologically around 4^{th} or 5^{th} week. Initially at the level of c3- c5, thereafter following truncal growth, reaches the T10-L3 level, its normal final position around 10 th week, following which a clock wise rotation of 90 degrees occursaround longitudinal axis, hence dorsal midline forms the greater curvature and ventral becomes lesser curvature.

Fundus outgrowth occurs at eighth month and gastric rugae makes its appearance by eigth week and muscularis develops by 8-14 weeks and glandular pits appear all over the stomach by 10^{th} week. By 11^{th} and 12^{th} week, parietal and chief cells are formed respectively.



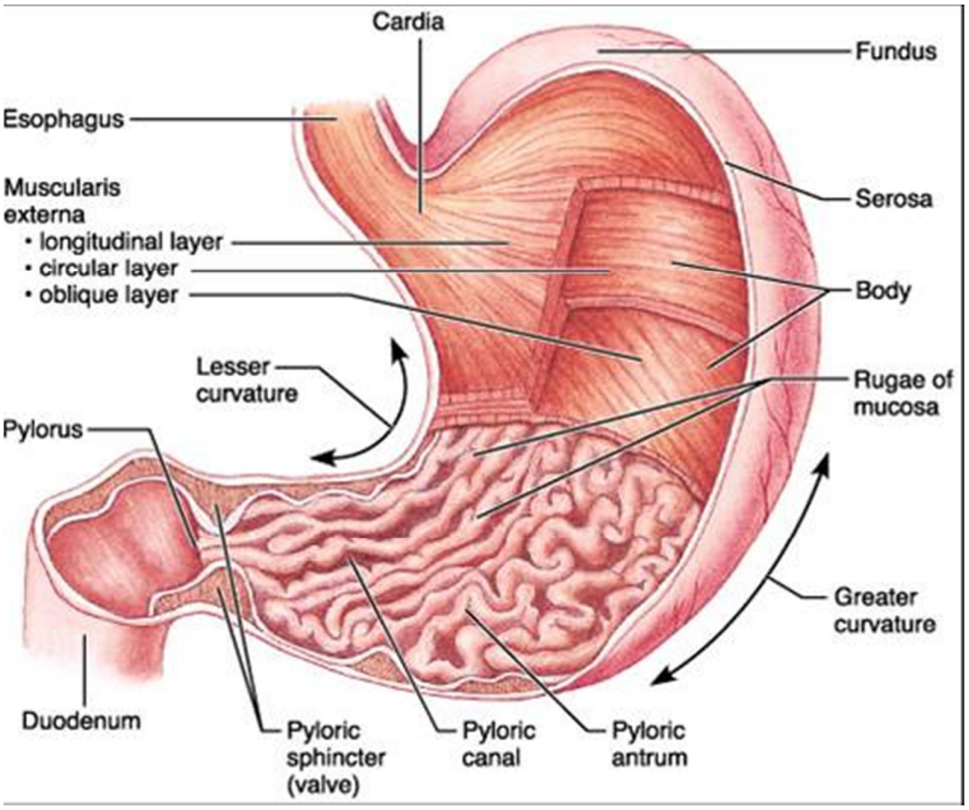
SURGICAL ANATOMY

MORPHOLOGY OF STOMACH:

Stomach begins from gastro-esophageal junction, 2-3 cms below diaphragm and ends in pyloro-duodenic junction and comprises of

1. CARDIA:,where the esophagus joins and forms the OG junction.
2. FUNDUS: part of stomach above cardia
3. BODY: between fundus and pylorus
4. PYLORUS: divide into 2 parts a. Antrum- the proximal most part which starts at the level of angular notch at the lesser curvature and b.pyloric canal.

The line of demarcation of the pylorus and duodenum is considered to be the pre-pyloric vein of Mayo.



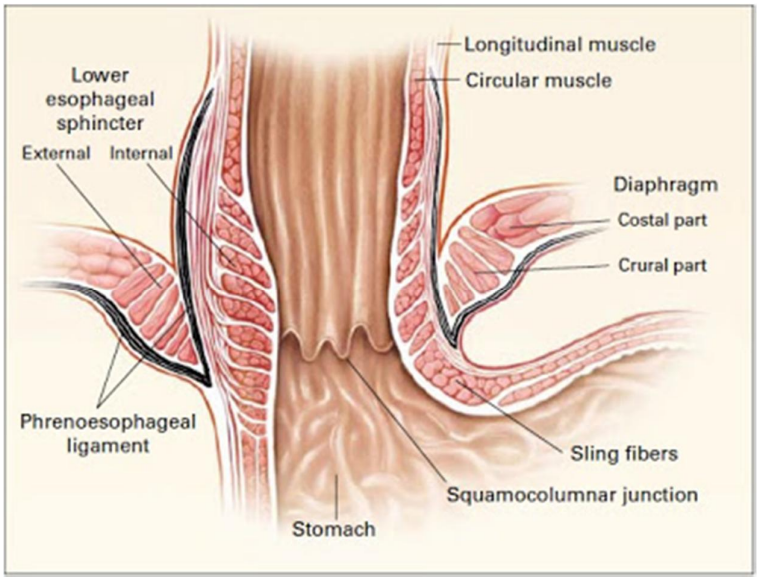
Surgically, stomach is divided into 2 by the line joining the first branch of left gastric artery to the midpoint of gastroepiploic vessels as

1. Proximal gastric unit: comprising the og junction, fundus and body
2. Distal gastric unit: consisting of pylorus and first part of duodenum.

Anatomy of GASTRO-ESOPHAGEAL JUNCTION:

The length of the abdominal oesophagus varies from 0.5-2.5 cm and its related anteriorly to posterior surface of liver and posteriorly to the diaphragm and aorta .

Caudate lobe lies to his right and fundus to the left of it. According to the endoscopist, GE junction lies at the demarcation of mucosa from pale to pink, but to the surgeon its inside the stomach next to oesophageal stump penetrating the diaphragm where it is lined by endo abdominal fascia.



ANATOMY OF GASTRODUODENAL JUNCTION:

The duodenum anchors the pyloric antrum. Hence mucosa lining is of 3 types:

1. Antral
2. Transitional
3. Jejunal

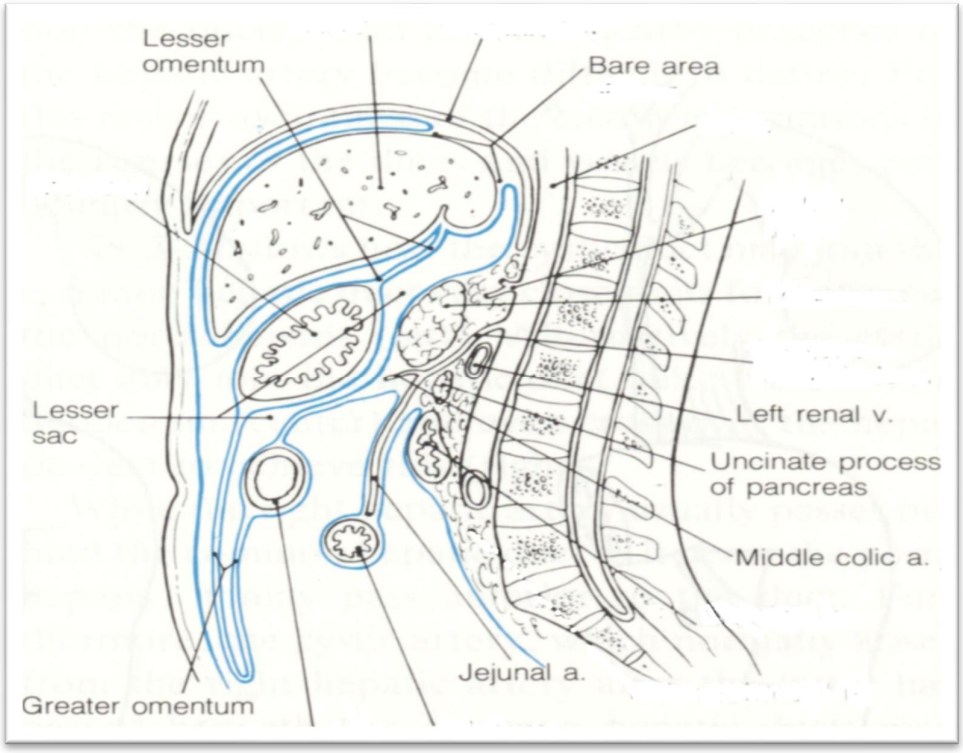
   It is anterior to IVC & not fixed to anatomic entities of posterior abdominal wall.

PERITONEAL REFLECTIONS:

The peritoneum covers the anterior and posterior portions of stomach.lesser omentum extends from liver hilum to stomach and duodenum via hepatogastric and hepatoduodenal ligaments.

Proximally it encircles the stomach and continues as gastrophrenic and gastrosplenic ligament, distally it forms greater

omentum descending and ascending again to reach the pancreas.



GASTROESOPHAGEAL WALL:

Stomach wall consists of

1. Mucosa – innermost layer comprising of columnar epithelium of glands

Glandular epithelium is classified into

a. digestive /exocrine cells:

1. parietal cells

2. chief cells

3. mucus secreting cells

b. gastric function/ endocrine cells:

1. G cells secreting gastrin

2.D cells secreting somatostatin.

Cardia contains mostly mucus cells. Body contains mostly parietal and chief cells. Parietal cells are absent in fundus and antrum. G cells are present in large quantities in antrum.

2. sub mucous layer:

Strongest and rich vascular supplied layer by anastamotic vessels and meissner's plexus of autonomic nerves

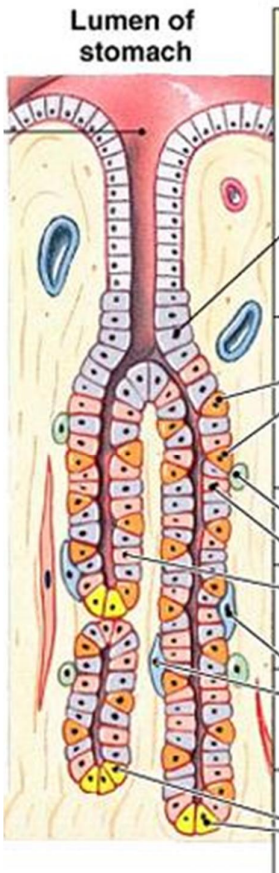
3.muscular layer: comprising of

a. outer longitudinal layer

b. middle and

c. inner circular layer

4.peritoneum forming the serosal surface.



Cell Types	Substance Secreted
Mucous neck cell	Mucus (protects lining)
	Bicarbonate
Parietal cells	Gastric acid (HCl)
	Intrinsic factor (Ca++ absorption)
Enterochromaffin-like cell	Histamine (stimulates acid)
Chief cells	Pepsin(ogen)
	Gastric lipase
D cells	Somatostatin (inhibits acid)
G cells	Gastrin (stimulates acid)

BLOOD SUPPLY:

STOMACH IS SUPPLIED BY 4 MAJOR ARTERIES.

1. left gastric artery- largest ⟹ along the lesser curvature

2. right gastric artery

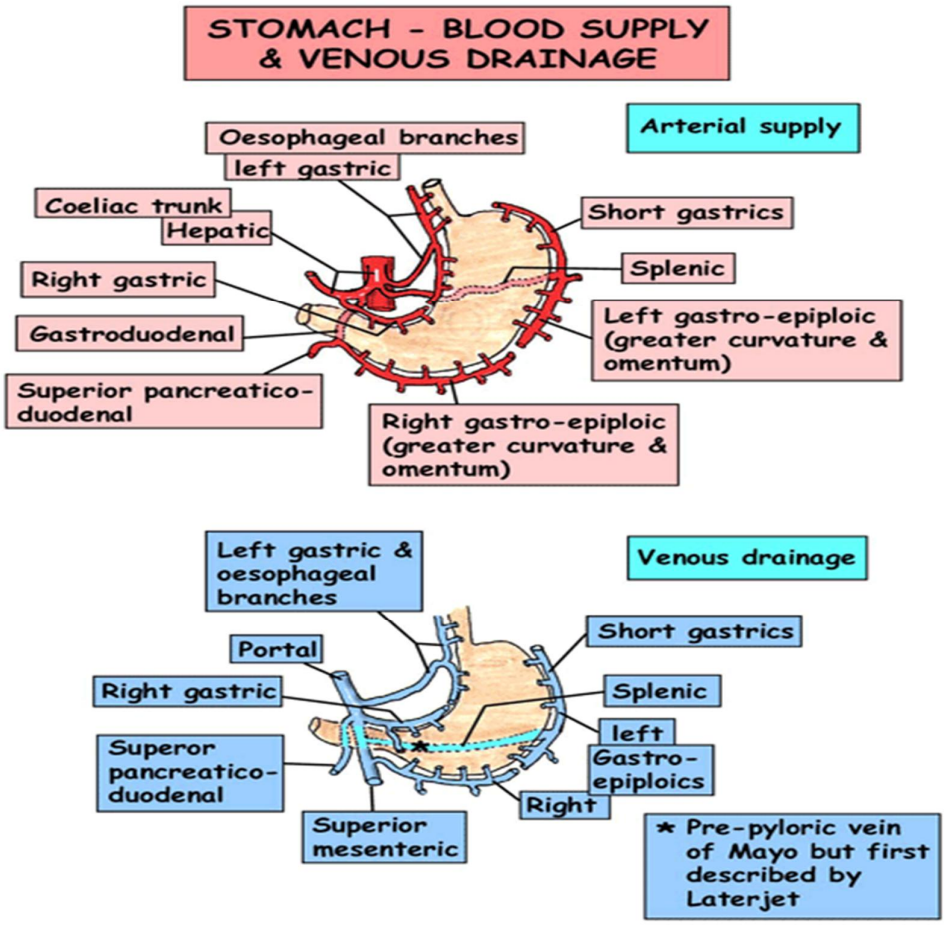
3. right gastroepiploic artery ⟹ along the greater curvature

4. left gastrepploic artery

Also by 5. Inferior phrenic artery and

6. short gastric arteries from splenic artery.

Veins are corresponding to arteries.



Lymphatic drainage:

Superior part of lesser curvature drains to nodes along left gastric and paracardiac nodes. Inferior antral segment drains intosuprapyloric nodes

It is divided into 4 LEVELS:

LEVEL drainage OF subpyloric and omental nodes

LEVEL II drainage of pancreatic and splenic nodes

LEVEL III drainage of superior gastric nodes

LEVEL IV drainage of supra pyloric nodes

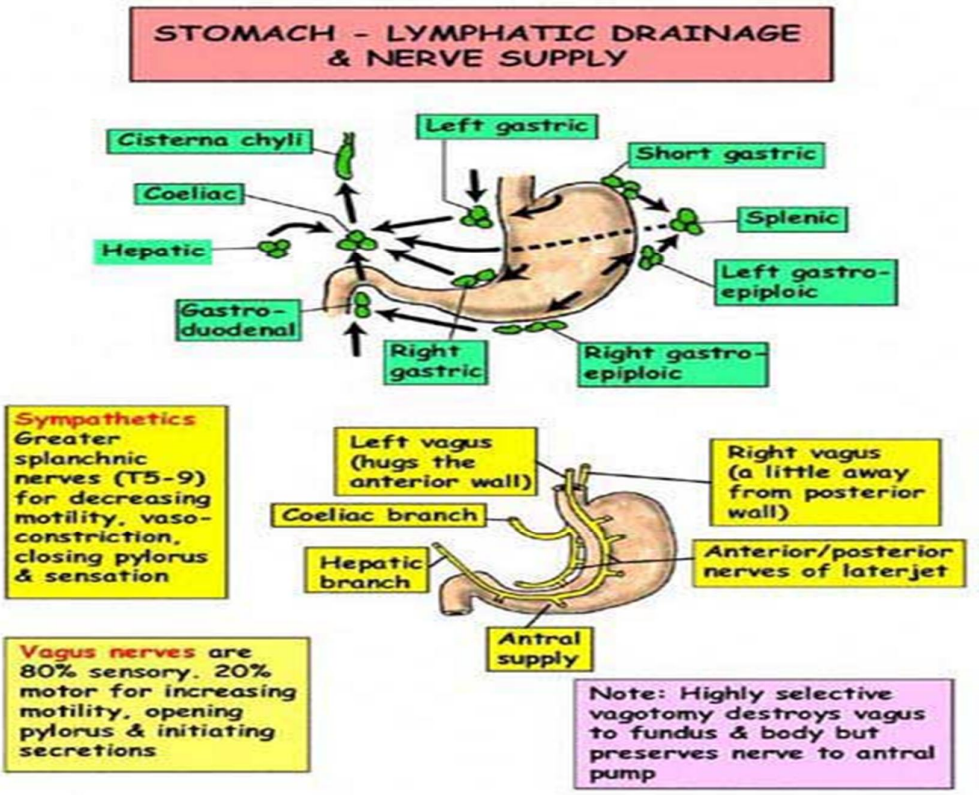
NERVE SUPPLY:

1. PARASYMPATHETIC SUPPLY is via vagus nerve.

Left vagus nerve is anterior and supplies left lobe of liver and continues as anterior nerve of latarjet

Right vagus nevr is posterior which forms the celiac plexus and continues as the posterior nerve of latarjet

2. sympathetic supply is from T5-10 which forms celiac ganglion and supplies to stomach via meissner’s and auerbach’s plexus



PHYSIOLOGY:

GASTRIC MUCOSA is constantly in contact with secreted acid and foreign objects such as food and hence more prone for injury. Its is protected from injury through the following mechanisms

1. increased blood flow helps in rapid turnover of epithelium and buffers the effect of acid in the lumen

2. bicarbonate acts as a acid buffer

3.mucus creates a barrier between contents and epithelium.

4.increased blood flow by prostaglandins

5.bombesin increases prostaglandin secretion.

Acid secretion is mediated by 3 phases:

1.cephalic mediated by vagus

2.gastric maintained by gastric distension and luminal peptides

3. intestinal phase which is an inhibitory phase.

It is maintained at low basal rate during fasting by D cells secreting somatostatin which inhibits acid secretion

Pepsinogen and its Secretion

Chief cells secrete mainly pepsinogens, stored by granules of zymogen. These are the precursors of pepsins (proteases) present in gastric secretions. As soon as secreted, pepsinogen I is activate into the active protease pepsin by acidic medium.

It is an endopeptidase initiating protein digestion into peptides and polypeptides. A pH 1.5–2.5 is essential and pH of above 5.4 is inactivated. Its release is effected by vagal stimulation .*Pepsinogen* may also be released during periods of hypoglycaemia and prolonged increased intracranial pressure.

GASTRIN:

Gastrin causes

1. acid secretion by parietal cells

2. secretion of intrinsic factor

3. Increased mitotis of stomach and small bowel mucosa

4. LES contraction.

5. insulin, glucagon release.

6. stimulation of pancreas also bile flow

7.Small bowel secretion

8.increased peristalsis

9. gastrocolic reflex

SOMATOSTATIN:

Somatostatin inhibits the release of growth hormone of pituitary gland.In stomach it is present in the pyloric and oxyntic cell mucosal zones and not in thecardiac zone.it not only suppresses the secretion of growth hormone, it inhibits other pituitary and extrapituitary secretions. Itsuppresses insulin along with exocrine secretions of pancreas, secretin by the intestine, and secretion of gastrin, HCl and pepsin by the stomach. Somatostatin suppresses gastric acid secretion by

direct action on the parietal cells . Thus in acidic pH, it inhibits gastrin secretion through a negative feedback loop .

Other Hormones

Encephalin

Are considered as endogenous . consists of :, endorphin and enkephalin. It is found everywhere the alimentary canal, it is highest in pyloric antrum.

Galanin

Galanin regulates gastrointestinal motility. It is usually found along with VIP-containing nerves.

Neurotensin

Ileal mucosa secretes this hormone. It inhibits gastric acid and pepsin secretion and delays gastric emptying, which leads controlled chime release to duodenum

REVIEW OF LITERATURE

GASTRIC CARCINOMA

Epidemiology

Carcinoma stomach was the commonest cancer worldwide in the late 20 th century and is now next to lung cancer among cancer related deaths. Gastric carcinoma incidence varies geographically, with highest rates in Japan and Europe. Rates are rising in India.

In Gastric cancer male preponderance is seen and sex ratio is 2:1 , age also increases the incidence progressively, and highest incidence is during the seventh decade. Study on people who migrated from high incidence areas to low incidence areas suggest that environmental exposure , cultural or genetic factor also predispose to gastric cancer. There is change in trend in the anatomic location of gastric cancer from distal gastric unit to proximal gastric unit in past 30 years. The carcinoma of OG junction is increasing , whereas in other area s has decreased.

Risk Factors

Studies on diet reveal the following risk factors:

1. animal protein and fat low diet

2, complex carbohydrates rich diet.

3. meats and fish which are salted.

4.with high levels of nitrates and *H. pylori* in drinking water .

Diets protective for gastric carcinoma are the consumption of :

1. greeneries,

2. citrus like lemon

3. fiber rich breads .

Vitamin C and β-carotene available in fruits has antioxidants, and ascorbic acid prevents conversion of nitrates to nitrites , a well known risk factor

The presence of IgG antibodies against *H. pylori* correlates with the incidence, mortality of stomach cancer. In H.pylori infection with the *cagA* strain, mucosal inflammation is more compared to *cagA*-

negative strains and risk for gastric cancer is more . Interleukin-1 gene cluster polymorphisms are risk factors for hypochlorhydria and gastric cancer.

The link between prior stomach operation for benign disease and gastric cancer was reported by Balfour in 1922. Atrophic gastritis along with gastritis cystica profunda is associated with dysplasia in 5% of patients, for which endoscopy is indicatedas surveillance

Pernicious anemia , autoimmune inflammation of oxyntic mucosa raises gastric cancer risk, like other chronic inflammatory states.. Achlorhydria is pathognomonic due to destruction of chief and parietal cells resulting in atrophiuc mucosa , antral and intestinal metaplasia.

Hyperplastic polyps,which are benign are increased risk for gastric cancer because of their occurrence in gastritis.

Adenomatous polyps are at higher risk for malignancy. Pedunculated lesions are removed endoscopically which is adequate if margeins are negative but If a sessile and large >2 cm polyp has a malignant focus, surgery is required.

Genetic abnormalities with association with gastric carcinoma are:

1. oncogene activation

2. tumor suppressor genes are inactivated

3. cellular adhesion reduction,

4. telomerase reactivation, and

5. presence of microsatellite instability.

The c-*met* proto-oncogene, k-*sam* and c-*erbB(HER2/NEU) are overexpressed* oncogenes. The *p53* and *p16* are inactivated stomach cancers. Mutations of Adenomatous polyposis coli gene are common in intestinal-type stomach cancers.

Pathology

Adeno carcinomas are s95% of all malignant stomach neoplasms are . Other histologic types include

1.squamous cell carcinoma,

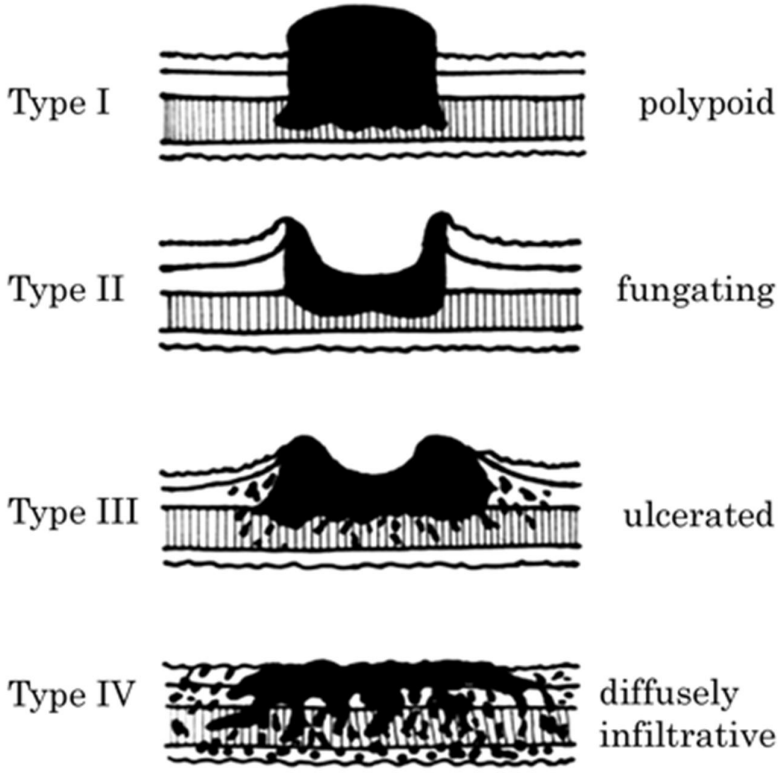
2.adenoacanthoma,

3. carcinoid tumors,

4. GI stromal tumors, and

5. lymphoma.

The Borrmann classification system developed in 1926 is for endoscopic findings. It divides gastric into 5 types depending on macroscopic appearance of lesions.



Linitis plastica is type 4 carcinoma as it involves entire thickness of stomach. The histologic classification system by Borders in 1942 classified gastric carcinomas based on

1. cellular differentiation degree

2. morphology, and

Ranging from 1 (WDC) to 4 (anaplastic).

Lauren in 1965 classified gastric adenocarcinoma into intestinal or diffuse types based on histology . The intestinal variant occurs fromprecancerous condition such as atrophic mucosa or intestinal metaplasia. Men are most commonly affected than women..

INTESTINAL	**DIFFUSE**
Environmental	Familial
Gastric atrophy, intestinal metaplasia	Blood type A
Men >women	Women >men
Increasing incidence with age	Younger age group

Gland formation	Poorly differentiated, signet ring cells
Hematogenous spread	Transmural/lymphatic spread
Microsatellite instability *APC* gene mutations	Decreased E-cadherin
p53, p16 inactivation	*p53, p16* inactivation

The diffuse gastric carcinoma is:

1. poorly differentiated,

2. no gland formation, and

3.presence of signet ring cells.

4. spread submucosally

5. less inflammatory infiltration, and

6.metastasizes early

7. association with blood type A and familial occurrences.

American Joint Cancer Commission (AJCC) tumor node metastases (TNM) staging system.

CATEGORY	CRITERIA
Primary Tumor (T)	
TX	Primary tumor not assessible
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or muscularis mucosae OR SUBMUCOSA
T2	Tumor invades MUSCULARIS PROPRIA
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures

CATEGORY	CRITERIA
T4a T4b	Tumor invades serosa Tumour involves adjacent structures
Regional Lymph Nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in more than 7 regional lymph nodes
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

TABLE 3 Anatomic stage/prognostic groups, gastric cancer

Stage 0 Tis N0 M0

Stage IA T1 N0 M0

Stage IB

T2 N0 M0

T1 N1 M0

Stage 2A

T3 N0 M0

T2 N1 M0

T1 N2 M0

Stage 2B

T4a N0 M0/T3 N1 M0

T2 N2 M0/T1 N3 M0

Stage 3A T4a N1 M0 /T3 N2 M0

T2 N3 M0

Stage3B- T4b N0 or N1 M0

T4a N2 M0

T3 N3 M0

Stage3C- T4b N2 or N3 M0

T4a N3 M0

Stage 4- Any T Any N M1

Clinical Presentation

Gastric adenocarcinoma uaually presents at late stages in view of vague symptoms like epigastric discomfort and indigestion, which usually diagnosed as gastritis,treated symptomatically. Advanced disease presents with loss of weight and appetite, fatigue, or vomiting.

Gastroesophageal junction tumors present with swallowing difficulty, antral malignancy present as GOO gastric outlet obstruction. Linitis plastica leads to early satiety

Patients come with following a palpable epigastric mass, supraclavicular node (Virchow's) or periumbilical aka Sister Mary Joseph's lymph node, pouch of doughlas deposits (Blummer's shelf), or ovarian mass aka Krukenberg's tumor.

Preoperative Evaluation

When stomach cancer diagnosis is considered , flexible oesophagogastroduodeno endoscopy is the investigation of choice. During endoscopy, multiple biopsy samples (six or more) should be taken around ulcer . When multiple biopsy specimens are taken , sensitivity of procedure nears 98%.. Also , the size, location, and tumor morphology is noted. In selected patients with advanced stages, esophagogastroduodenoscopy plays a palliative role through laser ablation, dilation, or tumor stenting.

Endo usg is used to stage early gastric cancers.After confirmation of gastric cancer, CBC, RFT, AND LFT, coagulation profile, CXR, and CT scan abdomen. In women, a pelvic CT scan or ultrasound is MUST. CT chest is needed for proximal gastric cancers. CT detects metastasis and malignant ascites. The major limitations of CT are detection of small (<5 mm) mets in the surface of liver or on peritoneum.Diagnostic laparoscopy is the next logical step in evaluation. Laparoscopy can detect metastasis in 20% to 40% of patients judged as eligible for curative resection.

Subjecting the diagnostic peritoneal lavage fluid for cytology may reveal carcinamatous deposits, just like with macroscopic stage IV disease.

The term *R status* by Hermanek in 1994 describes the tumor status following resection.

R0 - microscopically margin-negative resection

R1 macroscopic margin free, but microscopic margins positive for tumor.

R2 indicates gross residual disease.

Table 47-9 -- Grouping of Regional Lymph Nodes by Location of Primary Tumor According to Japanese Classification of Gastric Carcinoma

		LOCATION OF PRIMARY TUMOR IN STOMACH

LYMPH NODE STATION (NO.)	DESCRIPTION	Upper Third	Middle Third	Lower Third
1	Right paracardial	1	1	2
2	Left paracardial	1	3	M
3	Lesser curvature	1	1	1
4sa	Short gastric	1	3	M
4sb	Left gastroepiploic	1	1	3
4d	Right gastroepiploic	2	1	1
5	Suprapyloric	3	1	1
6	Infrapyloric	3	1	1
7	Left gastric artery	2	2	2
8a	Anterior comm. Hepatic	2	2	2
8p	Posterior comm.	3	3	3

		LOCATION OF PRIMARY TUMOR IN STOMACH		
LYMPH NODE STATION (NO.)	**DESCRIPTION**	**Upper Third**	**Middle Third**	**Lower Third**
	Hepatic			
9	Celiac artery	2	2	2
10	Splenic hilum	2	3	M
11p	Proximal splenic	2	2	2
11d	Distal splenic	2	3	M
12a	Left hepatoduodenal	3	2	2
12b,p	Posterior hepatoduodenal	3	3	3
13	Retropancreatic	M	3	3
14v	Superior mesenteric vein	M	3	2

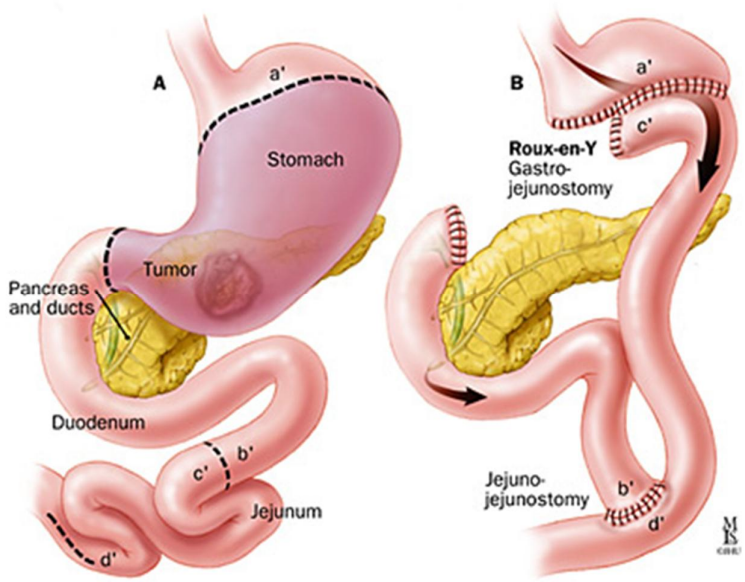
		LOCATION OF PRIMARY TUMOR IN STOMACH		
LYMPH NODE STATION (NO.)	**DESCRIPTION**	**Upper Third**	**Middle Third**	**Lower Third**
14a	Superior mesenteric artery	M	M	M
15	Middle colic	M	M	M
16al	Aortic hiatus	3	M	M
16a2,b1	Para-aortic, middle	M	3	3
16b2	Para-aortic, caudal	M	M	M

M, lymph nodes regarded as distant metastasis.

Surgical Treatment

The surgical management of gastric cancer is tailored according to the spread and location of disease. Aggressive surgical resection is justified only in absence of metastasis. AsJ Gastric tumors have extensive intramural spread, resection margins should be at least 6 cm from the tumor mass

Proximal gastric unit comprises for 30% to 50% of all gastric cancers. For proximal lesions, either total gastrectomy or oesophagogastrectomy done



Fig,subtotal gastrectomy with roux –en-y gaso jejunostomy with jejunojejunostomy

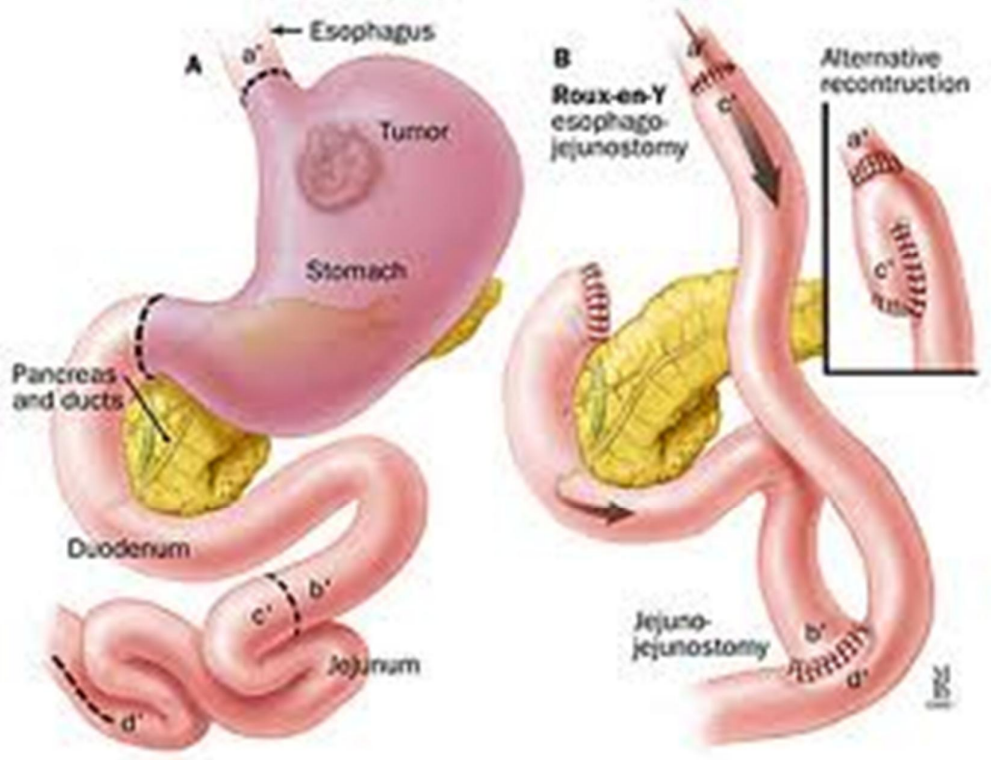
Distal gastric unit account for about 35% of all gastric cancers. Subtotal gastrectomy is done for whom a negative margin resection is achieved with same 6 cms margin.

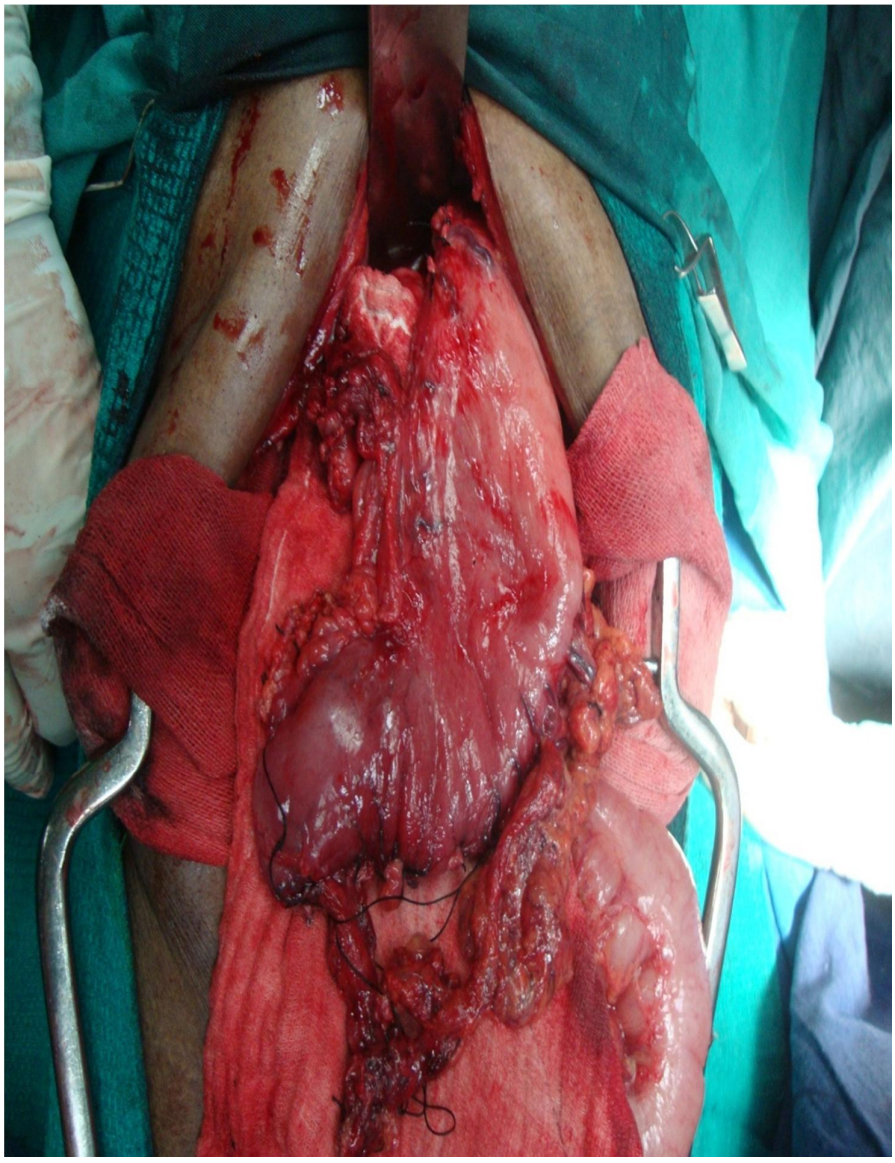
The role of extended lymphadenectomy are best described by the Japanese, The groupings, according to primary site,

1. D1 resection means complete removal of group 1 nodes,

2. D2 dissection -group 1 and 2,

3. D3 resection - D2 resection and removal of para-aortic lymph nodes.





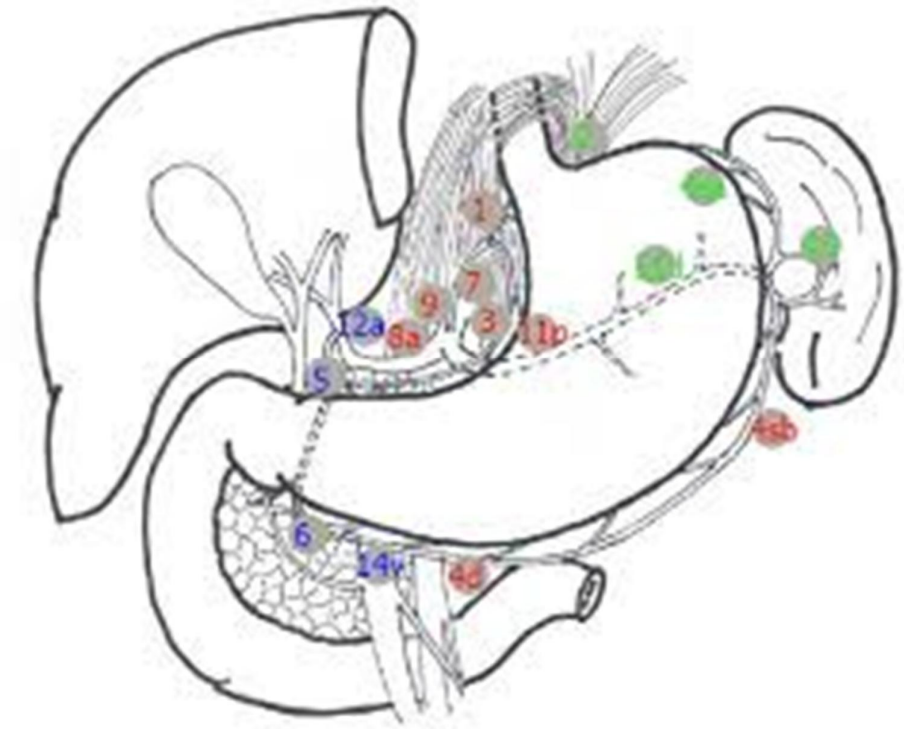
pic 1. Total gastrectomy

Splenectomy is now not recommended for gastrectomy for cancer because increased morbidity and mortality

Extended D2 lymph node dissection is routine procedure in Japan , proved a survival benefit over D1 dissections[] Extended lymph node dissections for stomach cancer is performed at higher centers as a part of clinical trial .

Palliative Treatment

Nearly half of patients present with stage 4 disease, necessitating palliative surgery.Surgical palliation includes resection/ bypass alone or with endoscopic, and radiotherapy techniques. Non surgical procedure include laser recannulization ,endoscopic dilation +/- stent placement. Patients who undergo stent placement for obstruction frequently take solid foods ,also don't require additional interventions.



T reatment protocols: Treatment plans should be planned with tumour board based on stage of disease, surgical fitness , the preference of patient and his comorbidities

Stage 0 to IA

- Endoscopic mucosal resection / surgery is treatment of choice early stage gastric cancer; but complete surgical resection gives long-term survivial.

Stage IB to IIIC, potentially resectable, medically fit

- Perioperative, neoadjuvant chemotherapy / chemo radiotherapy followed by surgery done

Stage IB to IIIC, potentially resectable, medically unfit

- Chemoradiotherapy or chemotherapy

Stage IV

- Chemotherapy for metastatic disease; local therapy is not indicated

NEOADJUVANT CHEMOTHERAPY:

- Paclitaxel DOSE 50 mg/m^2 IV on day 1 **;**carboplatin IV on day 1; weekly for 5wk[3, 4] **or**
- Cisplatin 75-100 mg/m^2 IV on day 1; 5-fluorouracil (750-1000 mg/m^2/day IV continuous on days 1-4 and 29-32 IN single 35 day cycle[6]**or**
- Cisplatin 30 mg/m^2 IV on day 1 **;** capecitabine 800 mg/m^2 PO BID on days 1-5; weekly for 5wk[7]

PERIOPERATIVE CHEMOTHERAPY:

Treatment IS 3 cycles PREOPERATIVELY and 3 cycles POSTOPERATIVELY, for adenocarcinoma of the distal esophagus or og junction.[1]

- Epirubicin 50 mg/m^2 IV on day 1 ; cisplatin 60 mg/m^2 IV on day 1;5-FU 200 mg/m^2/day IV continuous daily for days 1-21; every 21d cycle 1-3 preoperatively and cycles 4-6 postoperatively[2

Postoperative Chemoradiotherapy Regimens

The postoperative chemoradiotherapy regimens include those for og junction.

- Leucovorin 20 mg/m^2 IVP IS GIVEN on days 1-5 **;** 5-FU 425 mg/m^2 IVP daily on days 1-5; every 28d (cycles 1, 3, and 4 given before and after radiation), for cycles 2 give leucovorin 20 mg/m^2 IVP on days 1-4 and 31-33 **plus** 5-FU 400 mg/m^2 IVP daily on days 1-4; every 35d (cycle 2 given with radiation)

First-Line Chemotherapy for Metastatic or Locally AdvaNCED CANCER

Stage IV

For HER2-NEU overexpressing adenocarcinomas[1] :

- Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, then 6 mg/kg IV; every 21d with chemotherapy[29] or
- Trastuzumab 6 mg/kg IV loading dose on day 1 of cycle 1, then 4 mg/kg IV every 14d with chemotherapy *Preferred regimens*[1]

- Docetaxel 75 mg/m^2 IV on day 1 **plus** cisplatin 75 mg/m^2 IV on day 1 **plus** 5-FU 1000 mg/m^2/day continuous IV infusion on days 1-5; every 28d[30]

Outcomes

5-year survival rates following gastric cancer diagnosis are 10% to 21%. .Patients who undergo R0 resection have a better prognosis.

Recurrence rates after gastrectomy is roughly around 40% to 80% . recurrences mostly occur within a span of 3 years. The local failure rate is highest ranging from 38% to 45%, whereas peritoneal dissemination is an important aspect of failure occurring in 54% of patients . Isolated distant metastases are rare cause most patients with metastasis have locoregional recurrence as well. Locoregional recurrence occurs at anastomosis, bed of tumour and in regional nodes. Blood spread to many sites.

Surveillance

Systematic follow up is essential cause most recurrences occur within 3 years, Follow-up should include a

1.complete history clinical examination thrice for 1st year,

then half yearly for 2 years, and then yearly once thereafter

Laboratory investigations, including complete hemogram and LFTs is obtained as clinically indicated. Many get chest x-rays as well as CT abdomen and pelvis done as routine. Yearly endoscopy is considered in patients who had subtotal resection

Her 2/neu

ERBB2, Which is well known proto-oncogene, located at 17q12(long arm of chromosome 17). HER2 derives its name based on the similarity it shares in structure of human epidermal growth factor receptor HER1. cell line from rodent glioblastoma , neural tumor type gives its name to neu. *ErbB-2* derives its name based on similarity to *ErbB* , Gene cloning reveals HER2, Neu, and ErbB-2 are encoded by same orthologs.

Protein

ErbB family consists of 4 plasma membrane-bound receptor tyrosine kinases. All four contain

1. intracellular domain.

2. transmembrane domain,

3. extracellular ligand binding domain,

Interactions occur with a multitude of signaling molecules thus exhibit both ligand-dependent and independent activity. HER2 , a well known heterodimeriser ,is the preferred dimerisation form of other ErbB receptors. Autophosphorylation of tyrosine residues occur in the cytoplasmic recpetors initiating various signaling pathways.

The other family members are

1.Epidermal growth factor receptor,

2. erbB-3 and

3. erbB-4.

Signal transduction

HER2 activates following pathways

1.protein kinase activated by mitogen

2.phosphoinositide 3-kinase

3.phospholipase c

4.protein kinase c

5.Signal transducer and transcription activation

In summary, her 2 promotes cell proliferation and opposes apoptosis actively and therefore should be under strict regulations to prevent tumorigenesis.

HER2 and cancer

Amplification or over-expression of the *ERBB2* gene mainly occurs in breast cancers around 20%. It is strongly associated poor prognosis.[6] Over-expression also occurs in

1.ovarian,

2. stomach, and

3. uterine cancer,

HER2 is accompanied by gene GRB7 amplification, associated with breast, testicular germ cell, gastroesophageal tumours.

As stated the HER2 is identified in lot of tumors of which some carry point mutations in the her 2 sequence. Substitution of valine for glutamic acid results in dimerization of this protein with absent ligand.

Drugs targeting HER2

Monoclonal antibody trastuzumab (Herceptin) tagets against her 2 and effective only in HER2 over-expressed cancers. Trastuzumab binds to HER2 resulting in increase in p27, a proliferation inhibitor

protein. Pertuzumab, also inhibits HER2 and HER3 receptors, and also approved by the FDA for combination use with trastuzumab.

NeuVax , immunotherapy based on peptide drives T cells to target and destroy cancer cells with HER2 over expression..

The expression of HER2 is being regulated in order estrogen receptors signalling. Estradiol and tamoxifen , causes estrogen receptor down-regulate HER2 expression.. However, when the ratio of the coactivator AIB-3 is greater than that of the corepressor PAX2, the expression of HER2 is upregulated in the presence of tamoxifen, which results in tamoxifen-resistant breast cancer.

Recent evidence shows HER2 signaling in responsible for resistance to the EGFR-targeted cancer drug cetuximab.

MATERIALS AND METHODS:

Our hospital is a referral centre for gastro intestinal diseases with attached institute of surgical gastroenterology. Cases of carcinoma stomach were selected randomly from from 2012 -2013:

1. Dept. Of general surgery(all 7 units)
2. Dept . of surgical gastroenterology
3. Dept . of medical oncology
4. Dept . of medical gastroenterology
5. Endoscopy clinic.

Samples were either in the form of endoscopy biopsy or gastrectomy specimens.

Samples were collected after obtaining consent from the patient and transported to pathology lab via formalin or saline containers and tissue processing.

The patients were given full knowledge of the study and explained its merits and demerits and obtained consent from them.

Tissues were mounted on paraffin blocks . then paraffin blocks were used for slide preparation one for routne histopathology thus

determining its staging , grading and margin positivity whenever possible.

The other slide is prepared for immunohistochemistry and subjected to immunohistochemistry. A thorough history and clinical examination obtained from the patient and evaluation done.

IMMUNOHISTOCHEMISTRY:

Immunohistochemistry is a golden method to demonstrate presence and proteins location in tissues by staining..

Immunohistochemical staining is based on antibodies which recognize the target protein. The antibody binds only to protein of interest in the tissues as they are highly specific. The antibody-antigen interaction is seen by chromogenic technique in which an conjugation of enzyme to antibody cleaves substrate producimg colored precipitate at location of protein

IHC-P refers to staining of fixed tissues and paraffin embedded before sectioning. The basic steps of IHC-P protocol are :

1. tissue fix and embedding

2. section cut and mount

3. removal of paraffin & rehydration of section

4. antigen retrieving

5. Immuno histo chemical stain

6. Counter stains

7. Dehydration and mount stabilising

8.microscopic examination

A. Optimisation of new Ab

1. retrieval of Ag

2. concentration of 1* Ab

3. Detecting

B. Fixing

C. paraffin removal

D. Ag retrieving

1. Buffer solutions -epitope retrieval

2. epitope retrieving methods

3. retrieving of Ag by enzymes

E. Immunohistochemical staining

1. guidelines

2. Protocols

3. Control

4. amplification of signal

F. Resource

G. Additional buffers primary and secondary reagents are obtained from the company “Thermo” and the slides used were chrome alum slides and various reagents were used.

Then the slides were observed under light microscopy and they were graded as 1+ , 2+ and 3+ based on positivity. Since the facility of fluorescent in situ hybridisation not available in our hospital, it is not done.

Table 1 – Classification of HER2/NEU expression determined by THERMO) immunochemical method.

SCORE Expression Staining Pattern

0 means Negative or No staining , or membrane staining is <10% of tumor cells.

1+ Negative A faint perceptive membrane staining detected > 10% of tumor cells. Cells are only stained in part of membrane.

2+ Positive weak complete membrane stain observed in 10% of tumor cells.

3+ Positive strong complete membrane stain observed in >10% of the tumor cells.

The evaluation of carcinoma stomach in our institution follows a protocol;

a. All patients presenting to op with vomiting/ dysphagia/melena /hematemsis/ loos of weight and appetite are subjected to thorough history and clinical examination and subejected to endocopy examination.
b. All patients presenting with abdominal pain and dyspepsia above the age of 40 years is subjected to the same and endoscopy is done as an extension of clinical examination
c. Those who are less than 40 years with abdomen pain and dyspepsia, if not resolved after initial treatment are subjected to endoscopy.

d. Those who are diagnosed to have endoscopic findings of malignancy are admitted to ward and evaluated thoroughly
e. We employ a technique of multiple biopsies from the lesion. A minimum of six bits of specimen is taken and sent for histopathological examination
f. A complete blood count, renal function tests , liver function tests, chest x ray, and ecg are obtained for the patient.
g. Pre operative planning done for the patient
h. Usg of the abdomen isdone as a screening procedure. If it shows any signs of metastasis, patients are subjected to palliative treatment
i. If usg shows no sighns of metastasis, CECT ABDOMEN is done to stage the disease if CECT also rules out metastasis,
j. A diagnostic laparoscopy is done to look for surface metastasis, peritoneal metastasis , subcentimetric metastasis
k. If all rules out out malignancy, pt is proceeded with surgery
l. A minimum of subtotal or total gastrectomy with D 2 lymphadenectomy is done as a curative procedure. And the specimen is subjected to histopathological examination

revealing the the tumour grading , staging , margins and lymphnode status and subjected to her 2/neu IHC.

m. If it is not operable, then a palliative procedure is attepted if the patients presents with obstruction, or else, patient is given chemotherapy as palliation

n. All patients who underwent surgery are subjected to adjuvant chemotherapy and followed up regularly.

TOTAL POPULATION:

50 CASES

INCLUSION CRITERIA: :

A. All cases of gastric and gastro oesophageal junction adenocarcinomas

B. Patients who are under follow up for a minimum period of six years.

EXCLUSION CRITERIA:

A. The tumours of stomach other than adenocarcinoma

B. Esophageal malignancies

C. Those who don't come for follow up.

RESULTS:

A TOTAL population of 50 cases were studied for her 2 /neu. The results od the study will be discussed as follows:

In our study ofgastric adenocarcinoma cases, there was a male preponderance. Male- 39 and female 11 and thus incidence of 78% and 22 % respectively. The results are depicted as in table 1

	male	**female**
cases	39	11

Table 1.gender distribution

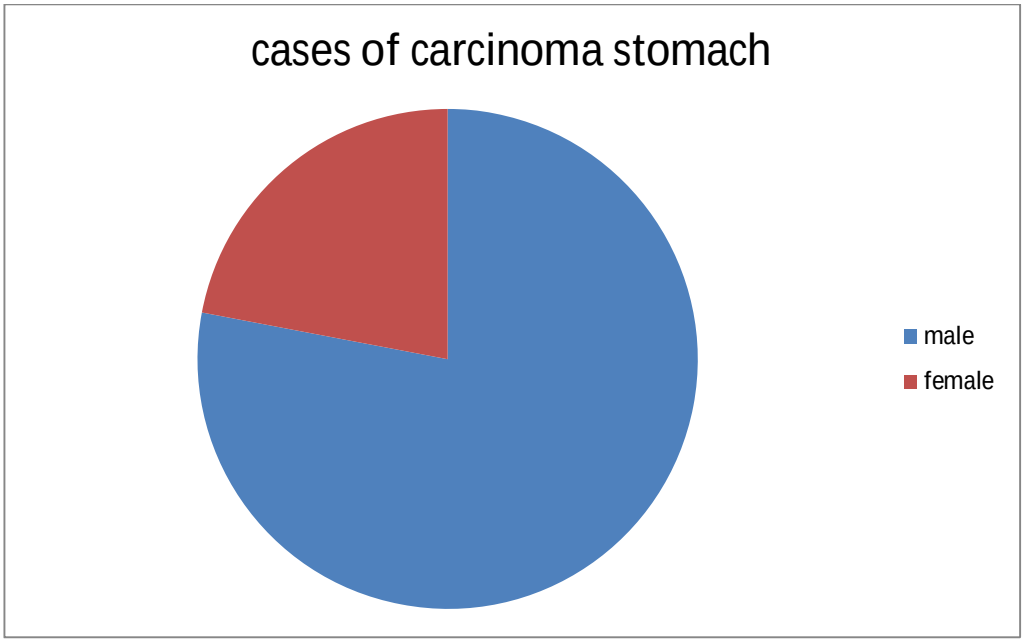


Chart 1: gender distribution

The age distribution distribution varies from 20 years to 82 years. But the peak distribution of cases were in the sixth and seventh decades 30% and 34% respectively. In females the ae distribution curve doesn't show any peaks and the incidence remains the same in almost all age groups, but in males the age incidence gradually raises as described in table 2.

The mean age of presentation is calculated to be 53. Even though ,it is a disease of old age, cases so young like 20 years of age are reported.

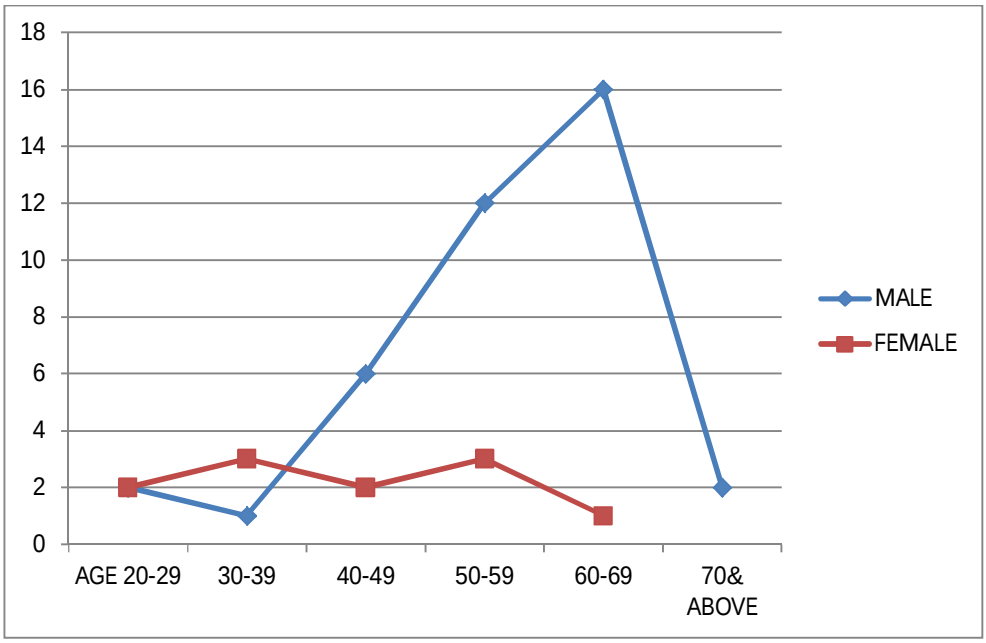


chart 2. age distribution curve

In our study, we found that there is a high incidence of antral carcinomas than proximal gastric unit cancers. Antral carcinomas are found to contribute to 48% of all gastric carcinomas. (Table 3)

Based on locality, the incidence of gastric adenocarcinomas are as follows:

1. OG JUNCTION TUMOURS-16%-8 cases
2. FUNDUS-8%-4 cases
3. BODY-22%-11 cases
4. ANTRUM 48%-24 cases

A special entity of stump carcinomas arising from gastrojejunal stomas are found to contribute 6% of all gastric adenoarcinomas.

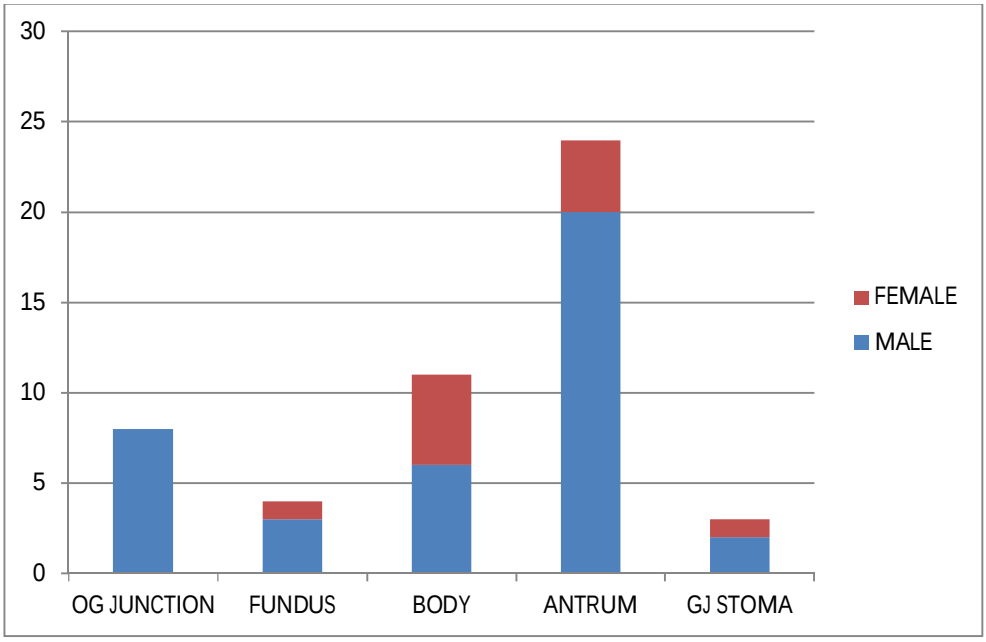


Chart 3. location of tumours and incidence.

Endoscopy was done for all cases and the findings as seen on endoscopy are as follows:

Most of them were with ulceroproliferative tumours by endoscopy. Some were found to be ulcerative like gastric ulcers . and polypoid growths were also found on endoscopy. Only one case of schirrous carcinoma was seen. (Table 4)

According to Bormann classification, the proportion of cases to be seen as in endoscopy findings are:

1. Type 1- 18%
2. Type 2-2%
3. Type 3-78%
4. Type 4-2%

Those cases which were operated , morphological comparison also has been correlating to findings on endoscopy.

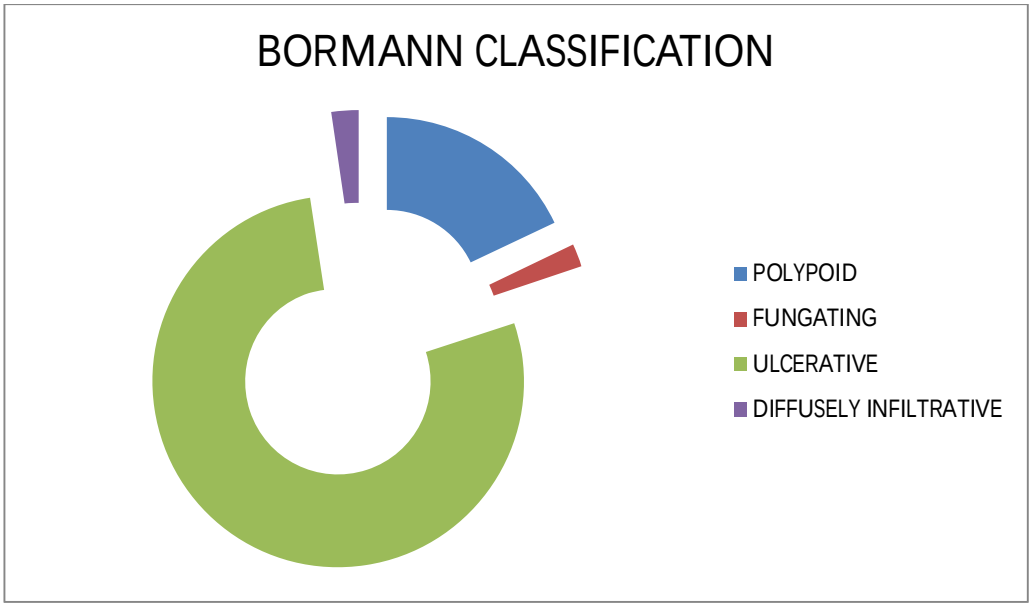


chart 4. Bormann classification proportion of cases.

Histopathological examination of the cases were done and the level of differentitation were noted and the results were as follows:

Dividing into two broad categories according to Lauren classification, it is divided as

a. Intestinal
b. Diffuse variety

Intestinal variety included both well and moderately differentiated carcinomas which are found to show some degree of gland formation and found to be occurring in equal proportions to diffuse variety.

Diffuse variety included poorly differentiated and signet ring cell carcinomas were also existing equally.- 50%

Table 2. case distribution based on laurens classification

	male	female
intestinal	19	6
Diffuse	20	5

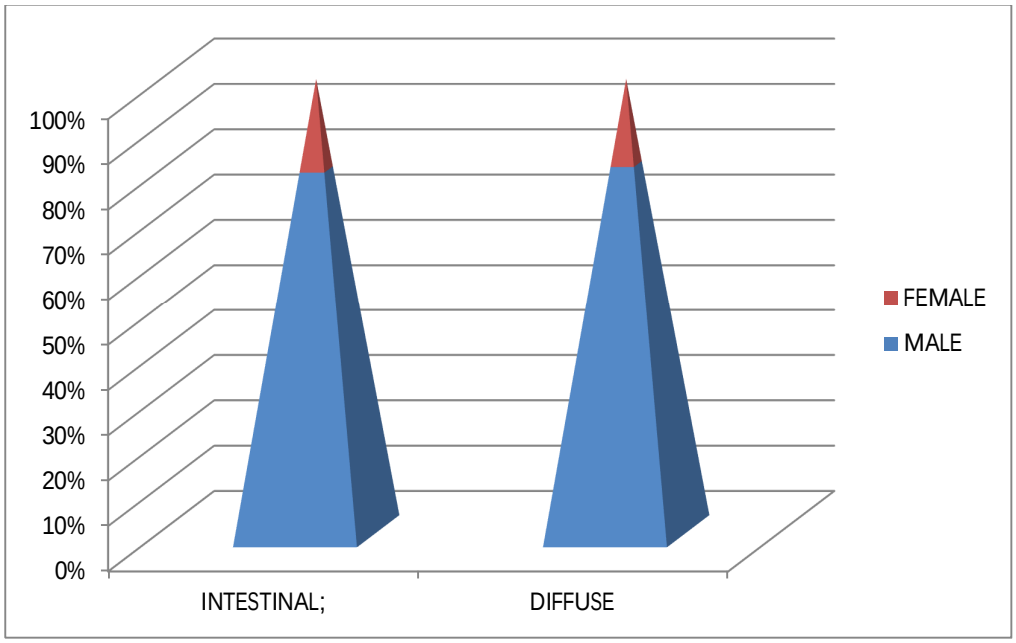


Chart 5. Laurens classification

Based on the degree of differentiation, poorly differentiated carcinomas were majority contributing to 50 % of cases. Well differentiated carcinomas were not common contributing to only 12% and moderately differentiated carcinomas was found to be 38%.(Table 6)male and female cases are proportionate according to gender distribution.

Table 3. case distribution based on differentiation

	WDC	MDC	PDC
male	5	14	20
female	1	5	5

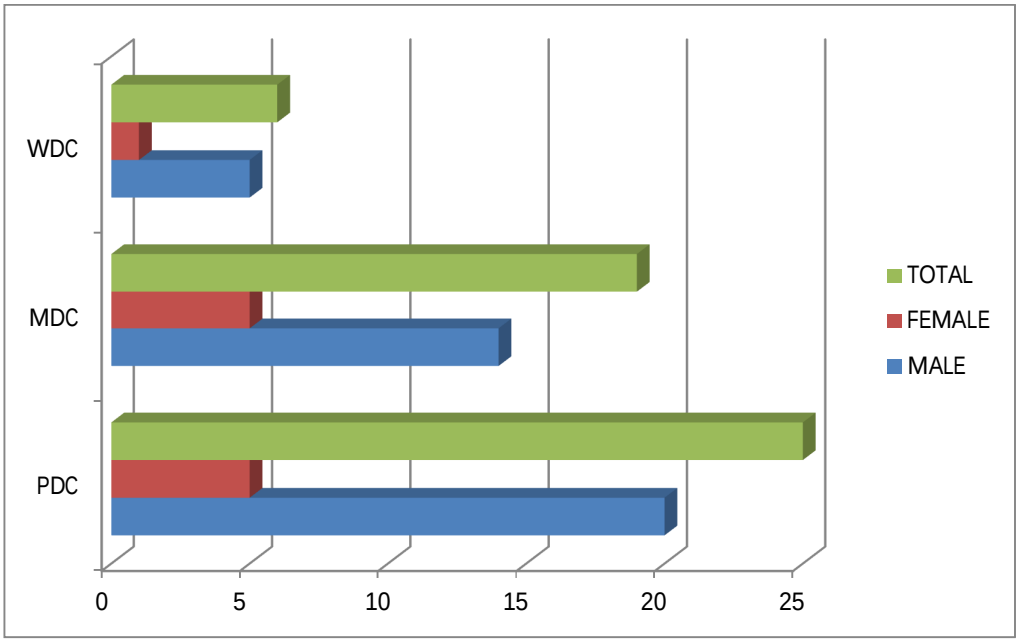


Chart 6. . case distribution based on differentiation

In our study we found that 30% of tumours were metastatic at the time of presentation.(table 7) We also found of the 15 cases found to be metatstatic, 11 are identified primarily by radio imaging techniques like USG abdomen and CECT abdomen and 4 cases (25%) which were found to be negative for metastasis were proven to be malignant by diagnostic laparoscopy.(Table 8)

We practice diagnostic laparoscopy as a protocol for those cases who were found to be negative for metastatic disease by radiological imaging.

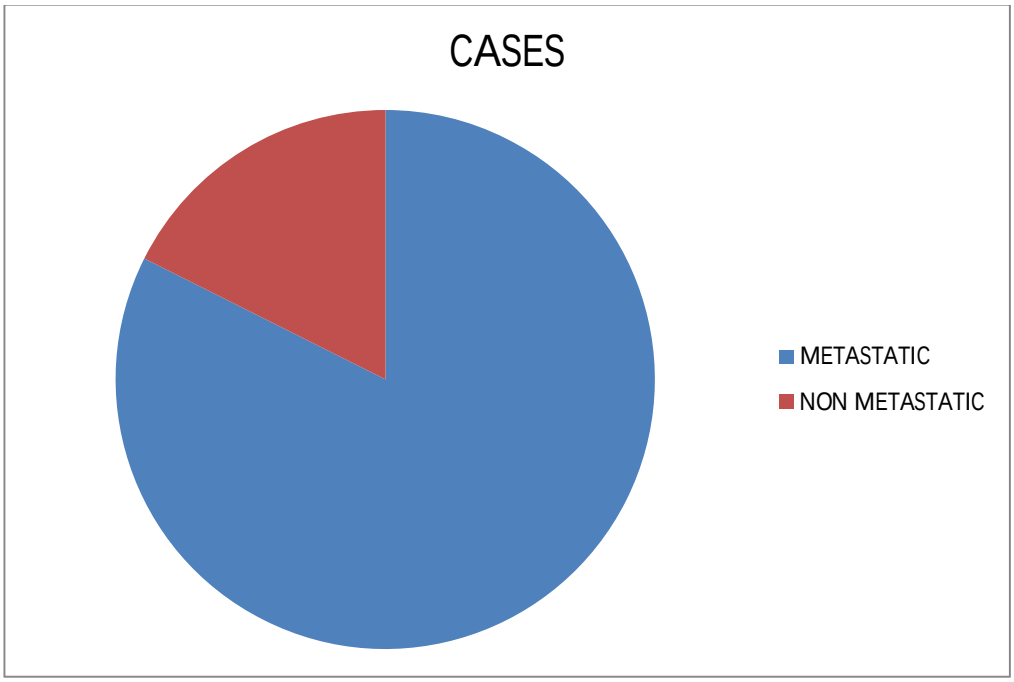


Chart 7.case proportion based on metastasis

Table 4.case proportion based on metastasis.

	imaging	D -lap
metastasis	11	4

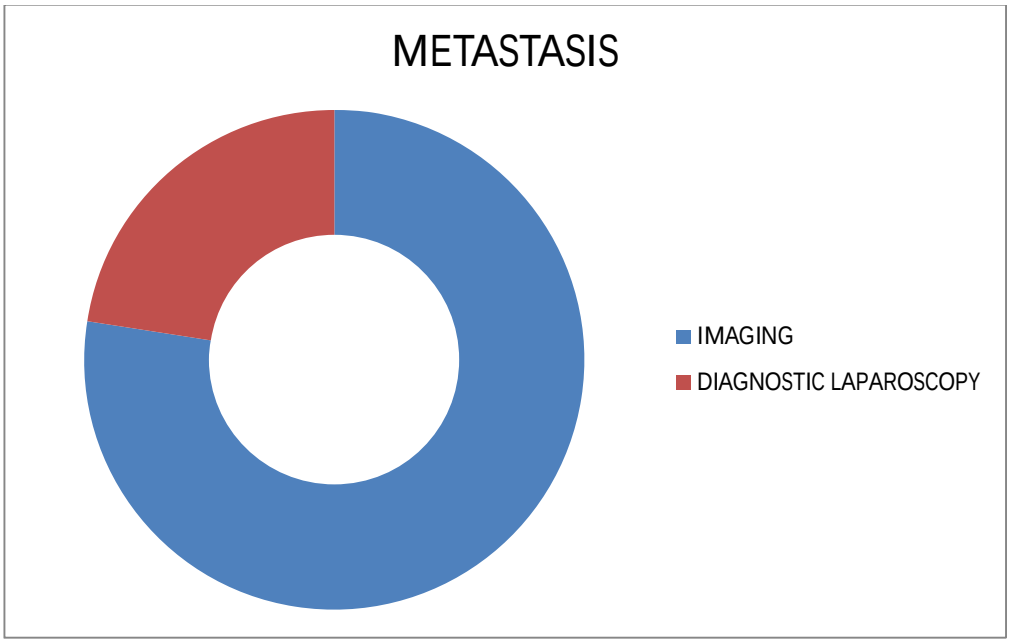


Chart 8> metastasis identification techniques

In our study, we found the clinical staging presenting to us were as follows;

	Stage 1	Stage 2	Stage 3	Stage 4
cases	1	19	16	15

Table 5. staging proportion

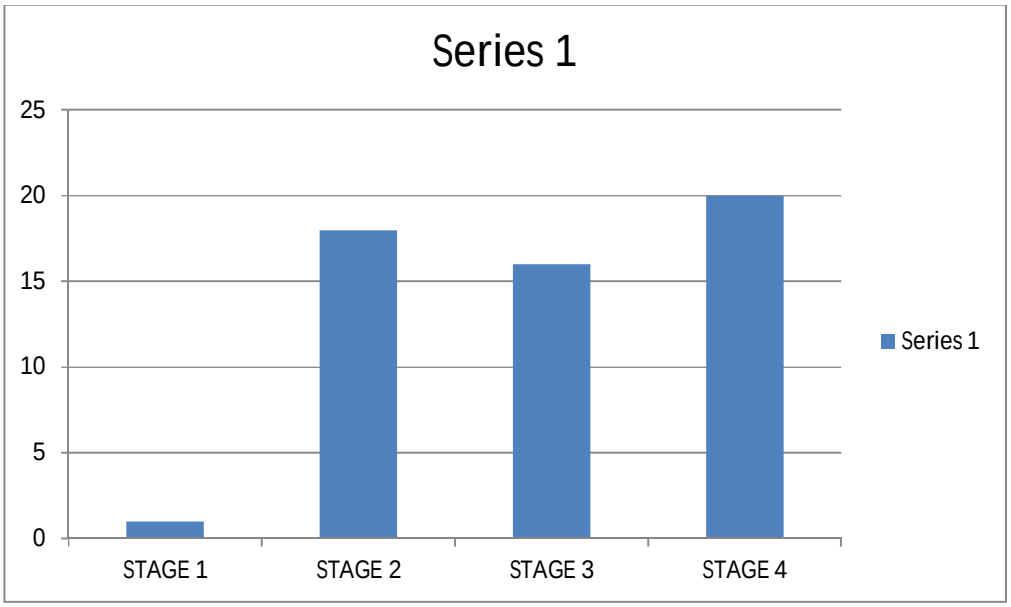


Chart .9 case distribution according to staging.

Stage 1: 1 case – 2%

Stage 2: 19 cases-38%

Stage 3: 16 cases-32%

Stage 4: 15 cases -30%

In our study , most carcinomas were found to be in stage 2 followed by stage 3. Hence most carcinomas were operable

About the treatment given , subtotal gastrectomy was the most common treatment offered contributing to 36 % (18 cases).the various treatments offered are(:table 10)

a. Subtotal gastrectomy 18 cases -36%

b. Total gatrectomy 11 cases- 22%

c. Anterior gastrojejunostomy with jejunostomy 9 cases – 18%

d. Feeding jejunostomy 12 cases -24%

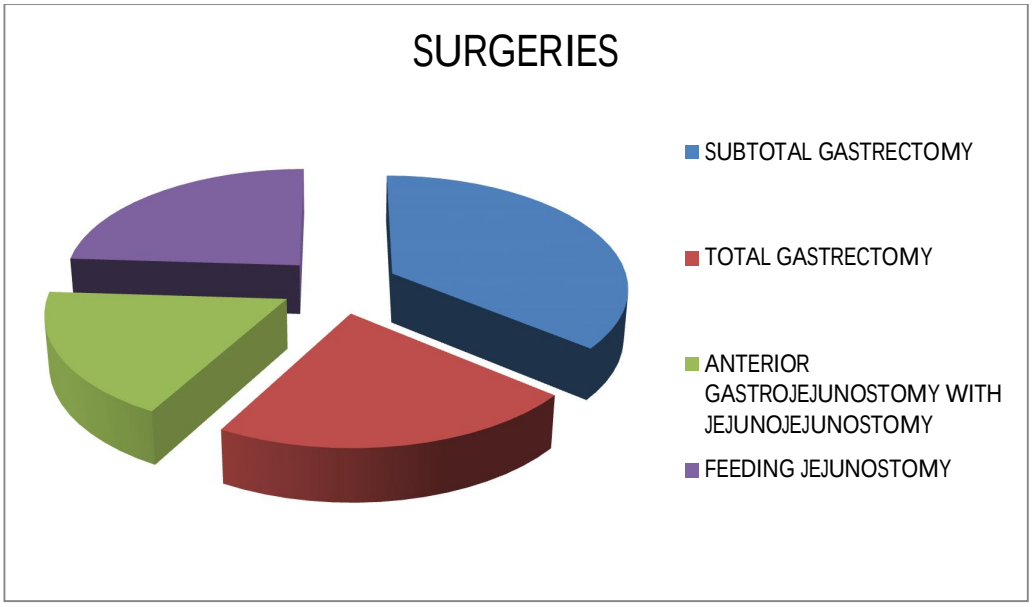


Chart 10.treatment offered

All cases were given chemotherapy . the subdivisions are:

a. adjuvant chemotherapy 28 cases-56%

b. neoadjuvant chemotherapy- 7cases -14%

c. palliative chemotherapy- 15 cases-30%

Neoadjuvant chemotherapy was offered for non metastatic patients but inoperable patients to downstage the disease

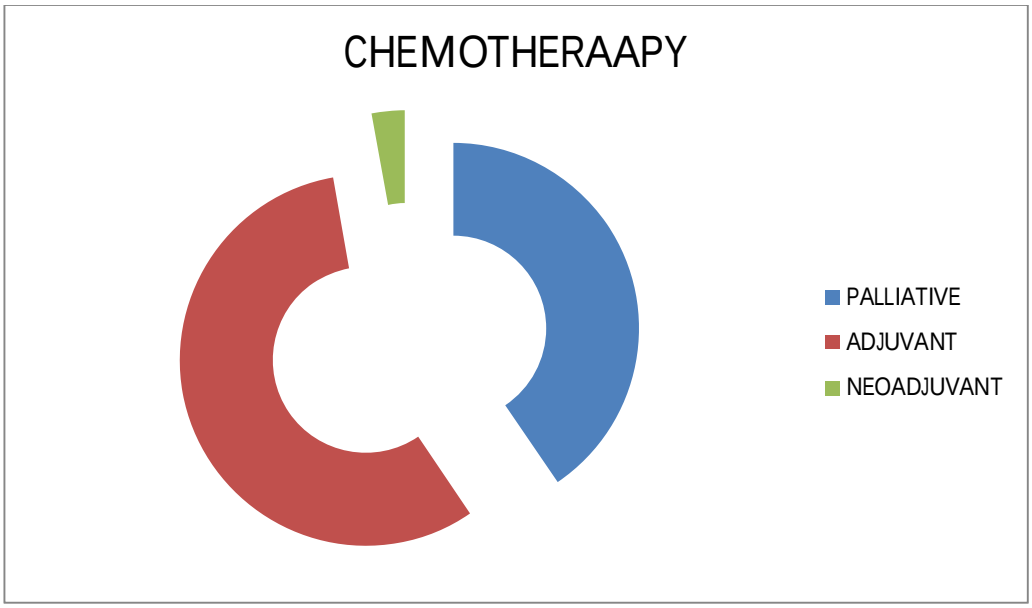
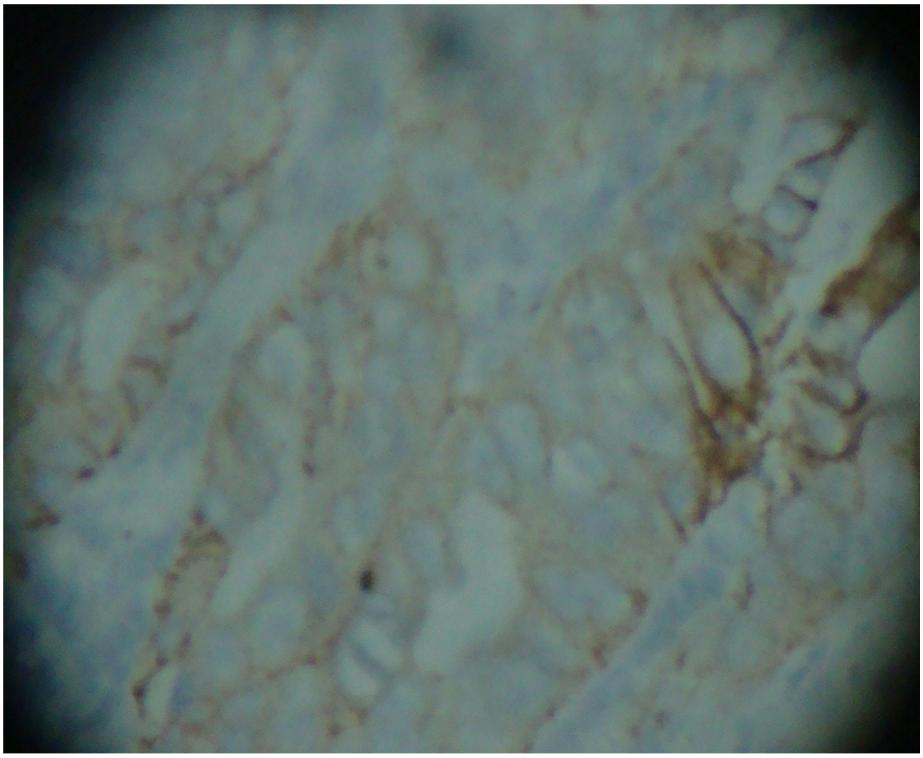


Chart 11. Chemotherapy offered

The results of immunohistochemistry for HER2/neu protein over expression is as follows(:table 12)

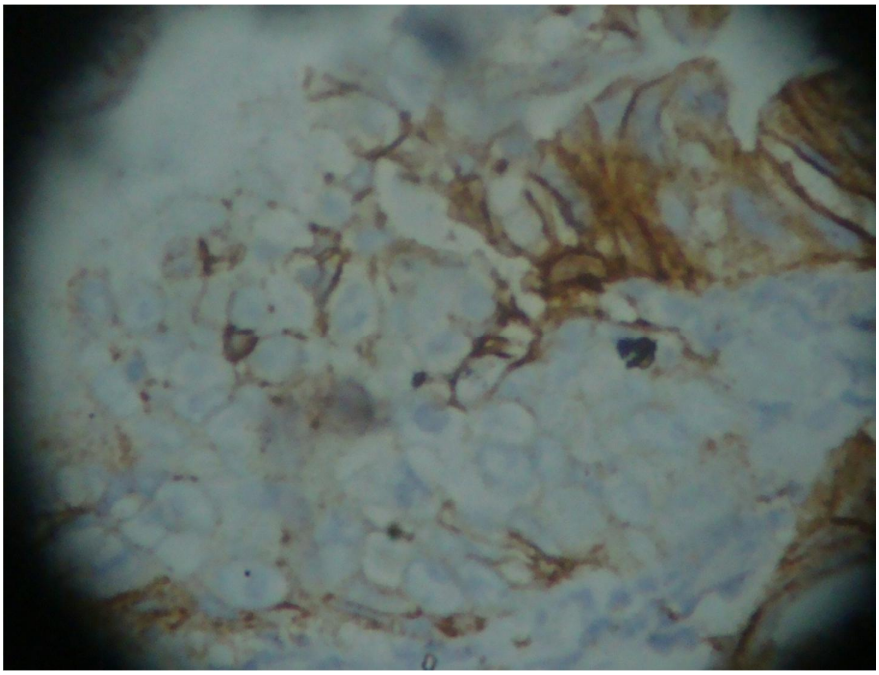
3 cases came as positive for HER/neu- 6% positive

47 cases came as negative for HER2/neu- 94% negative



pic. Her 2/neu positivity- membrane staining > 10% of cells

A strong positive in a case of poorly differentiated carcinoma . pic shows staining of membranes more than 10 % of cells.

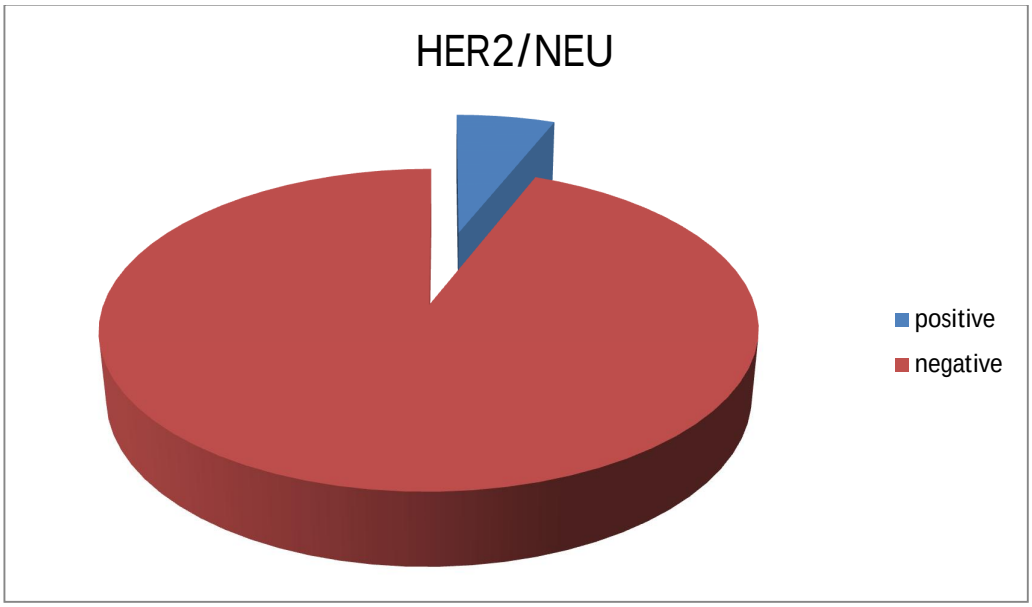


pic. Her 2/neu positivity

All the three positive cases were poorly differentiated carcinomas.

Table 12. HER2/NEU POSITIVITY

	Her2/neu +ve	-ve
cases	3	47



ALL THE THREE patients were male above 50 years.

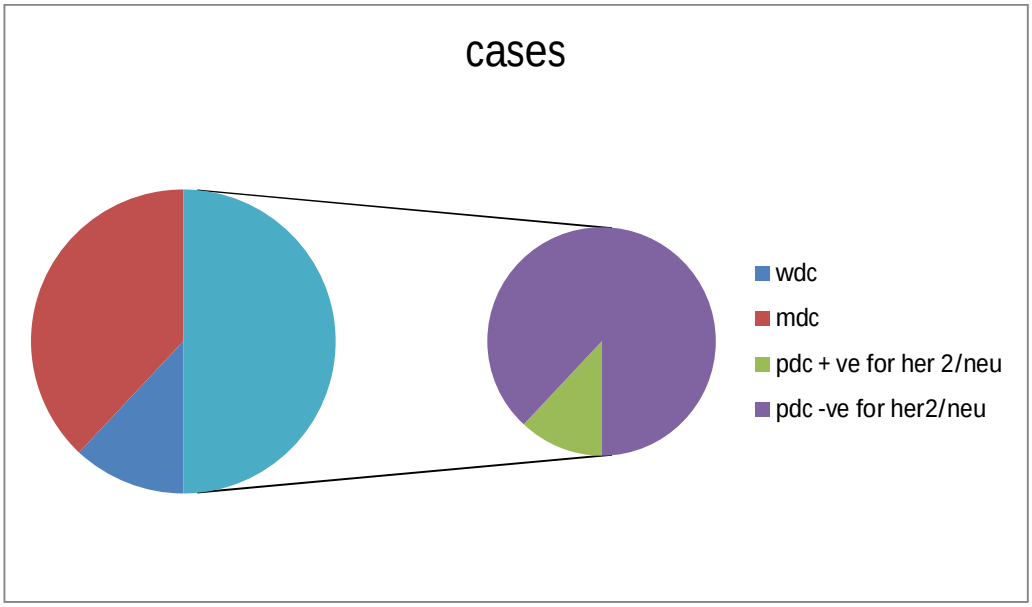
All the three positive cases were poorly differentiated adenocarcinomas.

Two of them were arising OG JUNCTION AND CARDIA and the other from ANTRUM.

Two had ulceroproliferative growth and one had polypoid growth on endoscopy.

One presented with metastatic disease and all the three presented with serosal disease.

Table 13..her 2/neu and differentiation of tumours



Thus 12% of poorly differentiated adenocarcinomas were positive for her 2 /neu.

Results also show 25 % of OG junction carcinomas(2/8) were her2/neu positive

About 10 % of carcinomas presenting with stage 3 and 4 disease are found to be positive for HER2/NEU.

Of the 2 positive cases in stage 3, who were offered, neoadjuvant chemotherapy responded poorly and subsequently developed metastasis during follow up.

In all 3 positive CURATIVE surgery could not be attempted either owing to metastasis or inoperability

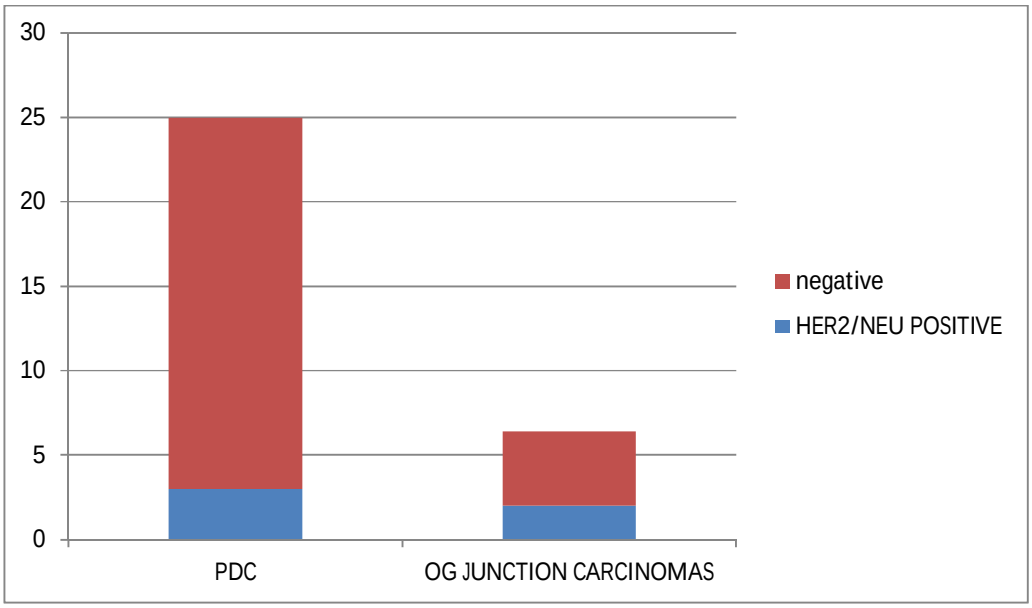


Table14. her 2/neu status comparison

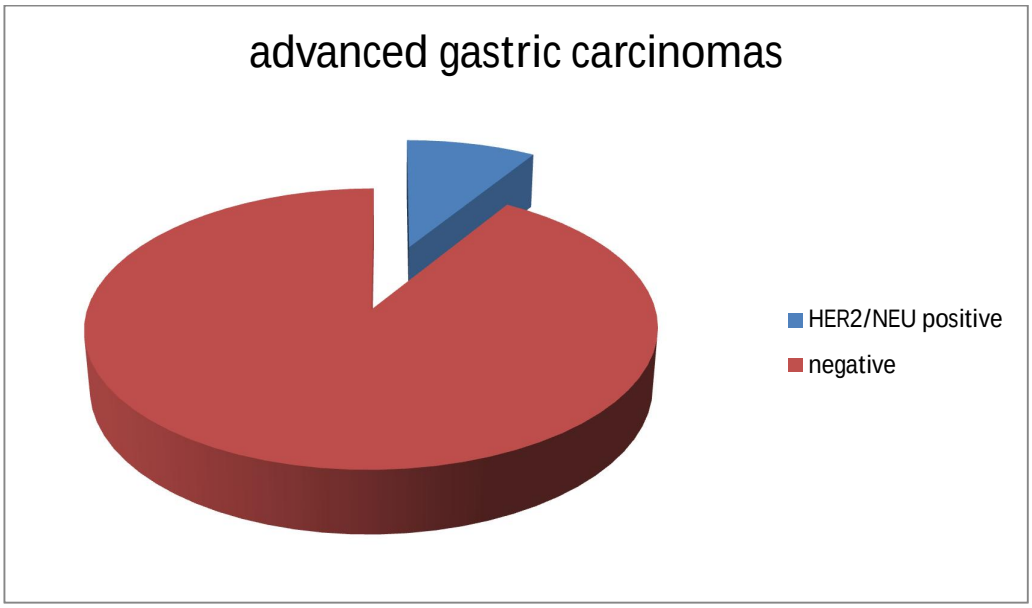


Table 15. proportion of positive cases in advanced gastric malignancies

DISCUSSION

Sex difference with male preponderance is correlating with others studies owing to risk factors such as smoking and drinkind are common among males. Gastric adeno carcinoma even thogh it is a disease of the 6^{th} and seventh decade , occurred at even young age of 20 years. A.Ieni and his colleagues studied the incidence of her2/neu in gastric carcinoma patients. The mean age in their study 68.3 years and the youngest incidence was 41 years{A.IENI, 2013 #2}. But our study reveals the mean age to be a decade less than Sicilian study. Antral carcinomas are common which could be explained by association with H.pylori infection.

Most of the carcinomas were ulceroproliferative on endoscopy. The histological type was correlating as diffusetype contributing almost 50 % of the cases in our study as in a study by Fernando and colleagues{CIRNE-LIMA, 2009 #4}.

But coming to the histopathological grading, again poorly differentiated carcinomas were common in our population contributing 50 % , but the rates were very high in Brazilian study{CIRNE-LIMA, 2009 #4}, as .91%..

Many stud ies have already documented HER2 amplification in gastric carcinoma, but association with survival or TNM status of patients is still debatable . Giuffrè *et al* encountered a HER2 overexpression rate of 21.10% in a small population done by a single pathological unit (16), and found consistent with the results that is reported elsewhere in the literature (11,19,21,25-28), in which the mean HER2 positivity rate, was 19.2% (range, 7.1-42.6%) (25) . In our study, a population from a single hospital of 50 cases and IHC done by a single pathological unit,HER2 overexpression was identified in 3 (6%) of 50 samples . This rate is much lower than the mean HER2 positivity that is previously cited (25). The incidence rate is still low taking into consideration only the IHC studies available in the literature, which is performed on 3264 AGC samples (25), the mean HER2-positive rate was 17.6% (range, 6.8-34.0%). In our population the incidence is on lower range. But in the study by Sekaran et al on Indian population, they reported a higher incidence of 44 %, but they didn't find any clinicopathological correlation. In 2008, a study from Switzerland reported 4.9% her-2/neu positivity by immunohistochemistry12The variability of her 2/neu studies in gastric cancer is explained either by genetic variations between different tumours or by diagnostic facility available. The most reliable results are from methods at protein level

detection (RT-PCR, FISH, quantitative PCR), but costs turn them unavailable for broader use in our hospital. Uchino16 detected 2% positive staining of HER2/NEU protein in poorly differentiated gastric carcinomas where as in our study it is found to be 6%, and Tsujimoto17 found no amplification of HER2/NEU gene in undifferentiated type carcinoma by Western Blot. But in our study we found HER2/NEU expression only in poorly differentiated carcinomas .

It is reported that HER2/ neu gene amplification is more common in gastroesophageal Junction carcinomas with positive rate of 24%- 32%, which is more than that (9.5% 18%) of other parts of stomach and the related mechanism remains unclear. In our study,the rate of HER2/ neu gene amplification in patients with primary cancer in OG junction is 25% ($p< 0.05$)correlating to previous reports compared to other parts of stomach.

In most studies, reports say that HER2/neu gene amplification and protein overexpression in gastric cancer does not with clinicopathologic parameters such as depth of tumor, invasion and lymph node metastasis, but were associated with the the poor prognosis of patients. But in our study, we found that all the three cases were in either stage 3 or stage 4. One case had a metastatic presentation and the other two had a serosal disease infiltrating to adjacent structures.

Becker[18]and Kameda et al.[19] described as no Her-2/Neu gene amplification was found in diffuse type gastric cancer and they found 20% of amplification in intestinal type. Correlation is high between HER2 expression - intestinal type had been reported by many authors in late 20 the century . In Finnish study,associtation of her2/neu amplification with poor carcinoma-specific survival is strong particularly more in intestinal type subgroup of cancers , but the contradicting fact is it should have better prognosis than diffuse type of gastric carcinoma.[45] the same also reported in a Korean study.[30] Finally, in ToGA trial, HER2 positivity varied by histological subtype (intestinal 34%, diffuse 6%, mixed 20%). But in our study we found no HER2/NEU positivity in intestinal type of adenocarcinomas and we found only in diffuse type carcinomas ($p<0.05$). All the three had a poor prognosis and two did not respond for chemotherapy as well. FISH and trastuzumab were not available in our institution, hence we were not able to study the response to herceptin in these patients.

CONCLUSION

There is a low prevalence of HER2/NEU positivity 6% in the population of gastric carcinoma patients studied. The low incidence can be explained by the difference in genetics in gepgraphical population or due to the diagnostic facility available. FISH could have helped more in identifying more positive cases.

HER2/neu positivity occurred more in OG junction tumours 25% and hence can be used as prognostic indicator for OGJunction subtype cancers . The positivity for HER2/neu also indicates advanced gastric carcinoma and poor prognosis and occurred mostly in poorly differentiated diffuse carcinomas contradicting to previous studies published.

This could be explained either as a result of small population studied or diagnostic facility availability. However, studies on larger population with hybridisation techniques is essential so that we could add more years to patients with poor prognosis and improve the quality of life.

In a developing country like India, where use of trastuzumab should be cost effective for our patients, more studies are warranted in this area, so as to get the broader picture of the same.

BIBLIOGRAPHY

1. Ross JS and McKenna BJ: The HER-2/neu oncogene in tumors of the gastrointestinal tract. Cancer Invest 19: 554-568, 2001.

2. Latif Z, Watters AD, Bartlett JM, *et al*: Gene amplification and overexpression of HER2 in renal cell carcinoma. BJU Int 89: 5-9, 2002.

3. Leyland-Jones B: Trastuzumab therapy for the metastatic patient: does the primary match? Ann Oncol 13: 993-994, 2002.

4. Oxley JD, Winkler MH, Gillatt DA and Peat DS: Her-2/neu oncogene amplification in clinically localised prostate cancer. J Clin Pathol 55: 118-120, 2002.

5. Haddad R, Colevas AD, Krane JF, *et al*: Herceptin in patients with advanced or metastatic salivary gland carcinomas. A phase II study. Oral Oncol 39: 724-727, 2003.LENI *et al*: HER2 STATUS IN SICILIAN A DVANCED GASTRIC CANCER 1594

6. Latif Z, Watters AD, Dunn I, *et al*: HER2/neu gene amplification and protein overexpression in G3 pT2 transitional cell carcinoma of the bladder: a role for anti-HER2 therapy? Eur J Cancer 40: 56-63, 2004.

7. Hansel DE, Ashfaq R, Rahman A, *et al*: A subset of pancreatic adenocarcinomas demonstrates coamplification of topoisomerase IIalpha and HER2/neu: use of immunolabeling and multicolor FISH for potential patient screening and treatment. Am J Clin Pathol 123: 28-35, 2005.

8. Ugocsai K, Mándoky L, Tiszlavicz L and Molnár J: Investigation of HER2 overexpression in non-small cell lung cancer. Anticancer Res 25: 3061-3066, 2005.

9. Tapia C, Savic S, Wagner U, *et al:* HER2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Res 9: R31, 2007.

10. Bang YJ, Van Cutsem E, Feyereislova A, *et al*; ToGA Trial Investigators: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376: 687-697, 2010.

11. Tanner M, Hollmén M, Junttila TT, *et al*: Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 16: 273-278, 2005.

12. Hede K: Gastric cancer: trastuzumab trial results spur search for other targets. J Natl Cancer Inst 101: 1306-1307, 2009.

13. Moelans CB, Milne AN, Morsink FH, *et al*: Low frequency of HER2 amplification and overexpression in early onset gastric cancer. Cell Oncol (Dordr) 34: 89-95, 2011.

14. Gravalos C and Jimeno A: HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 19: 1523-1529, 2008.

15. Rüschoff J, Dietel M, Baretton G, *et al*: HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 457: 299-307, 2010.

16. Giuffrè G, Ieni A, Barresi V, *et al*: HER2 status in unusual histological variants of gastric adenocarcinomas. J Clin Pathol 65: 237-241, 2012.

17. Crocetti E and AIRTUM Working Group: Incidence and mortality cancer trends of the Italian Network of Cancer Registries (AIRTUM), 1998-2005. Epidemiol Prev 33 (Suppl 1): 36-37, 2009.

18. Bosman FT, Carneiro F, Hruban RH and Theise ND (eds): WHO Classification of Tumours of the Digestive System. 4th edition. IARC, Lyon, France, 2010.

19. Albarello L, Pecciarini L and Doglioni C: HER2 testing in gastric cancer. Adv Anat Pathol 18: 53-59, 2011.

20. Barros-Silva JD, Leitão D, Afonso L, *et al*: Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 100: 487-493, 2009.

21. Marx AH, Tharun L, Muth J, *et al*: HER-2 amplification is highly homogenous in gastric cancer. Hum Pathol 40: 769-777, 2009.

22. Grabsch H, Sivakumar S, Gray S, *et al*: HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic values - conclusions from 924 cases of two independent series. Cell Oncol 32: 57-65, 2010.

23. Yan B, Yau EX, Bte Omar SS, *et al*: A study of HER2 gene amplification and protein expression in gastric cancer. J Clin Pathol 63: 839-842, 2010.

24. Jørgensen JT: Targeted HER2 treatment in advanced gastric cancer. Oncology 78: 26-33, 2010.

25. Hofmann M, Stoss O, Shi D, *et al*: Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 52: 797-805, 2008.

26. Yano T, Doi T, Ohtsu A, *et al*: Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. Oncol Rep 15: 65-71, 2006.

27. Kumashiro Y, Yao T, Aishima S, *et al*: Hepatoid adenocarcinoma of the stomach: histogenesis and progression in association with intestinal phenotype. Hum Pathol 38: 857-863, 2007.

28. Gálvez-Muñoz E, Gallego-Plazas J, Gonzalez-Orozco V, *et al*: Hepatoid adenocarcinoma of the stomach -a different histology for not so different gastric adenocarcinoma: a case report. Int Semin Surg Oncol 6: 13, 2009.

29. Jouret-Mourin A, Hoorens A, De Hertogh G, *et al*: Analysis of HER2 expression and gene amplification in adenocarcinoma of the stomach and the gastro-oesophageal junction: rationale for the Belgian way of working. Acta Gastroenterol Belg 75: 9-13, 2012

PROFORMA

A.NAME:

B.AGE

C.SEX:

D.IP.NO:

E.DATE OF ADMISSION:

F.DATE OF SURGERY:

G.DATE OF DISCHARGE:

H. HISTORY OF PRESENTING ILLNESS:

1.H/O DYSPEPSIA AND DYSPHAGIA

2. **H/O ABDOMEN PAIN:**

- SITE
- ONSET
- PROGRESSION
- RADIATION
- TYPE

- AGGRAVATING/RELIEVING FACTORS

3.H/O VOMITTING

4. H/O HEMATEMESIS

5. H/O LOSS OF WEIGHT AND LOSS OF APPETITE

6. H/O JAUNDICE

7.H/O MELENA

I.PAST HISTORY:

H/O DM/SHT/ASTHMA/TB/EPILEPSY/IHD

H/O PREVIOUS SIMILAR/MEDICAL/SURGICAL ILLNESS

J.PERSONAL HISTORY:

H/O INTAKE OF SALTY FISH, SMOKED FOOD

H/O DRUG INTAKE

H/O SMOKING OR ALCOHOLIC

K.FAMILY HISTORY:

L.CLINICAL EXAMINATION:

M.GENERAL EXAMINATION

N.SYSTEMIC EXAMINATION:

- CVS:
- RS:
- PER ABDOMEN:

CNS:

O: CLINICAL DIAGNOSIS

INVESTIGATIONS:

P. ENDOSCOPY AND BIOPSY:

SITE:

1. OG JUNCTION
2. FUNDUS
3. BODY
4. ANTRUM
5. GJ STOMA

Q . HER 2/NEU EXPRESSION IN BIOPSY

R .CECT ABDOMEN

S. ROUTINE INVESTIGATIONS:

T. DIAGNOSTIC LAPAROSCOPY

U. STAGING

V. TREATMENT

W. COMPLICATIONS

X. CHEMOTHERAPY

Y. COMPLICATIONS

Z. FOLLOW UP

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A study on role of HER2/NEU over expression in gastric Carcinoma in south Indian population

Principal Investigator : Dr.B.S.Venkatesh

Designation : PG in M.S.(Gen.Sur)

Department : Department of General Surgery
Government Stanley Medical College,
Chennai-10

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.04.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

11/12/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

வயிற்றுப் புற்றுநோயில் **HER 2 / NEU** வின்
பங்கை கண்டறிதல்

ஆராய்ச்சி நிலையம் : பொது அறுவை சிகிச்சைப்பிரிவு
அரசு ஸ்டான் மருத்துவக் கல்லூரி
சென்னை - 600 001.

பங்கு பெறுபவரின் எண் :

பங்கு பெறுபவரின்
பெயர் மற்றும் விலாசம் :

எனக்கு வயிற்றில் புற்றுநோய் இருப்பதை மருத்துவர் மூலம் அறிந்து கொண்டேன். மேலும் அதற்கு சிகிச்சை செய்வதற்காக எக்ஸ்-ரே, மருந்து செலுத்தி சி. டி.வயிறு உடல் கூறு ஆய்வு மற்றும் என்டோஸ்கோப்பி (வயிற்றில் குழாய் போட்டு சோதனை) மூலம் திசு எடுத்து அதனை சோதனை செய்வது, அந்த திசுவில் HER2/NEU பங்கை சோதனை செய்வது ஆகியவை செய்ய வேண்டிய அவசியத்தை மருத்துவர் மூலம் அறிந்து கொண்டேன். அதற்கு முழு மனதுடன் சம்மதம் தெரிவிக்கிறேன்.

மேலும் திசுப்பரிசோதனை முடிவுகளும், என்னுடைய மற்ற பரிசோதனை முடிவுகளையும் மருத்துவரும், மருத்துவமனையும் பயன்படுத்திக் கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

இது தொடர்பான விளக்கங்களையும் விளைவுகளையும் மருத்துவர் எனக்கு தெரிந்த மொழியில் விளக்கி கூறினார்.

பங்கு பெறுபவரின் கையொப்பம் ..... இடம் ..... தேதி.....

பெற்றோர்/கணவர்/மனைவி கையொப்பம்.....

ஆய்வாளரின் கையொப்பம்..... இடம் ..... தேதி.....

சுய ஒப்புதல் படிவம்

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமைப் பொறுப்புகள்

உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் நீங்கள் முழுமையாக ஒத்துழைக்க வேண்டும் என்று உங்களைக் கேட்டுக் கொள்கிறோம். சிகிச்சையளிக்கும் மருத்துவர் அளிக்கும் அறிவுரைகளை பின்பற்ற வேண்டும் என்றும், என்னென்ன செய்ய வேண்டும், என்னென்ன செய்யக்கூடாது என்று உங்களிடம் கூறப்பட்டுள்ளவற்றிருந்து சற்றும் விலகக்கூடாது என்றும் நீங்கள் எதிர்பார்க்கப்படுகிறீர்கள்.

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமைப் பொறுப்புகள்

இந்த ஆய்வில் உங்கள் பற்கேற்பு தன்னிச்சையானது மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்விருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். எப்படியிருந்தாலும், உங்கள் உடல் நிலைக்கேற்ப உங்களுக்கு பொறுத்தமான சிகிச்சை அளிக்கப்படும். ஆய்வில் பங்கேற்க நீங்கள் மறுப்பதால், அடுத்து வரும் ஆராய்ச்சி ஆய்வுகளில் உங்கள் பங்கேற்பை மறுப்பது போன்ற எந்த வித அபராதமும் விதிக்கப்படாது. உங்களை கவனித்துக் கொள்ள மருத்துவருடன் முழுவமையாக ஒத்துழைக்க நீங்கள் சம்மதிக்க வேண்டும். எந்த ஒரு நேரத்திலும், நீங்கள் மோசமாக உணர்ந்தாலோ அல்லது வேறு ஏதேனும் உடல்நலக்குறைவு உண்டானாலோ, தயவுசெய்து உங்களை கவனித்து வரும் மருத்துவரிடம் உடனடியாக தெரிவிக்கவும். சிகிச்சை உங்களுக்குப் பொருத்தமாக இருக்காது என்று தோன்றினால் உடனடியாக நிறுத்தப்படும். உங்கள் சம்மததம் இன்றியேகூட ஆய்வு நிறுத்தப்படுவது சாத்தியமே, ஆய்வின்பொழுது ஏதேனும் புதிய தகவல் தெரியவந்தால், அதைப்பற்றி உங்கள் மருத்துவர் உங்களுக்கு தெரிவிப்பார்.

ஆய்வில் பங்கேற்பவர்/சட்டபூர்வமாக
ஏற்கப்பட்ட நபர் கையொப்பம்
அல்லது
பெருவிரல் பதிவு

MASTER CHART

NAME	AGE	SEX	IP.NO	PRE.COMP	LOCATION	BORMAN N TYPE	LAUREN TYPE	HISTOLOGY	IMAGING FOR MET	D-LAP-SURFACE METS	OPERABILITY	STAGING	TREATMEN	CHEMO	HER 2/ NEU STATUS
ARUMUGA	60	M	35324	2	BODY	3	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
GOPINATH	60	M	44639	3	ANTRUM	2	DIFFUSE	PDC	N	P		FOUR	AGJ	PALLIATIVE	NEGATIVE
RAMALING	50	M	87949	1,2	ANTRUM	3	DIFFUSE	PDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
DEIVANAYA	35	F	47567	1,2	GJ STOMA	1	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
LALITHA	29	F	40796	2,5	BODY	1	DIFFUSE	PDC	N	N	P	THREE	TOTAL	ADJUVANT	NEGATIVE
SELVAKUM	20	M	44588	1,5	OGJ,FUNDU	3	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
PRATHESH	23	M	51822	2,3	BODY, ANT	3	DIFFUSE	PDC	N	N	P	THREE	TOTAL	ADJUVANT	NEGATIVE
MOHAMM	65	M	3277	3	GJ STOMA	3	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
JAGANATH	70	M	50624	1	OGJ	1	DIFFUSE	PDC	N	N	N	THREE	FJ	NEOADJUV	POSITIVE
RAVICHAN	43	M	7395	2,3	ANTRUM	3	DIFFUSE	PDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
RAGAVAIYA	60	M	13740	3,5	GJ STOMA	3	DIFFUSE	PDC	N	N	N	THREE	TOTAL	ADJUVANT	NEGATIVE
MOORTHY	52	M	33739	1	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
SELVAM	51	M	36815	1	ANTRUM	3	DIFFUSE	PDC	N	P	N	FOUR	AGJ	PALLIATIVE	NEGATIVE
RAJ	70	M	30573	2,3	ANTRUM	3	DIFFUSE	PDC	P			FOUR	AGJ	PALLIATIVE	POSITIVE
RANGANAT	82	M	41469	1,2	BODY, FUN	4	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
RANI	43	F	53817	1,5	FUNDUS	3	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
RAJI	53	M	8072	2,3	BODY	3	DIFFUSE	PDC	P			FOUR	FJ	PALLIATIVE	NEGATIVE
DURAI	55	M	7694	2,3	BODY,FUNI	1	DIFFUSE	PDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
NARASIMM	49	M	15768	2,3	ANTRUM	1	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
JAIGANESA	60	M	2108	2,3	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
SHEIK ALAU	63	M	55817	2,5	OGJ, FUND	1	INTESTINAL	MDC	N	N	P	THREE	TOTAL	ADJUVANT	NEGATIVE
PREMA	36	F	35470	2,3	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
MARIMUTH	65	M	5674	1,5	OGJ	3	INTESTINAL	MDC	N	N	P	TWO	TOTAL	ADJUVANT	NEGATIVE
DILLI	70	M	5796	2,3	ANTRUM	3	INTESTINAL	MDC	N	P	N	FOUR	AGJ	PALLIATIVE	NEGATIVE
KALLIAPPA	78	M	5474	2,3	BODY,ANTF	3	INTESTINAL	WDC	N	N	P	ONE	TOTAL	ADJUVANT	NEGATIVE
MARIMUTH	33	M	53000	2,3,5	BODY	3	INTESTINAL	MDC	N	N	P	TWO	TOTAL	ADJUVANT	NEGATIVE
PATTAMM	65	F	55174	2,3	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
AMMAIYAF	55	M	21796	2,3,5	ANTRUM	3	INTESTINAL	MDC	N	N	P	THREE	TOTAL	ADJUVANT	NEGATIVE

ARUMUGA	53	M	36851	1,5	OG	3	DIFFUSE	PDC	N	N	N	FOUR	FJ	ADJUVANT	POSITIVE
ANANDHAI	41	M	39059	2,3	ANTRUM	2	DIFFUSE	PDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
MOHAN	52	M	39214	3,5	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
KANNIYAPF	58	M	40369	2,3	ANTRUM	3	INTESTINAL	WDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
SHANMUG	50	M	39529	3,5	ANTRUM	1	INTESTINAL	WDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
MARIMUTH	45	M	39000	3,5	ANTRUM	1	DIFFUSE	PDC	P			FOUR	AGJ	PALLIATIVE	NEGATIVE
SELVI	32	F	35202	3,5	BODY	1	DIFFUSE	PDC	N	N	P	THREE	TOTAL	ADJUVANT	NEGATIVE
KRISHNA	53	M	37747	1,2	OGJ	3	INTESTINAL	WDC	N	N	P	TWO	TOTAL	ADJUVANT	NEGATIVE
MANNAMN	55	F	30423	4	ANTRUM	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
GANGAN	70	M	32379	1,2	OGJ	3	INTESTINAL	MDC	N	N	N	THREE	FJ	ADJUVANT	NEGATIVE
NANGOOR	53	M	31781	2,3	ANTRUM	3	INTESTINAL	MDC	N	P	N	THREE	AGJ	ADJUVANT	NEGATIVE
LOGANATH	65	M	30714	2,3	ANTRUM	3	DIFFUSE	PDC	N	N	P	THREE	SUBTOTAL	ADJUVANT	NEGATIVE
DHANALAK	58	F	28328	2,3	3,4	3	INTESTINAL	WDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
PADMAVA	43	F	29578	2,3	ANTRUM	3	INTESTINAL	MDC	P			FOUR	AGJ	PALLIATIVE	NEGATIVE
MURUGAN	61	M	29004	1,5	OGJ	3	INTESTINAL	MDC	N	N	N	FOUR	FJ	PALLIATIVE	NEGATIVE
SELVANATH	40	M	26818	2,3	BODY	3	DIFFUSE	PDC	N	N	N	FOUR	SUBTOTAL	ADJUVANT	NEGATIVE
AARON	55	M	25052	1,2,3	FUNDUS,BO	3	DIFFUSE	PDC	N	N	N	FOUR	TOTAL	ADJUVANT	NEGATIVE
ISMAIL	70	M	24897	2,3	ANTRUM	3	INTESTINAL	WDC	N	N	N	FOUR	AGJ	ADJUVANT	NEGATIVE
MYMOON	29	F	27083	2,3	BODY	3	INTESTINAL	MDC	N	N	P	TWO	SUBTOTAL	ADJUVANT	NEGATIVE
NAGABHUS	53	F	26831	2,3	BODY,ANTF	3	DIFFUSE	PDC	P			FOUR	AGJ	PALLIATIVE	NEGATIVE
SHANMUG	62	M	22968	1,2	FUNDUS,BO	3	INTESTINAL	MDC	N	N	N	FOUR	FJ	NEOADJUV	NEGATIVE
ALLASAMY	65	M	25707	2,3	ANTRUM	3	INTESTINAL	MDC	N	N	P	THREE	SUBTOTAL	ADJUVANT	NEGATIVE