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Clinico-Pathological Spectrum of Adenocarcinoma of Stomach Presenting With Gastric Outlet Obstruction With Special Reference to Her 2 Neu and P53 Status in A Tertiary Care Hospital in Eastern Part of India

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Abstract

Introduction: There are approximately 990,000 new cases of gastric cancer each year, accounting for 6.8% of all malignant tumors and 738,000deaths, accounting for 8.8% of all cancer deaths[6].The average incidence of gastric carcinoma is 32.1 per 100,000 among males and 13.2 among females in Eastern Asia. A nationally representative survey in 2010 found that a total of 556400 deaths occur due to cancer in India and the mortality rate of stomach cancer is 12.6% in India[7]. The role of cancer biomarkers is to identify tumor cells at early stages and predict treatment response, ultimately leading to a favorable therapeutic outcome [11]. Her-2 gene is a proto-oncogene that is located on chromosome 17q21 & its overexpression in stomach carcinoma varies with differentiation (moderately differentiated greater than poorly differentiated) and histologic type (intestinal-type greater than diffuse type)[12]. Ognjenovic and colleagues showed significant correlation between HER2 protein expression and intragastric localisation of gastric carcinoma (P = 0.005), and the tumour grade of differentiation (P = 0.034). There was also a positive correlation between HER2 protein expression pattern and positive lymph nodes in patients with gastric carcinoma (P = 0.03)[13]. Over-expression of p53 was associated with worse overall survival (OS) as well as well-known prognostic factors such as vascular invasion and lymph nodemetastasis[16]. Present study would help to correlate between HER2 neu and P53 expression with clinico-pathological characteristics of adenocarcinoma of

stomach patients presenting with gastric outlet obstruction in the study population.

Aim and objectives

- To study modes of presentation of gastric outlet obstruction.
- To study the distribution of histological findings of adenocarcinoma of stomach causing gastric outlet obstruction.
- To study the Her 2 and P53 status of adenocarcinoma stomach causing gastric outlet obstruction.

Materials and Methods: Hospital based prospective observational study conducted in Department of gastroenterology, school of digestive and liver diseases**,** IPGMER & SSKM hospital, Kolkata with in a period of one and half year. Data was analysed by JASP software version using appropriate statistical tests.

Results: Out of 60 patients, 42 (70 %) were males, 18 (30%) were females. M: F ratio was 2.3: 1. Median age of included patients (N=60) was 56.5 years with range 20-80 years. A significant proportion {(n=33) (55%)} of the patients were in the range of 40-60 years. Majority of patients {(n=45) (75%)} presented with vomiting, abdominal pain & early satiety. Ulcero-proliferative growth was found among significant proportion (95 %) of the patients. Upper gastro-intestinal endoscopy shows a significant proportion {(n=39) (65%)} of the lesions in body and antro-pyloric region together as compared to antro-pyloric region alone. Diffuse type of lesions was found in a significant proportion (55%) of patients. Tubular variety was found in 45%. A significant proportion (96 %) of patients was found Her 2 neu status negative. Her 2 neu 2+ status & her 2 neu 3 + status was found among 2 % & 2 % respectively. All the patients were found negative P 53 status. A significant proportion 18 (30%) of the patients had no nodal involvement. Involvement of 1 node was found in 15 (25 %) of patients. More than 1 node involvement was found in 15 (25%) of patients. More than 2 nodal involvements was found in 12 (20%) of patients. Distal gastrectomy with gastrojejunostomy is done for 15 patients. Sub-total gastrectomy with gastrojejunostomy is done for 12 patients. Total gastrectomy with esophago-jejunostomy is done for 3 patients. Feeding jejunostomy performed for 6 patients who had diffuse infiltration to surrounding structures. Following surgery all of them received chemotherapy. Neoadjuvant chemotherapy given to 12 patients and scheduled for surgical resection and anastomosis. Resection was not feasible among 06 patients & they received chemotherapy only. Chemotherapy & resection both are not feasible among 06 patients. A statistically significant correlation (P <0.05) was found between younger age group (less than 40years) and diffuse variety of adenocarcinoma stomach. No statistically significant result was found between HER 2 & node status.

Conclusion: Most of the previously conducted studies are retrospective and include small number of patients. This is a prospective observational study with bigger sample size as compared to most of the previously stated studies.

Abbreviation: HER-Human Epidermal Growth Factor Receptor.

Keywords: Vomiting, Endoscopy, Distal Gastrectomy, Adenocarcinoma

Introduction

Gastric outlet obstruction is a clinical condition caused by diseases impeding gastric emptying mechanically. This can be complete or incomplete obstruction of distal stomach, pylorus or proximal duodenum[1]. The causes include both benign and malignant conditions[2].

Gastric outlet obstruction is the clinical and pathophysiological consequence of diseases producing

mechanical obstruction to gastric emptying [3]. This may be due to external compression or due to obstruction from acute oedema, scarring and fibrosis or a combination[1,4].

In the past peptic ulcer disease was more prevalent, benign causes were the most common, however, the scenario has changed dramatically with the advent of potent medical treatments like H2 receptor antagonists, proton pump inhibitors. A recent review shows that only 37% of patients with gastric outlet obstruction have benign disease and remaining patients have obstruction secondary to malignancy[5].

There are approximately 990,000 new cases of gastric cancer each year, accounting for 6.8% of all malignant tumors and 738,000deaths, accounting for 8.8% of all cancer deaths[6].The average incidence of gastric carcinoma is 32.1 per 100,000 among males and 13.2 among females in Eastern Asia. A nationally representative survey in 2010 found that a total of 556400 deaths occur due to cancer in India and the mortality rate of stomach cancer is 12.6% in India[7].

Gastric adenocarcinomas have traditionally been divided into intestinal and diffuse subtypes according to the Laurén classification based on the histological characteristics of the tumours[8]. The proximal stomach is now the most common site for gastric carcinoma in the west but in Japan and developing countries like India the distal gastric cancer (antrum 13% and pylorus 7%) still predominates[9]. In addition to gastric cancer and pyloric stenosis, other causes of gastric outlet obstruction include- adult hypertrophy of pylorus, proximal gastrointestinal tumours like leiomyoma, carcinoma head of the pancreas, ampullary cancer, duodenal cancer, cholangiocarcinoma, tuberculous pyloric stenosis, foreign bodies and bezoars like phytobezoar, trichobezoar, pancreaticobiliary disease, corrosive strictures at the pylorus, gall stone obstruction (Bouveret's syndrome), pancreatic pseudo cyst etc[10,19].

The role of cancer biomarkers is to identify tumor cells at early stages and predict treatment response, ultimately leading to a favorable therapeutic outcome. Human epidermal growth factor receptor 2 (Her-2) has tyrosine kinase activity and is a member of the epidermal growth factor receptor family.[11]Her-2 gene is a proto-oncogene that is located on chromosome 17q21. It acts as an oncogene due to its amplification, which leads to the over expression of Her-2 protein in many solid tumors. 30% of breast cancers and in 9% to 38% of gastric carcinoma patients. Overexpression in stomach carcinoma varies with differentiation (moderately differentiated greater than poorly differentiated) and histologic type (intestinal-type greater than diffuse type)[12].

Ognjenovic and colleagues showed significant correlation between HER2 protein expression and intragastric localisation of gastric carcinoma (P = 0.005), and the tumour grade of differentiation (P = 0.034). There was also a positive correlation between HER2 protein expression pattern and positive lymph nodes in patients with gastric carcinoma (P = 0.03)[13].

P53 gene is a tumor suppressor gene and is one of the first oncogenes to be identified. As a transcription factor, P53 regulates the cellular response to multiple forms of stress through a complex network that monitors genomic integrity and cellular homeostasis[14]. Rhaman observed that there were 52 cases with (73.2%) *p53* mutation. Among the 51 *H. pylori* positive cases, 41 (80%) had *p53* mutation (P = 0.033). Tumor size and lymph node status were found to be associated with the gene mutation (P = 0.05). Age also had strong correlation with the mutation (P = 0.015). Gene mutation was found mostly among the younger (≤ 40 years) group of patients (94.4%)[15].

According to those studies, over-expression of p53 was generally associated with worse overall survival (OS) as well as well-known prognostic factors such as vascular invasion and lymph nodemetastasis[16].

Present study would help to correlate between HER2 neu and P53 expression with clinico-pathological characteristics of adenocarcinoma of stomach patients presenting with gastric outlet obstruction in the study population.

Aim and objectives

- To study modes of presentation of gastric outlet obstruction.
- To study the distribution of histological findings of adenocarcinoma of stomach causing gastric outlet obstruction.
- To study the Her 2 and P53 status of adenocarcinoma stomach causing gastric outlet obstruction.

Methodology

Study area- Gastroenterology department, School of Digestive and Liver Diseases, Kolkata.

Study population- All gastric adenocarcinoma causing gastric outlet obstruction which are treated on in patient and out patient basis.

Study period- one and half years.

Sample size- all patients fulfilling the inclusion criteria.

Study design- Prospective observational study.

Inclusion Criteria

Gastric adenocarcinoma causing gastric outlet obstruction which are treated on in- patient and outpatient basis

Exclusion Criteria

1. Patients below 18 years of age,
2. Combined with other tumors or previous histories of malignancy,
3. No radiotherapy, chemotherapy, surgery was used before diagnosis.

Statistical analysis

- Data were entered in MS Excel sheet and analyzed by using SPSS statistics software
- Categorical data were represented as percentages and proportions.
- For numerical data, measure of central tendency were by mean and median while dispersion were analyzed by range, standard deviation, frequency (whichever is applicable)
- For analysis of Categorical variables: chi-square test.

Operational Definitions

Gastric Outlet Obstruction: Gastric outlet obstruction (GOO, also known as pyloric obstruction) is not a single entity; it is the clinical and pathophysiological consequence of any disease process that produces a mechanical impediment to gastric emptying.

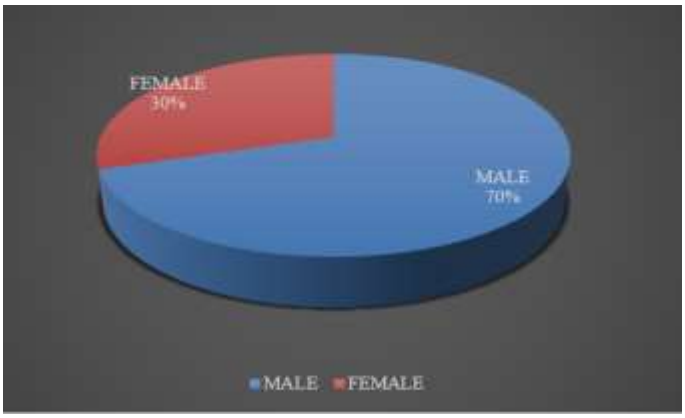
Results and Analysis

60 consecutive patients taken between January 23 and June 24.

Demographic and Clinical Features

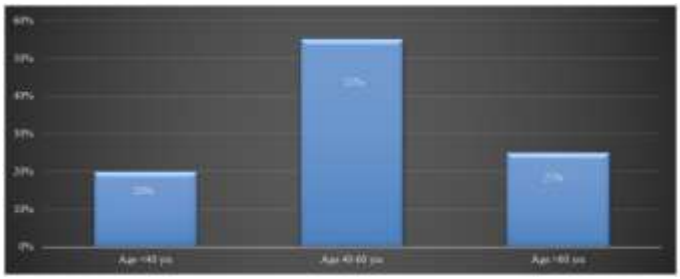
Sex Wise Distribution

Out of 60 patients, 42 (70 %) were males, 18 (30%) were females. M: F ratio was 2.3: 1.



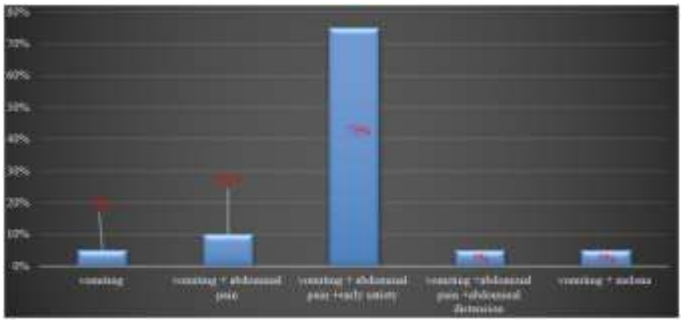
Age Wise Distribution

Median age of included patients (N=60) was 56.5 years with range 20-80 years. A significant proportion {(n=33) (55%)} of the patients were in the range of 40-60 years.



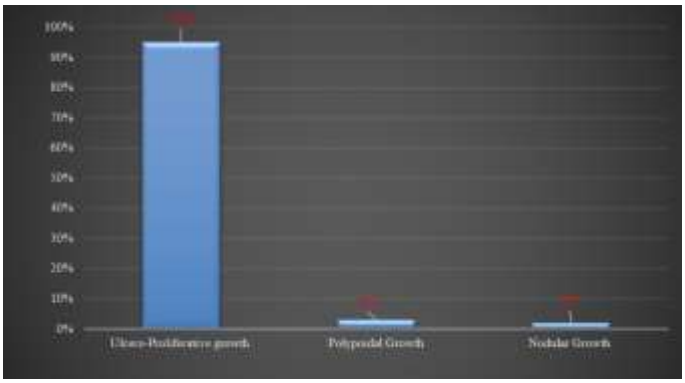
Mode of Presentation

Majority of patients {(n=45) (75%)} presented with vomiting, abdominal pain & early satiety.



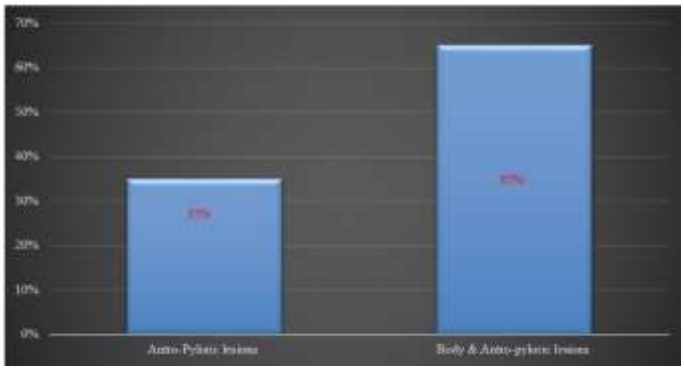
Endoscopic Findings

Ulcero-proliferative growth was found among significant proportion (95 %) of the patients.



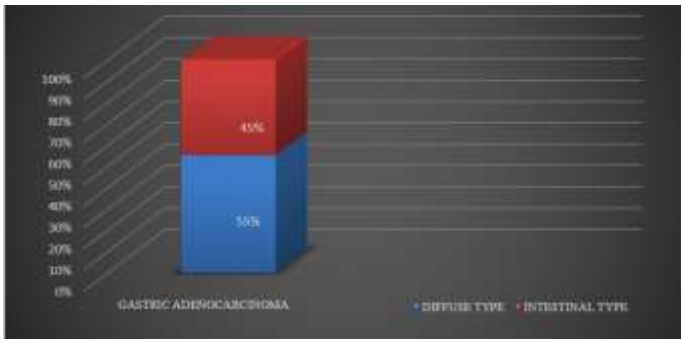
Distribution of Lesions

Upper gastro-intestinal endoscopy shows a significant proportion {(n=39) (65%)}of the lesions in body and antro-pyloric region together as compared to antro-pyloric region alone.



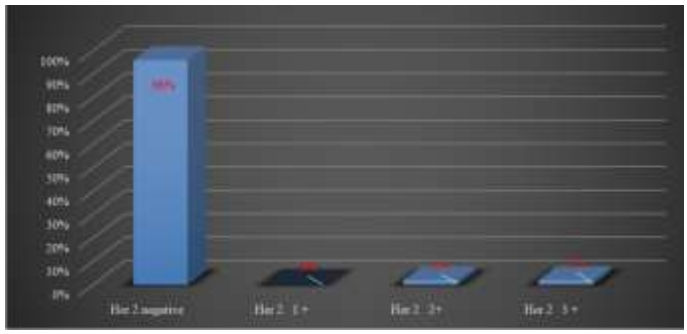
HPE Findings

Diffuse type of lesions was found in a significant proportion (55%) of patients. Tubular variety was found in 45%.

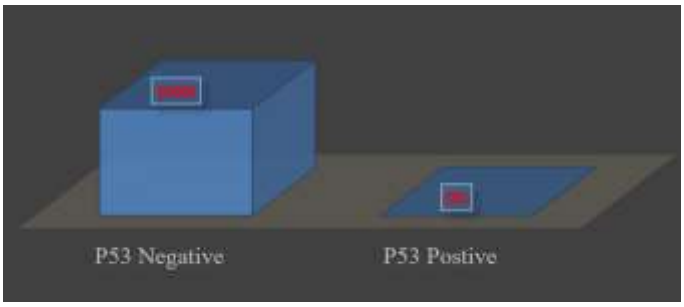


Her 2 Neu Status

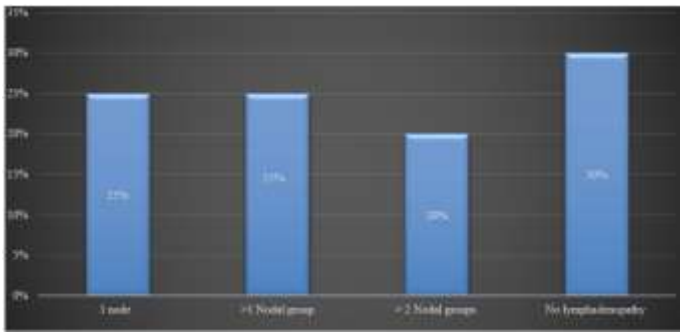
A significant proportion (96 %) of patients was found Her 2 neu status negative. Her 2 neu 2+ status & her 2 neu 3 + status was found among 2 % & 2 % respectively.



P53 Status: All the patients were found negative P 53 status.

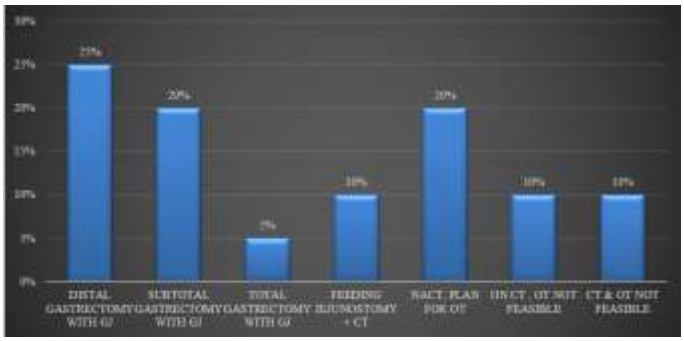


Patterns of Nodal Involvement: A significant proportion 18 (30%) of the patients had no nodal involvement. Involvement of 1 node was found in 15 (25 %) of patients. More than 1 node involvement was found in 15 (25%) of patients. More than 2 nodal involvements were found in 12 (20%) of patients



Types of Surgical Procedures & Other Management Done in This Study

Distal gastrectomy with gastrojejunostomy is done for 15 patients. Subtotal gastrectomy with gastrojejunostomy is done for 12 patients. Total gastrectomy with esophagojejunostomy is done for 3 patients. Feeding jejunostomy performed for 6 patients who had diffuse infiltration to surrounding structures. Following surgery all of them received chemotherapy. Neoadjuvant chemotherapy given to 12 patients and scheduled for surgical resection and anastomosis. Resection was not feasible among 06 patients & they received chemotherapy only. Chemotherapy & resection both are not feasible among 06 patients.



Age Wise Distribution with Diffuse & Intestinal Types

A statistically significant result (P <0.05) was found between younger age group (less than 40 years) and diffuse variety of adenocarcinoma stomach.

Contingency Tables

AGE<40 =1,AGE 40-60=2,AGE>60	Diffuse type=1, Intestinal type=2 1	2	Total
1	11	1	12
2	14	19	33
3	8	7	15
Total	33	27	60

Chi-Squared Tests

	Value	df	P
X²	8.644	2	0.013
N	60		

On Follow-Up

Distal gastrectomy with gastrojejunostomy is done for 15 patients. Out of 15, till date 10 patients died & 5 patients are alive. Out of 5 patients, all of them are receiving chemotherapy. One of patient is having ascites, presently under follow-up. Subtotal gastrectomy with gastrojejunostomy is done for 12 patients. Out of 12, till date 6 patients died & 6 patients are alive. All of them are on chemotherapy. One of the patient having deep jaundice and on evaluation multiple liver metastatic lesions are found. Total gastrectomy with esophago-jejunostomy is done for 3 patients. Out of 3, 2 patients expired & 1 patient is alive. Currently patient is on chemotherapy and received 3 cycles of chemotherapy. Feeding jejunostomy performed for 6 patients who had diffuse infiltration to surrounding structures. On average 6-9 months' follow-up 4 no patients died. Rest of them are on chemotherapy. Neoadjuvant chemotherapy given to 12 patients and scheduled for surgical resection and anastomosis. Average 6-9 months follow-up showed 7

nos of patient expired. Most of them had received 4-6 cycles of chemotherapy. Had a metastatic deposit on peritoneum/liver/ other site before surgical intervention. Rest patients are on chemotherapy & planning for resection & anastomotic surgery. Resection was not feasible among 06 patients & they had received chemotherapy only. Till date after 2-3 months of follow-up revealed 50 % mortality. Chemotherapy & resection both are not feasible among 06 patients. Till date 4 patients died. General condition of rest 2 patients is poor, ecog score is 04. Patients had surgical site infection and they are treated with frequent changing of dressing and antibiotics changed according pus culture report. 3 patients had Postop pyrexia and 3 patients had pneumonia and treated with chest physiotherapy and antibiotics. One of them had enterocutanous fistula with surgical site infection and patient was treated with nil per oral, TPN supplement, and antibiotics.

Discussion & Analysis

This discussion is based on analysis and observation derived from 60 known adenocarcinoma of stomach patients, who attended gastroenterology outpatient department & in patient department, Institute of Post Graduate Medical Education & Research and Hospital from January 2023 to June 2024. In this study, out of 60 patients, male preponderance (70 %) was seen. In patel et al[12] study also male group (57.4%) was more affected compared to female group (42.6%), which corrborates with present study. Present study shows mean age was 56.5 years with range 20-80 years. A significant proportion (55 %) of the patients were in the range of 40-60 years in the present study. In patel et al[12] study age of patients ranged from 21-81 years & mean age was 59.4, which is comparable with present study. As per our study showed majority (75 %) of the patients presented with vomiting, abdominal pain & early satiety is also comparable with the study of patel et al[12] where most of the patients were presented with overlapping features. We observed after endoscopy evaluation ulcero-proliferative growth was found among significant proportion (95 %) of the patients. In patel et al[12] study most of endoscopic findings were ulcero-proliferative growth (92.6%), which is comparable with present study. Most (65 %) of the lesions were found in body and antro-pyloric region. In patel et al[12] study 68.1 % lesions were found in body and antro-pyloric region, which is comparable with present study. Present study showed after histological evaluation diffuse type of was found among 55% of patients. Tubular variety was found in 45%. In patel et al[12] study 53.2% % diffuse type & 46.8% tubular type. The above findings are comparable with the present study. We noticed statistical significant ($P<0.05$) between younger age group (less than 40 years) and diffuse variety of adenocarcinoma stomach. Our study showed after immune-histochemistry evaluation of her 2 neu status, a significant proportion (96 %) of patients was found negative. Her 2 neu 2+ status & her 2 neu 3 + status among 2 % & 2 % respectively. All the patients were found negative P 53 status. In patel et al[12] study 55.3 % cases were her 2 neu negative. Her 2 neu 2 + & her 2 neu 3 + among 10.6% & 21.3 % respectively. Above results are not comparable with present study. Present study showed after radiological evaluation in the form of contrast enhanced CT scan of whole abdomen, a significant proportion 18 (30%) of the patients had no nodal involvement. Involvement of 1 node was found in 15 (25 %) of patients. More than 1 node involvement was found in 15 (25%) of patients. More than 2 nodal involvements was found in 12 (20%) of patients. We observed no statistical significant ($P >0.05$) results between her 2 neu with nodal status. In patel et al[12] study

no significant difference between HER2 Neu and nodal status, which is comparable with present study.

Conclusion

This study used to determine the clinico-pathological spectrum of adenocarcinoma stomach of gastric outlet obstruction with special reference to her 2 neu & p53 status in our area. This study is based on sixty number of patients, with average 6-9 months follow up. However, some conclusion are arrived from this study are as follows

1. Male preponderance has been observed in the known cases of adenocarcinoma stomach presenting with gastric outlet obstruction. Patients in the age group of 40-60 years are mostly affected.
2. A significant proportion (75 %) of the patients presented with all together symptoms i.e vomiting, abdominal pain & early satiety.
3. Histopathological examination revealed significant correlation between younger age group (<40 years) & diffuse variety.
4. Upper gastro-intestinal endoscopy study reveals dominancy of ulcero-proliferative lesions with majority of the lesions involving body & antrum both.
5. Histopathological examination gives marginal preponderance of diffuse variety compared to intestinal type.
6. Immuno-histochemistry study of her 2 neu status showed only 2 positive her 2 neu status. Negative p53 status has been observed in all cases.
7. Distal, subtotal & total gastrectomy with gastrojejunostomy have been performed in majority {30(50%)} of the patients. On follow-up (average 6-9 months), most of the patients {18(60%)} died.
8. Feeding jejunostomy has been performed among 6 nos of patients those are planned for resection & anastomotic surgery. But intraoperative findings are suggestive of diffuse infiltration to surrounding structures leading to cancellation of surgery. On follow up (average 6-9 months), all of them died.

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