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Evaluationof HER2/neu status in Gastric Carcinoma

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Abstract: *Gastric Carcinoma is the second leading cause of cancer related death. Most of the patients present in an advanced stage. Though there are few prognostic factors, till date there is no predictive factor except HER2. Treatment of Gastric Cancer with systemic therapy has showed a survival of only 11 months. HER2 Overexpression if analysed in patients with metastatic gastric cancer and if treated with HER2 antibodies an overall survival benefit is seen. We analysed the expression of HER2 in gastric carcinoma patients and its relation to clinicopathological characteristics.*

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I. Introduction

Gastric carcinoma is the fourth most commonly diagnosed cancer in the world and is the second leading cause of cancer related death. Over 870,000 cases of stomach cancer diagnosed each year[1 2] It is more common in Eastern Asia where it accounts for more than 50% of all malignancies. In India Gastric cancer is the fifth most common malignancy in males and seventh most common in females (3).

In Asian population most of the malignancies are in the distal stomach where as in the West it is more in the proximal stomach. (4) Although relapse after complete surgical resection occurs most commonly in the tumor bed and nodal regions, systemic pattern of relapse is known to occur commonly in gastric cancer.(5) The overall 5-year survival rate of all people with stomach cancer is only about 28%.

Early diagnosis is challenging because of absence of symptoms in this stage of disease. Most of the patients with gastric cancer present in advanced, unresectable stages, thus making cure impossible. Not more than 50% of these patients are amenable to curative surgical resection at presentation. Even after surgery around two-thirds of these patients will experience recurrence within two years. The median survival after diagnosis of metastatic disease is approximately 10-11 months with currently available therapies.Systemic treatment is the only option for the patients presenting in advanced stages. Despite the introduction of multimodality treatment, and newer chemotherapeutic regimens, there is only a minimal impact on the relapse free survival and overall survival of these patients. Many single agents and combination chemotherapeutic agents are active in the treatment of metastatic disease. Objective response rates ranging from 10% to 30% for single-agent and 30% to 60% for combination regimens have been reported. Although a large number of chemotherapy regimens are available, there is still no internationally accepted standard of care. Survival of patients presenting with advanced gastric cancer is still only 4% at five years.

The most meaningful prognostic indicators relate to extent of the disease which is otherwise the stage of the disease. The other important prognostic factors include the grade of the tumor and also presence of lymphovascular invasion and perineural invasion. Newer therapies are urgently needed for their better outcome. Recently, understanding of the molecular basis of cancer has contributed to the development of rationally designed molecular targeted therapies, which interfere with signaling cascades involved in cell differentiation, proliferation, and survival of which EGFR (HER2) plays an important role HER2 gene amplification and HER2 protein overexpression have been observed in various solid tumors other than breast, including gastric carcinomas.(6-11) .Evidence suggest that overexpression of this HER2 protein which is seen in20 t0 25% of gastric carcinoms is a new, independent prognostic factor for overall survival.(12,13)

There has not been any predictive marker for survival in gastric cancer until molecular studies were done. HER2 neu gene is one of the molecular markers which is usually overexpressed in breast cancer patients .Recently molecular studies have shown that HER2 neu gene is also overexpressed in 20-25% of patients with gastric cancer and treatment with HER2 neu antibody has shown to improve survival in HER2 neu overexpressed patients when given along with chemotherapy. This is the only known predictive factor in carcinoma stomach. Its role as prognostic factor is yet to be determined. (14) Owing to the importance of Erb B

proteins in cellular transformation and development, a lot of attention has been focused on this family of receptor tyrosine kinases (15)

Trastuzumab is one of the targeted drugs against EGFR2 (commonly known as HER2) and has recently shown to increase survival in patients with metastatic gastric carcinoma when given along with combination chemotherapy.Trastuzumab was used along with chemotherapy in clinical trials and has proven to increase the survival of patients with metastatic gastric cancer. ToGA (Trastuzumab for GastericCancer) was a phase 3, open-label, international, randomised controlled trial undertaken at 122 centres in 24 countries. Patients eligible for inclusion had gastric or gastro – oesophageal junction cancer and if their tumours showed gene amplification by fluorescence insitu hybridisation or overexpression of HER 2 protein by immunohistochemistry . Participants were randomly assigned in a 1:1 ratio to receive a chemotherapy regimen consisting of cisplatinplus capecitabine or 5 fluorouracil plus cisplatin alone or chemotherapy in combination with intravenous trastuzumab given every 3 weeks for. six cycles.

Median overall survival in patients assigned to trastuzumab plus chemotherapy was 13.8 months (CI 12-16) compared with 11.1 months (10-13) in those assigned to chemotherapy alone (CI 0.60-0.91; p=0.0046); corresponding to reduction in the death rate by 26%. Confirmatory analysis that included all 594 randomised patients provided consistent results.The adverse event profile was similar in both the groups. There was no difference between both groups in frequency of grade 3 or 4 adverse events apart from diarrhoea.

Recent evidence suggests that patients diagnosed with metastatic gastric cancer should have the HER2 status of their tumors determined as only patients with HER2 positive disease are eligible for treatment with Trastuzumab in combination with chemotherapy. We conducted this study to analyse the prevalence and significance of HER2 neu overexpression in patients with gastric carcinoma.

II. Aims And Objectives

The **aims** of this study are: 1) to assess HER-2/neu content in our gastric carcinoma patients 2) To assess the correlation between this receptor tumor content and clinico-pathologic characteristics.

III. Materials And Methods

The present study was a Prospective study conducted in the Department of Medical Oncology for a period of one year from January 2013 to December 2013. Informed written consent was obtained from all patients prior to the start of the study.

Inclusion criteria

1. Patients aged 18-65 years with gastric carcinoma proven by histopathology.
2. Only adenocarcinoma of stomach was included in our study.

Exclusion criteria

There was no specific exclusion criteria

Methods

All selected patients had Endoscopy done for diagnosis. Staging workup included CT abdomen .We used AJCC TNM cancer staging 7th edition for staging. Out of 50 samples , 25 were done in surgical specimen and 25 with Endoscopic biopsy specimen irrespective of whether palliative feeding procedure was done for them.

IHC Evaluation

Immunohistochemistry (IHC) and in situ hybridisation (ISH), are validated methods for determining HER2 status in gastric cancer .(28,29)IHC evaluation of HER2 neu was done in paraffin embedded tissue samples.Accurate HER2 testing in gastric cancer is dependent on adherence to the modified IHC scoring system described by Hofmann et al 2008 (30)and we had used the same.

IV. Results And Analysis Of Observed Data

Allour patients were from in and around Coimbatore. We analysed variousclinicopathologic characteristic features like age ,sexhistopathological type, grades etc to find out whether there is any particular predilection factor for HER2 neu gene.

Age Distribution

Most of our patients were above 50 years ,that is 33 of them (66%) and 22 (34%) of our patients were below 50 years .The mean age of study population was around 52 years with patients age ranging from 32 to 72 years.. There was no difference in the age at presentation in HER2 positive and negative patients .This suggest that HER2 positive patients had not presented at an earlier stage of life.

	HER 2	N	Mean	Std. Dev	P-Value
Age (years)	Negative	40	52.43	10.507	0.941
	Positive	10	52.70	10.328	

Sex Distribution

The sex distribution was such that in our population 33 were males (66%) and females were17 of them (34%.)The Male: Female was 2:1. When further analysis was done we found that in both HER2neu positive and negative patients males contributed to two third of the disease population. Females contributed to one third of patients irrespective of HER2 neu positivity or negativity.This indicates that there is no sex predilection for HER2 neu gene.

Gender	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Male	26	65.0	7	70.0	33	66.0	0.997
Female	14	35.0	3	30.0	17	34.0	
Total	40	100.0	10	100.0	50	100.0	

Symptoms

Analysis was done to find out whether there was any difference in the chief or presenting complaints of the patient between HER2 neu positive and negative patients. The duration of symptoms was between three to six months irrespective of their HER2 neu status. The most common complaint was abdominal pain and associated weight loss in 22 patients(44%),16 0f our patient(.32%) had presented to us with abdominal pain alone as their chief complaint and 11(22%)of our patients had come to us with vomiting and weight loss and one of our patient (2%) had come to us with vomiting alone as the only symptom , he was found to have features of acute intestinal obstruction and was taken up for surgery immediately. He was HER 2 neu negative. HER2neu gene positive patients did not have any particular symptom due to the overexpression of thiegene.Their way of presentation was similar to HER2 neu negative patients.

Complaint	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Pain	12	30.0	4	40.0	16	32.0	0.701
Pain, Weight loss	17	42.5	5	50.0	22	44.0	
Vomiting , Weight loss	10	25.0	1	10.0	11	22.0	
vomiting	1	2.5	0	0.0	1	2.0	
Total	40	100.0	10	100.0	50	100.0	

Site of Lesion in Endoscopy

All our patients had Endoscopy done . .At endoscopy 30(60%) of our patients were found to been having lesion in the antrum and 20 (40%)of them had lesion in the body .Though HER2 neu positive patients had predilection towards antrum ,when compared to the negative population, the P value was not significant. All 50 (100%) patients had proliferative type of growth.

Endoscopy site	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Antrum	22	55.0	8	80.0	30	60.0	0.279
Body	18	45.0	2	20.0	20	40.0	
Total	40	100.0	10	100.0	50	100.0	

Imaging

All our patients underwent CT abdomen as part of staging workup and to assess the feasibility of surgery .The regional nodes were Pyloric, Gastroduodenal, Gastroepiploic, Splenic, Pancreaticoduodenal, Peripancreatic,Rightgastric,Left gastric, hepatoduodenal, celiac and common hepatic nodes. Presence of Portal, Para aortic, Retroperitoneal, Retropancreatic and Mesentric nodes were considered to be metastatic disease.When imaging was done 26 patients (52%) had regional nodes by CT abdomen and 24 patients (48%) did not have nodes by imaging.Nodes were present in (45%) of HER2 negative patients. Though 60 % of HER2 positive patients had nodes, the difference between them was not statistically significant.

CT Nodes	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Absent	22	55.0	4	40.0	26	52.0	0.620
Present	18	45.0	6	60.0	24	48.0	
Total	40	100.0	10	100.0	50	100.0	

Ascites

We analysed whether more patients with HER2 positivity had ascites by imaging. 13 patients (26%) had ascites by imaging .There was no ascites in 37 (74%) of our patients by imaging. These 26% of our patients were inoperable at diagnosis itself and were considered only for palliative treatment. When analysed out of the 26% with ascites none of them was HER2 positive.

CT ascites	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Absent	27	67.5	10	100.0	37	74.0	0.091
Present	13	32.5	0	0.0	13	26.0	
Total	40	100.0	10	100.0	50	100.0	

Adjacent Organ Involvement by Imaging

In our series of patients 20 (40%) had adjacent organ infiltration .In most patients pancreas was infiltrated posteriorly . The other organs involved were duodenum , transverse colon, splenic flexure involvement .These patients had T4 disease. This makes Radical treatment impossible in this group of patients.40% of them in both HER2 positive and negative group had adjacent organ infiltration. There was no correlation between HER2 neu positivity and T stage of the disease.

CT adjacent organ infiltration	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%		%	
Absent	24	60.0	6	60.0	30	60.0	1.000
Present	16	40.0	4	40.0	20	40.0	
Total	40	100.0	10	100.0	50	100.0	

Omental Deposit by Imaging

Presence of omentalmetastsis in CT abdomen was looked in to Presence of omentalmetastsis indicates metastatic disease and that only palliation is feasible.Around 8 patients (16%) of our patients had Omental deposits by CT abdomen . 84% ,that is 42 of our patients did not have omental deposits by imaging When subset analysis was done none of the HER2 neu positive patients had omentaldeposit.Thus presence of omental deposit is not a clinical correlate associated withHER2 positivity.

CT Omental deposits	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Absent	32	80.0	10	100.0	42	84.0	0.289
Present	8	20.0	0	0.0	8	16.0	
Total	40	100.0	10	100.0	50	100.0	

Liver Secondaries by Imaging

When CT abdomen was done routinely as a part of staging workup,we found that13 patients (26%) had liver secondaries. 37 patients (74%) had no liver secondaries by imaging Presence of liver secondaries indicates a metastatic disease and aim in treating these patients will be to give them palliative care.30% of HER2 negative subset had liver secondarieswhere as only 10% in HER2 positive subgroup had liver secondaries.This excludes presence of liver secondaries as an associated feature with HER2 positivity.

CT liver secondaries	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Absent	28	70.0	9	90.0	37	74.0	0.375
Present	12	30.0	1	10.0	13	26.0	
Total	40	100.0	10	100.0	50	100.0	

Surgery

Our patients had undergone various type of surgeries like Total gastrectomy,Distalgastrectomy, Subtotalgastrectomy, Anteriorgastrojejunostomy and Feeding jejunostomy.

Out of 50 our patients 31 (62%) had undergone various types of surgeries..The type of surgeries done was Subtotal Gastectomy in 15 patients.(48%),Total gastrectomy in 7 patients(22%) ,Anterior Gastrojejunostomy in 4 patients(13%),Distal Gastrectomy in 3 patients (10%) and Feeding Jejunostomy in 2 patients (7%) Radical surgery was done in 9 patients. There was no difference between HER2 positive and HER2 negative patients

Type of Surgeries done

Surgery type	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Anterior gastrojejunostomy	4	16.0	0	0.0	4	12.9	0.549
Distal gastrectomy	3	12.0	0	0.0	3	9.7	
Feeding jejunostomy	2	8.0	0	0.0	2	6.5	
Subotalgastrectomy	11	44.0	4	66.7	15	48.4	
Total gastrectomy	5	20.0	2	33.3	7	22.6	
Total	25	100.0	6	100.0	31	100.0	

When subset analysis was done , we found that only 28% of HER 2 negative patients had undergone Radical surgery where as 50% in HER 2 positive population had undergone Radical surgery.

Palliative / Radical	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Palliative	18	72.0	3	50.0	21	67.7	0.583
Radical	7	28.0	3	50.0	10	32.3	
Total	25	100.0	6	100.0	31	100.0	

Size of the Tumor

In patients who underwent surgery we did analysis of the surgically resected specimen. In gross we saw whether there is a difference in the size of tumor between HER2 positive and negative groups. Only one patient had tumor size of less than 3ccentimeters.(4%), this patient was HER2 neu negative. In 15 patients (57%) of them had tumor size 3 to 6 centimeters . This accounted 50% of HER2 positive patients and 60% in HER 2 negative patients.10 patients (39%) had more than 6 centimeter tumor size. Subset analysis revealed that 35% of HER2 negative population and 5o% of HER2 positive had tumor size greater than 6 centimeter. Though HER2 positive patients had bigger tumor size ,it was not statistically significant.

Histopathology Size	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
< 3 cm	1	5.0	0	0.0	1	3.8	0.650
3 - 6 cm	12	60.0	3	50.0	15	57.7	
> 6 cm	7	35.0	3	50.0	10	38.5	
Total	20	100.0	6	100.0	26	100.0	

T stage by HPE

In the histopathological report we analysed the T stage of the tumor.The staging system used was AJCC 7 .In patients who underwent surgery only 2 patients(8%) had T2 disease and they were HER2 neu negative.15 patients (54%) had T3 disease . Subset analysis T3 stage showed that 50% in HER2 negative and 66% in HER2 positive had T3 stage . Totally out of 50 patients 11patients (38%) had T4 disease.In HER2 positive group 34% had T4 disease where as in HER2 negative population almost 41% had T4 disease.

T-Stage	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
T-2	2	9.1	0	0.0	2	8	0.651
T-3	11	50.0	4	66.7	15	54	
T-4	9	40.9	2	33.3	11	38	
Total	22	100.0	6	100.0	28	100.0	

Lymphovascular Invasion

In the histopathologicalspecimen lymphovascular invasion analysis was done. 18 patients (72%)hadlymphovascular invasion and it not seen in 7 (28%) of our patients. Though 83% of HER2 positive

patients had lymphovascular invasion when compared to 69% in HER2 negative subgroup of patients, there was no statisticalyl significant difference between both the groups.

Lymphovascular Invasion	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
No	6	31.6	1	16.7	7	28.0	0.851
Yes	13	68.4	5	83.3	18	72.0	
Total	19	100.0	6	100.0	25	100.0	

Perineural Invasion

When histopathlogical specimen was analysed for presence or absence pfperineural invasion, we had 14 patients(56%) with perineural invasion and 11 patients (44%) had no perineural invasion .Perineural invasion was found in 50% ofHER2 positive group and in 58% of HER2 negative subgroup with an insignificant P value on comparison.

Perineural Invasion	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
No	8	42.1	3	50.0	11	44.0	0.997
Yes	11	57.9	3	50.0	14	56.0	
Total	19	100.0	6	100.0	25	100.0	

Laurens Type of Tumor

Analtysis was done to find out whether HER2 positivty was associated with any particular pathological type in Laurens classification. We had 38 patients (76%) with intestinal type of cancer and 12 patients (24%) with diffuse type of cancer. All 10 patients with HER2 positivity had only intestinal type of cancer, In HER2 negative patients 28 (70%) had intestinal type of cancer and 12 patients(30%) had diffuse type of cancer. HER2 positivity is strongly associated with intestinal type of tumor. But as intestinal type was commoner even in HER2 negative tumor ,P value was not of statistical significance.

I / D	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Diffuse	12	30.0	0	0.0	12	24.0	0.116
Intestinal	28	70.0	10	100.0	38	76.0	
Total	40	100.0	10	100.0	50	100.0	

Metastasis

Out of 50 patients 20 (40%) of them had metastatic disease at presentation. They had presented with various types of metastasis like ascites, omental deposits, liversecondaries. 30 (60%) had no metastatic disease at diagnosis. 40% of patients in both the subgroups had metastatic disease at diagnosis.

Metastasis	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
No	24	60.0	6	60.0	30	60.0	1.000
Yes	16	40.0	4	40.0	20	40.0	
Total	40	100.0	10	100.0	50	100.0	

There was no significance of P value between HER2 positive and negative patients.

Grade of the Tumor

When analysis was done to analyse whether HER2 positivity was associated with any particular grade, we found that 52% of the patients had poorly differentiated carcinoma. 30% had moderately differentiated carcinoma and 18% had well differentiated carcinoma. In HER2 positive subgroup 50% had poorly differentiated grade, 40% with moderately differentiated grade and only 10% were well differentiated grade. In HER2 negative group 52% had poorly differentiated grade, 28% had moderately differentiated grade and 205 HAD WELL DIFFERENTIATED GRADE. When statistical significance was analysed there was no significance in P value between HER2 positive and negative tumors.

HPE grade	HER 2				Total		P-Value
	Negative		Positive				
	N	%	N	%	N	%	
Well differentiated	8	20.0	1	10.0	9	18.0	0.647
Moderately differentiated	11	27.5	4	40.0	15	30.0	
Poorly differentiated	21	52.5	5	50.0	26	52.0	
Total	40	100.0	10	100.0	50	100.0	

V. Discussion

Most of our observations made correlated well with the world literature. The prevalence of HER 2 neu over-expression in our study population was around 20% 10 of 50 patients had over-expression which correlated well with other studies.(8-27%).

The age at diagnosis in our methodology ranged between 35-75 with 66% more than 50 years of age. This was in contradictory to SEER data in 2010 which states the mean age at diagnosis of gastric cancer is around 70 years. Our patients are diagnosed at much earlier age .According to SEER data only 17% were below 50 years of age .We had 34% presenting at earlier age .The etiological and epidemiological factors leading to such drastic difference at presentation is to be looked in to seriously. There was no difference in age at presentation between HER2 neu positive and negative patients .50% of HER2neu positive patients were below 50 years of age and the rest 50% above 50 years of age. The P value was not statistically significant .This observation was similar to the studies made by YQ and Cai X et al.

The sex predilection of gastric cancer was seen looked in to, we had 33 of our patients in the male population (66%) and 17 (34%) of them were females. This is similar to the data by SEER in 2010 which showed the incidence of gastric carcinoma in males to around 64% and females around 36%.

The site of growth was looked in to. 30 (60%) of our patients were found to be having growth in the antrum of stomach and 20 (40%) patients had growth in the body of stomach .This was similar to results seen by Hermann RE et al.1(9)

When analysis was done for the significance of grade in relation to HER2 neu status we found that 25(50 %) 0f our patients had poorly differentiated carcinoma. When subset analysis was done 50% of them were HER2neu positive and 50% HER2 neu negative. When analysis was done only in HER2 neu positive population, 50% had poorly differentiated grade and 30% moderately differentiated grade and 20% well differentiated grade. This was similar to analysis done by park et al.(19).

CT abdomen was done in all our patients and we had analysed the presence of nodes by imaging, adjacent organ infiltration , liver secondaries and omental deposits .When comparison was done between HER2 positive and negative patients there was no difference between them. There was no correlation between TNM staging and HER2 positivity. This was similar to the study by GravalosC,MarquezA,Garcıa-Carbonero R et al.

The type of surgery done was analysed as to whether radical procedure could be done in HER2neu positive patients. There was no difference between HER2 neu positive and negative patients .Radical surgery was feasible in 50% of HER2 neu positive patients and only 28% of HER 2 neu negative patients underwent radical surgery. This clearly states that HER2 neupositvity is not aggressive at presentation. Tanner, M. Hollm ´en, T. T. Junttila et al. also observed similar findings in their study.

The Lauren pathological type of tumor and its association with HER2 neu was looked in to. All our HER2 neupatients had only intestinal type of tumor . This was similar to studies by Nakajima, et al, Park, et al. and Tanner, et al .The reason for association of HER2 with intestinal type of cancer has to be investigated further to identify the cause of this association and prevent if feasible.

We had 3 patients with equivocal result by IHC .Our analysis had the lacunae of not analyzing these equivocal cases by FISH .This was due to the lack of availability of FISH in our institution.

Our analysis shows that there is no clinicopathological correlation between HER2neu positivity and age, sex, presenting complaints, site of lesion, grade of tumor,TNMstaging.All this indicates that HER2 neu is an independent prognostic marker.When positive it predicts the response with Trastuzumab.Thus it is the first predictive factor available for gastric cancer and all gastric carcinoma patients should undergo HER2 neu testing to obtain its benefit. More centers should be equipped with the availability of IHC facility . Pathologists should to be trained to interpret HER2 neu in gastric cancer as it is different from interpreting breast cancer.

Our patients had presented at an earlier age when compared to the world literature and the epidemiological causes leading to this early age of presentation has to be seriously looked in to. Preventive measures can be taken if the cause for this easrly presentation is found out.

Clinico Pathologic Characteristics Associated with HER2 Overexpression

Clinicopathological data was obtained from patients who had undergone surgical resection for histologically proven gastric cancer representing the entire population of surgically operable gastric cancer patients at different institutions who had given consent for research by The results were analysed statistically

against available clinicopathological criteria -gender, age, tumour size, tumour stage,histological grade, vascular invasion, perineural invasion, lymphatic invasion and survival time. Survival was measured from the date of diagnosis until the date from death from gastric cancer, or was censored until the date of the last follow-up for non-gastric cancer related deaths and survivors). No significant relation was found between clinicopathologic variables (sex and age of the patients, and tumor diameter, differentiation, location) (20) HER-2 status was correlated with the depth of invasion, TNM stage, lymph node and distant metastasis ($P < 0.05$). No significant relation was found between clini-copathologic variables (sex and age of the patients, and tumor diameter, differentiation, location) (21)

HER2 positivity differed significantly by histological subtype (intestinal 34%, diffuse 6%, mixed 20%) and according to the site of the tumor (32% GEJ and 18% gastric localization). A higher rate of HER2 positivity was seen in GEJ tumors than in gastric cancer samples (34% vs 20%). The reasons quoted for the high positivity were the association of this oncogene with a specific histologic tumor type and that certain characteristics (e.g. HER2 overexpression and intestinal phenotype) may be expressed together preferentially. (12,13,14) . In the Finnish study, amplification of HER2 was strongly associated with poor carcinoma-specific survival, particularly evident in the subgroup of intestinal type ofcancers ($P = 0.0019$), which is usually considered to associate with more favorable prognosis than the diffuse type of gastric adenocarcinoma (22)Independent risk factors of nodal metastasis include the depth of submucosal invasion; tumor diameter greater than 3.0-3.5 cm; the presence of lymphovascular permeation; depressed or ulcerated lesions; and undifferentiated histology.(23,24) The role of HER2 as a prognostic factor in gastric cancer has been controversial because some of the initial studies failed to find its association with prognosis. With the current treatment available therapies 5 year survival rate for gastric carcinoma patients is less than 10%. Trastuzumab is the first biological agent which when added to cisplatin and 5fu has shown to provide survival benefit of two and half months in patients with HER2 positive gastric cancer. It also decreases the risk of death by 26% compared with chemotherapy alone. The survival benefit was most evident in patients with high levels of HER2over -expression ,that is whose tumor was FISH+ or IHC 3+ ,with median overall survival of 16.0 vs 11.8 months for patients with high and low levels of HER2 expression. "For gastric cancer, that's probably one of the largest differences we have seen in overall survival with the addition of just one agent in the recent decades..

Trastuzumab in combination with chemotherapy is now considered to be a new standard of care for patients with HER2-positive advanced gastric or oesophagogastric junction adenocarcinomas.

Trials are going to test the benefit of Trastuzumab in adjuvant and neoadjuvant setting to extend its benefit Further important questions such as duration of treatment ,its safety in combination with other regimens like ECF, remains to be determined Trials evaluating Trastuzumab beyond disease progression, and also in pre treated gastric cancer patients to improve their outcome. .

VI. Conclusion

The conclusions we made from our study

1. Our patients presented at a much earlier age than the age of incidence in the literature.
2. The prevalence of HER2 neu was around 20% in our population.
3.HER2neu overexpression was not associated with any particular Clinicopathologic correlate.
4.HER2neu is an independent prognostic factor.
5.Its overexpression is a predictive factor for response to Trastuzumab.
6.AsTrastuzumab has shown an overall survival improvement HER2neu

Overexpression should be looked for in all newly diagnosed gastric cancer patients

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