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STUDY OF HER2 NEU POSITIVITY IN GASTROINTESTINAL CANCERS AT A TERTIARY CARE HOSPITAL IN INDIA

Anatomy

Dr Ritu Jangir DNB Resident, Department of Pathology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur.

Dr Ajay Sharma* Senior Consultant , Surgical Gastroenterology & Liver Transplantation, Mahatma Gandhi Medical College & Hospital, Jaipur. *Corresponding Author

Dr Anjali Sharma Senior Consultant & Head Department of Pathology,Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur.

Dr Rateesh Sareen Consultant Pathology, Santokba Durlabhji Memorial Hospital & Research Centre, Jaipur.

ABSTRACT

Introduction- HER2 is now well recognized as a key factor in the development of certain solid human tumors .The expression of Her2/ Neu in gastrointestinal malignancies is new concept with paucity of literature.

Aim- The present study was conducted in a tertiary care cancer hospital in India to evaluate Clinicopathological features in resected cases of gastrointestinal cancer cases and their correlation with Her2/Neu expression by Immunohistochemistry.

Material & Methods- The present study was carried out in department of pathology at regional cancer tertiary centre from October 2017 to October 2019. The cases were selected on basis of inclusion & exclusion criteria.Her2/Neu expression was assessed in all 100 cases.

Results- In present study HER2/neu status was determined on 100 cases by immune histochemistry and all IHC 3+ are accepted as HER2/neu positive cases, 2+ were equivocal and 1+/0 were negative. Out of 100 cases, 8 cases (8%) show HER2/neu 3+, 5 cases were HER2/neu 2+, 20 cases showed HER2/neu 1+ score and 67 cases showed Her2 Neu score 0. The mean age of all tumors was 53.7year (Standard Deviation 14.08) (P =0.59). Mean age of gastric and GEJ cancer 57.1 year (SD-12.01), small intestine cancer 57.7 year (SD-7.41), pancreatobiliary cancer 55.50 year (SD-14.86),colon cancer 54.5 year (SD-13.94),rectal cancer 52.1 year (SD- 15.45).Out of 100 cases , 59 cases were male and 41 were female (M:F= 1.4:1In the GIT tumors no statistically significant association was found between her2/ neu status with histological type , T stage , size of tumor , grade and TNM stage . The only significant association of Her/ 2 Neu was found with Modified Astler coller staging.

Conclusion- Modified Astler Coller stage can be used as screening test for centers where facility of Her2neu test not available.

KEYWORDS

Her2/Neu , Gastrointestinal cancers , IHC

INTRODUCTION

Gastrointestinal tract cancers constitute about 20% of cancer burden in India.[1] HER2 is now well recognized as a key factor in the development of certain solid human tumors, most notably in breast cancer. HER2 gene amplification and protein over expression, which occur in 20% to 25% of breast cancer patients, have been recognized as prognostic and predictive markers for treatment.[2] HER2 amplification and/or over expression have also been observed in colon[3], bladder [4], ovarian [5], Fallopian tube [6], endometrial [7], lung [8], uterine cervix [9], head and neck [10], prostate [11], pancreatic [12], salivary gland [13], and esophageal [14] and gastric [15] carcinomas.

It is a member of the tyrosine kinase receptor family. Activation of HER2/neu leads to initiation of signalling pathways like MAPK/ P13K/AKT, essential for cell proliferation and differentiation.[16] HER2/neu overexpression was first described in 1986 using IHC.[17] Physiologically, HER2 is expressed in several tissues such as the nervous system, epithelial cells, or the mammary gland, where it promotes cell proliferation, controls differentiation, or suppresses apoptosis [18-19]. In case of uncontrolled activation of its associated pathway, this might result in excessive cell growth, angiogenesis, and tumorigenesis.[20] The role of HER2/neu directed therapy and its success in breast patients has led to evaluation of protein overexpression, gene amplification, and antitumor activity of Herceptin in multiple tumour types, including colorectal and gastric adenocarcinomas.[20,21]

There are very limited data available for Her2neu status in GI cancers in India. Most of the studies are available as retrospective analysis, very few prospective, randomized studies are available. This exercise is performed to collect data on GI cancers in Indian scenario in prospective analysis.

AIMS AND OBJECTIVE

Primary objective is to study incidence of HER2neu status in GIT tumors by IHC.

(1) Secondary objective is to study clinicopathological prognostic factor in GIT tumors.
(2) To correlate her2neu status with other prognostic factor in GIT tumors (TNM stage, grade, nodal metastasis, modified Dukes staging etc.)

MATERIAL & METHODS

The present study was conducted after obtaining approval from scientific and research committee followed by approval from the institutional Ethical Committee at Department of Pathology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur, Rajasthan. It was a prospective non- randomized, consecutive, observational, single center study. All patients presenting to the outpatient department of the Institute during the study period and who fits the study criteria for a period of 2 years from October 2017 to October 2019.

Sample size:

100 consecutive case. Sample size was calculated at 95% confidence level assuming 66% expression of Her2/neuprotein over expression in GI tumors as per result reference study* (Sadaf Farzand et al) [22]. At absolute allowable error of 10%, Minimum 87 cases of GI tumors was required for present study. Hence it was decided to include 100 cases for present study as final sample size.

INCLUSION CRITERIA:

(1) All cases of adenocarcinoma of GIT (from esophagus to rectum and pancreatobilliary) tumors diagnosed and treated at BMCHRC during study period.
(2) All age group cases
(3) Cases given consent to be a part of study

EXCLUSION CRITERIA:

(1) GIT tumor not treated at BMCHRC.

A detailed history regarding age, sex, clinical symptoms, family history were taken along with serum markers (CEA/ CA19.9)

Immunohistochemistry (IHC):

IHC was put on all 100 cases. Her2neu was assessed in all 100 cases., Antibodies from Biogenic Life Sciences were used. The clone of antibody used for Her2 was CB11 mouse species.

Reporting was done according to

HER2 (By immunohistochemistry) (AJCC CAP PROTOCOL 2017)

- Negative (score 0)
- Negative (score 1+)

- Equivocal (score 2+)
- Positive (score 3+)

No reactivity or membranous reactivity in <10% of cancer cells	0
Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	1+
Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	2+
Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	3+

Data collected was fed in Microsoft excel worksheet and statistical analysis was performed with SPSS software (SPSS version 18, Chicago, Illinois, USA) using chi square test. A univariate analysis comparing the variables with conversion was done. P value <0.05 was taken as statistically significant.

RESULTS

A total of 520 GIT malignancies were diagnosed in 2 year period at the institute. One hundred ninety out of 520 GIT cancer underwent radical surgery in hospital including Trans hiatal esophagectomy, Gastrectomy (complete/partial), Whipples, Ilial resection, Hemicolectomy (right/left), Anterior resection, Anterior-perineal resection and Low anterior resection surgery. Hundred consecutive cases who fulfilled the inclusion criteria were registered in our study. They were analysed with respect to age, sex, clinical features, prognostic factor like serum markers, location and size of tumor, appearance of the tumor (ulceroproliferartive/ ulceroinfiltrative/ ulcerative/polypoidal), cut surface of tumor (grey white/ mucinous/solid/cystic), distances from margins (lateral circumferential margin, proximal and distal cut ends), lymph node status, histological subtype, grade, extend of invasion, lymphocytic response, lymphovascular invasion, perinural invasion, necrosis, margin, lymph node status, pTNM staging, modified Astler Collar staging. In all cases Her2neu marker was done by IHC and results were analysed.

Table -1: Overall Incidence Rate and Her2neu Score in GIT Cancers

Her2neu score	No.	%
0	67	67
1+	20	20
2+	5	5
3+	8	8
Total	100	100

Table-2: Correlation of Her2neu Status with Site of Tumour

Site of tumour	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
Esophagus	0	0.00	0	0.00	0	0.00	0	0.00	0
Gastric & GEJ	9	75.00	3	25.00	0	0.00	0	0.00	12
GB & Pancreas	8	80.00	2	20.00	0	0.00	0	0.00	10
Small Intestine	4	100.00	0	0.00	0	0.00	0	0.00	4
Colon	24	63.16	8	21.05	3	7.89	3	7.89	38
Rectum	22	61.11	7	19.44	2	5.56	5	13.89	36
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 7.864 with 12 degrees of freedom; **P = 0.796** *(There was no statistically significant association between site of tumour and Her2neu status.)*

Table-3 Correlation of Her2neu Status with Age

Age (year)	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
≤30	6	66.67	2	22.22	0	0.00	1	11.11	9
31-40	7	70.00	3	30.00	0	0.00	0	0.00	10
41-50	15	71.43	2	9.52	1	4.76	3	14.29	21
51-60	15	57.69	8	30.77	3	11.54	0	0.00	26
61-70	16	72.73	3	13.64	1	4.55	2	9.09	22
>70	8	66.67	2	16.67	0	0.00	2	16.67	12
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 13.184 with 15 degrees of freedom; P = 0.589 *(No significant association was found in age and Her2neu status.)*

Table-4: Sex Wise Distribution of Her2neu Status

Sex	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
Male	38	64.41	12	20.34	3	5.08	6	10.17	59
Female	29	70.73	8	19.51	2	4.88	2	4.88	41
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square =1.001 with 3 degrees of freedom; P = 1.000 *(There was no statistical significance between gender and Her2neu scoring).*

Table-5: Correlation of Her2neu Status with Histological Type

Histological Types	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
Adenocarcinoma	54	66.67	16	19.75	5	6.17	6	7.41	81
Mucinous Adenocarcinoma	9	64.29	3	21.43	0	0.00	2	14.29	14
Signet Ring Cell Adenocarcinoma	4	80.00	1	20.00	0	0.00	0	0.00	5
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 2.459 with 6 degrees of freedom; P = 0.873*(There was no significant association was found between histological type of tumor and Her2neu scoring.)*

Table-6: Correlation of Her2neu Status with T Stage

T Stage	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
T1	1	50.00	1	50.00	0	0.00	0	0.00	2
T2	20	71.43	2	7.14	2	7.14	4	14.29	28
T3	41	65.08	17	26.98	2	3.17	3	4.76	63
T4	5	71.43	0	0.00	1	14.29	1	14.29	7
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 11.073 with 9 degrees of freedom; P = 0.274 *(No statistically significant correlation was found in T stage and Her2neu)*

Table-7: Correlation of Her2neu Status with Size of Tumor

Size of tumor (cm)	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
0-5	39	67.24	12	20.69	3	5.17	4	6.90	58
>5-10	28	66.67	8	19.05	2	4.76	4	9.52	42
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 0.252 with 3 degrees of freedom; P = 1.000 *(Tumor size was statistically insignificant with Her2neu scoring.)*

Table-8: Correlation of Her2neu Status with Grade of tumor

Grades	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
NA	8	61.54	3	23.08	1	7.69	1	7.69	13
Well Differentiated	21	60.00	6	17.14	3	8.57	5	14.29	35
Moderately Differentiated	32	69.57	11	23.91	1	2.17	2	4.35	46
Poorly Differentiated	6	100.00	0	0.00	0	0.00	0	0.00	6
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 8.184 with 9 degrees of freedom; P = 0.528 *(There was no statistically significance association found in grade of tumor and Her2neu scoring.)*

Table 9: Correlation Of Her2neu Status With TNM Stage

TNM Stage	Her2/neu score								Total
	0		1+		2+		3+		
	No.	%	No.	%	No.	%	No.	%	
1	11	73.33	2	13.33	1	6.67	1	6.67	15
2	1	50.00	1	50.00	0	0.00	0	0.00	2
2a	24	63.16	10	26.32	2	5.26	2	5.26	38
2b	4	66.67	2	33.33	0	0.00	0	0.00	6

2c	3	100.00	0	0.00	0	0.00	0	0.00	3
3a	6	60.00	0	0.00	1	10.00	3	30.00	10
3b	16	69.57	5	21.74	1	4.35	1	4.35	23
3c	2	66.67	0	0.00	0	0.00	1	33.33	3
Total	67	67.00	20	20.00	5	5.00	8	8.00	100

Chi-square = 18.020 with 21 degrees of freedom; P = 0.648 *(No significant correlation was found in stage and Her2neu status.)*

Table 10: Correlation of Modified AstllerColler Staging with Her2/Neu Score

Modified AstlerColler Staging	Her2/neu score								Total
	0		1+		2+		3+		
	N	%	N	%	N	%	N	%	
B1	9	64.29	3	21.43	1	7.14	1	7.14	14
B2	13	52.00	8	32.00	2	8.00	2	8.00	25
C1	0	0.00	0	0.00	0	0.00	3	100	3
C2	23	76.67	4	13.33	1	3.33	2	6.67	30
C3	1	50.00	0	0.00	1	50	0	0.00	2
Total	46	62.50	15	20.83	5	5.56	8	11.11	74

Chi-square = 36.228 with 12 degrees of freedom; P <0.001 (Statistically significant correlation was found with Modified AstllerColler Staging with Her2/Neu Score.)

RESULT

In present study HER2/neu status was determined on 100 cases by immune histochemistry and all IHC 3+ are accepted as HER2/neu positive cases, 2+ were equivocal and 1+/0 were negative. Out of 100 cases, 8 cases (8%) show HER2/neu 3+, 5 cases were HER2/neu 2+, 20 cases showed HER2/neu 1+ score and 67 cases showed Her2 Neu score 0. (Table -1) Atotal 12 cases were of gastric adenocarcinoma and GEJ adenocarcinoma, out of them 9 cases (75%) showed Her2neu score 0, 3 cases (25%) showed Her2neu score 1+. (Table -2) The mean age of all tumors was 53.7year (Standard Deviation 14.08) (P =0.59). Mean age of gastric and GEJ cancer 57.1 year (SD-12.01), small intestine cancer 57.7 year (SD-7.41), pancreatobiliary cancer 55.50 year (SD-14.86),colon cancer 54.5 year (SD-13.94),rectal cancer 52.1 year (SD- 15.45).(Table -3) Out of 100 cases , 59 cases were male and 41 were female (M:F= 1.4:1) (Table -4) In the study 4 cases (33.33%) were well differentiated, 4 cases (33.33%) were moderately differentiated, 3 cases (25%) were poorly differentiated. According to histological type 10 cases (83.33%) were adenocarcinoma, and 2 cases (16.67) were signet ring cell adenocarcinoma. (Table-5) In the GIT tumors no statistically significant association was found between her2neu status with histological type (Table-5), T stage (Table-6), size of tumor (Table-7), grade (Table-8) and TNM stage (Table-9). The only significant association of Her/ 2 Neu was found with Modified Astler coller staging.(Table-10)

DISCUSSION

The study concluded that there was lack of statistical significant association between Her2 /Neu expression with age, sex, location, histological type , size, grade, TNM stage , lymphovascular , perineural and lymph node metastasis in Gastro intestinal malignancies. The only statistically significant association was found between Her2/ neu expreassion and modified Astler coller staging. This finding could be of significance as this staging system done on routine histopathology could be used as screening test for centers where facility of Her2neu test not available, especially in developing countries.

There were no cases of esophageal adenocarcinoma in present study so we could not find any incidence of esophageal cancer. The incidence of Her2neu overexpression in GC and GEJ adenocarcinoma was found 0%. In a study by Ross JS et al.[23] mentions that Her2neu expression in gastric and gastroesophageal junction adenocarcinomas is 19% and 22% respectively. Farzand S et al showed the overexpression of Her2/neu in gastric carcinomas to be extremely variable ranging from 7% to 43% positivity.[22]

Difference in incidence of Her2neu expression in present study from literature could be due to a smaller number of adenocarcinomas at GEJ and a greater number of adenocarcinomas with low grade tumors, difference in scoring system, methodology and study population [24-26]

In the present study all cases of small intestinal adenocarcioama did not show Her2neu expression , the findings in concordance with other studies in literature by Aparicio et al.[27] with only 3.9 % tumors showing positivity for Her2/Neu and Overman et al. [28] with 2% Her 2/ Neu positivity.

In present study colon cancer showed 7.89% and rectum showed 13.89 % of Her2 neu overexpression. Kruszewski et al [29] mentioned HER-2 overexpression in 27% of 202 CRC patients, while Kavanagh et al [30] observed overexpression in 11% of 132 patients using IHC performed on whole sections. Kim et al[31] reported HER-2 overexpres- sion in 0.5% of 185 patients with CRC. The pancreaticobiliary cancers were very few to draw conclusion on Her 2/ Neu expression in the current study.

We did not find any statistical significance between Her 2 / Neu expression with age similar to studies by Asma Shabbir et al[32] ,Pathmanathan et al[33],N Sunitha et al[34] ,Sangram Keshari Panda et al[35], Kavanagh DO et al[30],Seo AN et al[36].Kim HJ et al[31]Dr. Sumita A Jain et al[16] and B Schuell et al[3] . In Our study Her2neu expression was not significant with size of tumor and study showed concordance with other studies in literature by Jinhua TU et al.[37] and Kim HJ et al[31]. However, Demirbas et al[38] reported an association between Her 2/neu overexpression and tumor size(>5cms).

In a study by An Na Seo et al.[36] HER2 protein over expression was significantly associated with tumor location in the colorectal cancer. Study by JinhuaTU et al.[37] there was no association between HER-2 overexpression and tumour site , similarly Xin-Yu Wang et al.[39] did not found significant association between Her2neu status and tumor site. According to Kavanagh DO et al[30], Schuell B et al[3], Seo AN et al[36], Pathmanathan et al.[33]and Sangram Keshari Panda et al[35], no relationship was observed between the HER2 positivity and tumor site, our findings concordant with these studies Patrick Sven Plum et al.[40]found that HER2 expression was correlated with low-grade (G1/2 vs. G3/4 p = 0.041) According to Pathmanathan et al [33] HER2 positivity was not statistically associated (p = 0.063) with the histological grade of the tumor; 50% of well differentiated and 30% of moderately differentiated tumors tested in positive for HER2 compared with 19% of poorly differentiated tumors. Concordant to our findings Vishal thakur et al [41] , Sumita A Jainet al.[16] and B Schuellet al.[3] did not find relationship found between HER-2 expression and tumor differentiation.

Patrick Sven Plum et al.[40] found the HER2 expression was correlated with lower pT-stages (pT1/2 vs. pT3/4, p = 0.038). Asma Shabbir et al [32], Vishal thakur et al [41], Gupta et al.[42] Kavanagh DO[30] et al, Schuell B et al[3] and Seo AN et al[36] findings were similar to our study as they also did not find any correlation between HER-2 overexpression with TNM staging. In a study by Shafizadeh et al[43] Her2neu positivity was found in high stage of tumor. Kim HJ et al[44] showed that in EHBC there was no significant correlation found between HER-2/neu protein expression and TNM staging of tumor. In a study by Antonio Lozano-Leon et al.[45] Her2 neu expression was found in stage 2.

Shoroq Mohamed Abas[46] found the HER2 neu overexpression in Duck stage A 22.2%, in stage B 28.6%, in stage C 50%, in stage D 0% Suma et al[47] in a study found that Her2neu expression is 18% in stage B, 4% and 2% of cases respectively from stage C and stage D of modified Astler Coller. In present study significant correlation was found between modified AstlerColler staging and Her2neu overexpression. (P<0.001)

CONCLUSION

There were few limitations of our study like limited number of cases and lack of FISH for cases with equivocal results for Her2/Neu which could have further increase incidence of Her2neu positive cases. It is pertinent to conclude that statistically significant association of modified Astler Coller stage with Her2neu status suggest that this staging on routine histopathological report can be used as screening test for centers where facility of Her2neu test not available.

Conflict of interest – Nil
Sources of Funding - Nil

Abbreviations:

CA 19.9	-	Carbohydrate Antigen 19.9
CCA	-	Cholengio Carcinoma
CEA	-	Carcino-embryonic antigen
CRC	-	Colorectal Cancer

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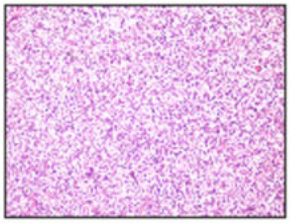
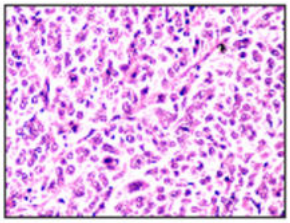
EAC	-	Esophageal Adeno-Carcinoma
EC	-	Esophageal Cancer
EHBC	-	Extrahepatic Biliary
Cholangiocarcinoma FH	-	Family History
GBC	-	Gallbladder Cancer
GC	-	Gastric Cancer
GC	-	Gastric Cancer
GEJ	-	GasroEsophageal Cancer
GIC	-	Gastrointestinal Cancer
H &E	-	Haematoxylin and Eosin
HER2	-	Human Epidermal Growth Factor
Receptor2 IHC	-	Immunohistochemistry
LN	-	Lymph Node
MAPK	-	Microtubule Associated Protein
Kinase PC	-	Pancreatic Cancer
PI3K	-	Phosphoinositide 3-Kinase
SIA	-	Small Intestinal Adenocarcinoma
SBA	-	Small Bowal Adenocarcinom


H&E 10X POORLY DIFFERENTIATED ADENOCARCINOMA OF STOMACH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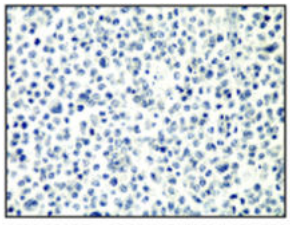
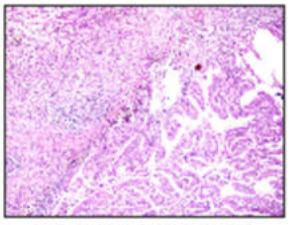
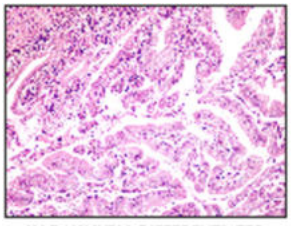
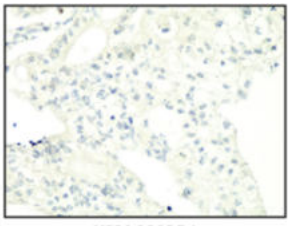
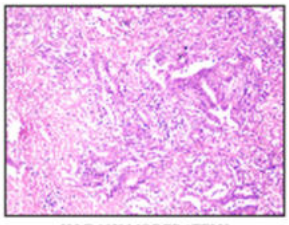
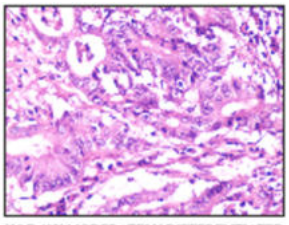

HER2 SCORE 0, POORLY DIFFERENCIATED ADENOCARCINOMA STOMACH (40X)

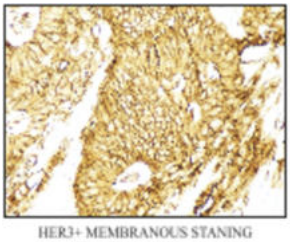

H&E 4X WELL DIFERENTIATED ADENOCARCINOMA, STOMACH

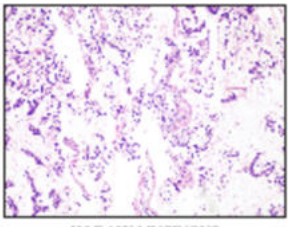

H&E 10X WELL DIFFERENTIATED ADENOCARCINOMA, STOMACH

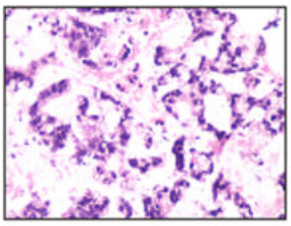

HER2 SCORE 0 ADENOCARCINOMA, STOMACH (40X)


H&E 10X MODERATELY DIFFERENTIATED ADENOCARCINOMA COLON


H&E 40X MODERATELY DIFFERENTIATED ADENOCARCINOMA COLON


HER3+ MEMBRANOUS STANING MODERATELY DIFFRENTIATED ADENOCARCINOMA COLON (40X)


H&E 10X MUCINOUS ADENOCARCINOMA RECTUM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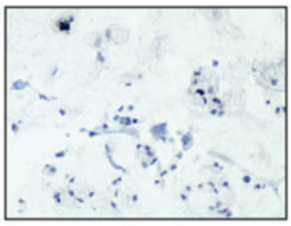
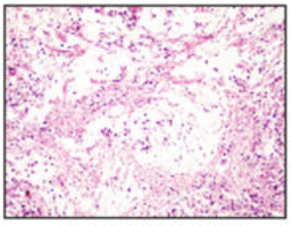
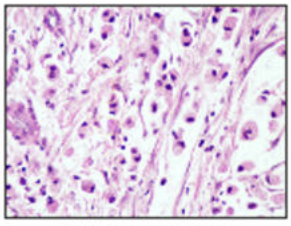
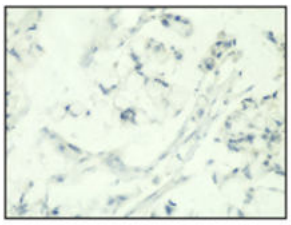
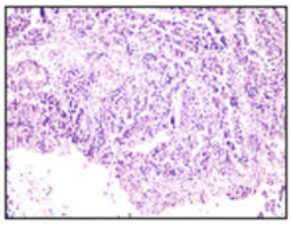
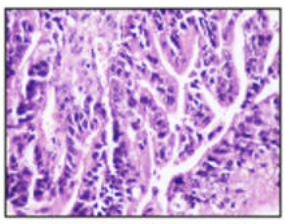

HER2 SCORE 0 MUCINOUS ADENOCARCINOMA RECTUM

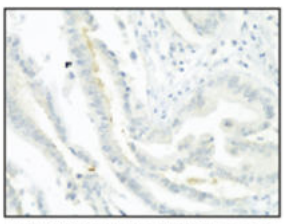

H&E 10X SIGNET RING CELL ADENOCARCINOMA GEJ

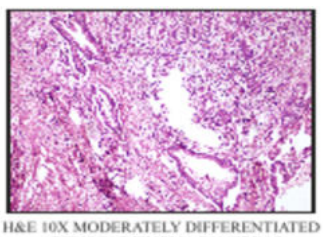

H&E 40X SIGNET RING CELL ADENOCARCINOMA GEJ

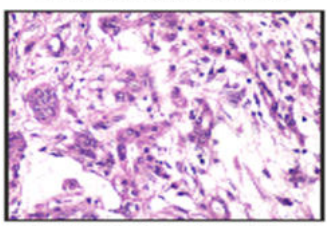

HER2 SCORE 0 SIGNET RING CELL ADENOCARCINOMA OF GEJ (40X)

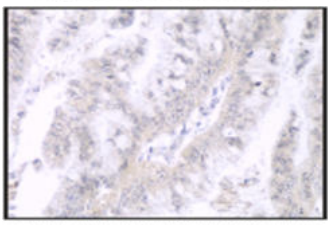

H&E 10X WELL DIFFRENTIATED ADENOCARCINOMA GALLBLADDER


H&E 40X WELL DIFERENTIATED ADENOCARCINOMA GALLBLADDER


HER2 SCORE 0 WELL DIFERENTIATED ADENOCARCINOMA ,GALLBLADDER (40X)


H&E 10X MODERATELY DIFFERENTIATED ADENOCARCINOMA PANCREAS


H&E 40X MODERATELY DIFFERENTIATED ADENOCARCINOMA PANCREAS


HER2 1+ MODERATELY DIFFERENTIATED ADENOCARCINOMA PANCREAS (40X)

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