Section: Pathology

Original Research Article

PROGNOSTIC SIGNIFICANCE OF HER2/NEU EXPRESSION IN ENDOMETRIAL, UROTHELIAL GASTRIC AND COLORECTAL CARCINOMAS – A COMPARATIVE STUDY

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Received *: 02/05/2025*
Received in revised form *: 18/06/2025*
Accepted *: 04/07/2025*

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DOI: 10.70034/ijmedph.2025.3.202

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 1096-1100

ABSTRACT

Background: Human epidermal growth factor receptor 2 (HER2) overexpression is an effective therapeutic target in endometrium and urothelial cancer(1). Although HER2 positivity has been reported in other malignancies, previous studies have focused on one cancer type. Comparing HER2/neu positivity across malignancies in different organs to verify it's validity and prognostic significance.

Materials and Methods: The present study is a retrospective study. A total 16 cases of Endometrial Carcinoma, 44 cases of urothelial carcinomas, 59 gastric adenocarcinomas and 55 colorectal carcinomas were enrolled in the study over a period of 3 years from 2020 to 2023.

Results: Our study shows grade of the tumor is significant in all Endometrial, Urothelial, gastric and colorectal carcinomas but stage and invasion of the tumor is not statistically significant in colorectal carcinomas. It is evident that there is significant statistical correlation between *Her2/neu* expression with grade of the tumor.

Conclusion: This study helped in evaluating the new molecular markers involved in the pathogenesis of various carcinomas. The immunohistochemical expression of *Her2/neu* is evaluated and correlated with various prognostic variables. *Her2/neu* overexpressing patients can be considered for targeted therapy and are associated with poorer prognosis(2).Treatment modalities depends on the intensity of *Her2/neu* expression.

Keywords: Endometrial carcinoma, urothelial carcinoma, HER2/NEU, prognostic factors

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) amplification/overexpression is an effective therapeutic target in many carcinomas.[1] Although HER2 positivity has been reported in different malignancies, other studies have focused on only one cancer type. Comparing HER2/neu positivity across malignancies in different organs to verify it's validity and prognostic significance. Gastric carcinomas, endometrial, urothelial and colorectal cancers showed HER2 positivity rates of 10 to 20%, 10 to 15%, 5 to 10% and 2 to 5% respectively.[2]

Aims and Objectives

1. To update the role of HER2/neu in endometrial, gastric, urothelial and colorectal carcinomas
2. Intensity of HER2/NEU expression in endometrial, gastric, urothelial and colorectal carcinomas
3. Correlating it's expression with other prognostic factors like grade of tumour, clinical stage, myometrial/muscle invasion to value on therapeutic target
4. To compare the prognostic significance of HER2/neu expression in endometrial, gastric, urothelial and colorectal carcinomas.

MATERIALS AND METHODS

The present study is a retrospective study. A total 36 cases of Endometrial Carcinoma, 44 cases of urothelial carcinomas, 59 gastric adeno carcinomas and 55 colorectal carcinomas were enrolled in the study over a period of 5 years from 2018 to 2023.

Inclusion Criteria:

In all Endometrial, urothelial, gastric and colorectal carcinomas only comparable prognostic factors for HER2/Neu expression are included in the study.

Exclusion criteria:

Autolyzed samples were excluded. Grading was done the using ISUP, WHO International Federation of Gynaecology and Obstetrics (FIGO) grading system. Tumour staging was performed according to the FIGO classification and TNM staging system. For assessing Her2/neu positivity, ASCO scoring system was used. According to this system, only membranous staining pattern was considered positive, and the level of Her2/neu expression was assessed semiquantitatively by the intensity & percentage of cells stained and scored on a scale of 0-3+. A cytoplasmic staining was considered nonspecific.[3] In present study, Scores of 0 or 1+ was considered tumour negative for HER2/neu expression and specimens with 2+or 3+ staining were considered positive for HER- 2/Neu antibody overexpression

Statistics chi-square test (X2) was used to evaluate the relation between histopathological parameters and immunohistochemical markers. The results were considered statistically significant if the P value was < 0.05.

RESULTS

In the present study total number of cases were 194 which included hysterectomy, cystectomy, gastrectomy and colorectal carcinoma specimens sent for histopathological examination. 194 cases including 36 Endometrial 44 urothelial 59 gastric and 55 colorectal carcinoma cases assessed for HER2/Neu expression.

Table 1: Histological types of different carcinomas

Type of carcinoma	Histological type	Number of cases
Endometrial carcinoma	Endometroid carcinoma	29
	Non Endometroid carcinoma	07
Gastric carcinoma	Intestinal type	34
	Diffuse type	25
Urothelial carcinoma	Low grade	22
	High grade	22
Colorectal carcinoma	Adeno carcinoma	49
	Signet ring cell carcinoma	02
	Mucinous Adenocarcinoma	04

Table 2: comparison of grade in various carcinomas in relation to her2/neu expression

Grade Of Carcinomas	HER2/NEU		Negative	HER2/NEU		Positive	P value
	0	1+		2+	3+		
Endometrial carcinoma							0.004*
GRADE 1 (15)	05	07	80%	03	00	20%	
GRADE 2 (07)	00	02	28%	02	03	72%	
GRADE 3 (14)	00	00	00%	00	14	100%	
Gastric carcinoma							0.021*
GRADE 1 (13)	08	03	85%	02	00	15%	
GRADE 2 (24)	03	02	21%	10	09	79%	
GRADE 3 (22)	00	02	09%	02	18	91%	
Urothelial carcinoma							0.019*
LOW GRADE (22)	15	02	77%	03	02	23%	
HIGH GRADE (22)	04	03	32%	07	08	68%	
Colorectal carcinoma							0.044*
GRADE 1 (25)	10	10	80%	03	02	20%	
GRADE 2 (25)	12	03	60%	06	04	40%	
GRADE 3 (05)	00	02	40%	00	03	60%	

Table 3: comparison of stage in various carcinomas in relation to HER2/NEU expression

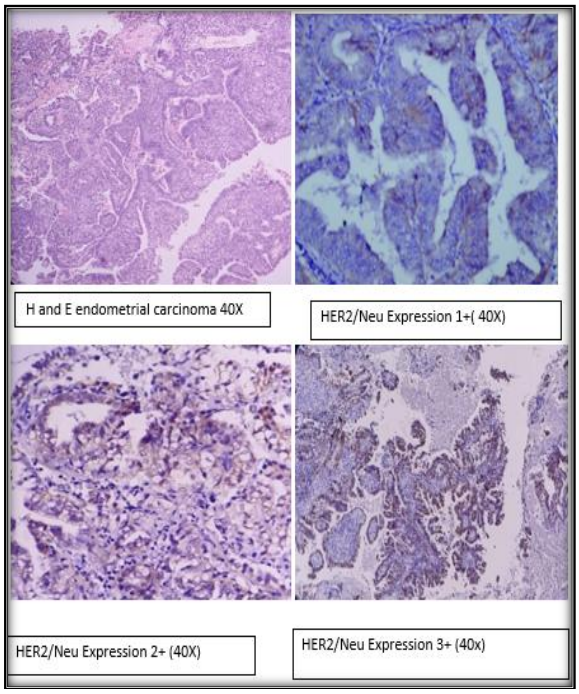
Stage Of Carcinomas	HER2/NEU		Negative	HER2/NEU		Positive	P value
	0	1+		2+	3+		
Endometrial carcinoma							0.004*
STAGE 1 (15)	03	06	60%	04	02	40%	
STAGE 2 (10)	04	01	50%	02	03	50%	
STAGE 3 (11)	00	02	18%	02	07	82%	
Gastric carcinoma							0.041*
STAGE 1 (11)	03	03	54%	02	03	46%	
STAGE 2 (23)	07	06	56%	05	05	44%	
STAGE 3 (25)	05	05	40%	07	08	60%	
Urothelial carcinoma							0.242

STAGE 1 (14)	07	00	50%	03	04	50%	
STAGE 2 (18)	05	05	55%	05	03	45%	
STAGE 3 (12)	02	05	58%	02	03	42%	
Colorectal carcinoma							0.632
STAGE 1 (42)	10	15	60%	15	02	40%	
STAGE 2 (13)	06	03	69%	02	02	31%	

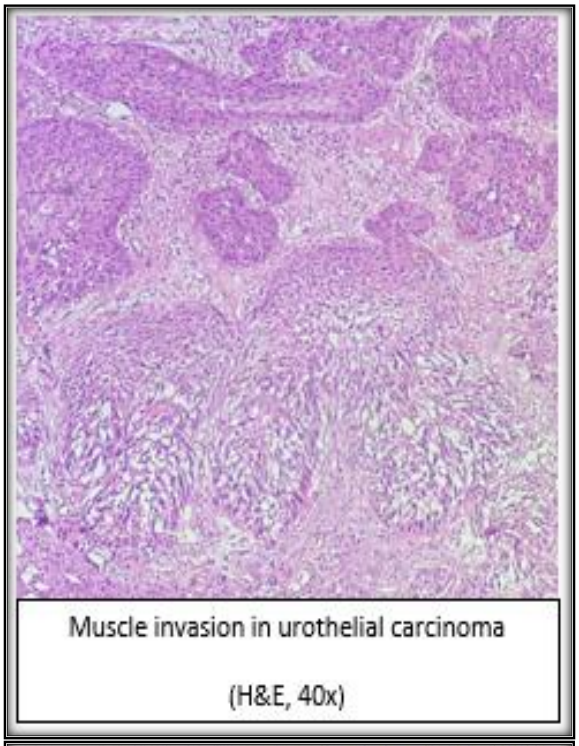
Table 4: Comparison of muscle invasion in various carcinomas in relation to her2/neu expression

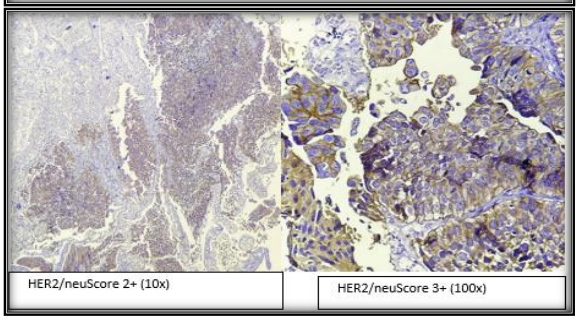
Stage Of Carcinomas	HER2/NEU		Negative	HER2/NEU		Positive	P value
	0	1+		2+	3+		
Endometrial carcinoma							0.004*
NO / <½ MYOMETRIAL INVASION (18)	05	05	55%	03	05	45%	
>½ MYOMETRIAL INVASION (18)	02	02	22%	06	08	78%	
Gastric carcinoma							0.056
NON INVASIVE (32)	02	03	16%	12	15	84%	
INVASIVE (27)	08	11	70%	07	01	30%	
Urothelial carcinoma							0.034*
NON INVASIVE (14)	05	04	64%	03	02	36%	
INVASIVE (30)	02	03	17%	10	15	83%	
Colorectal carcinoma							0.242
NON INVASIVE (13)	01	02	23%	08	02	77%	
INVASIVE (42)	18	20	90%	02	02	10%	

Microscopic picture of Endometrial carcinoma

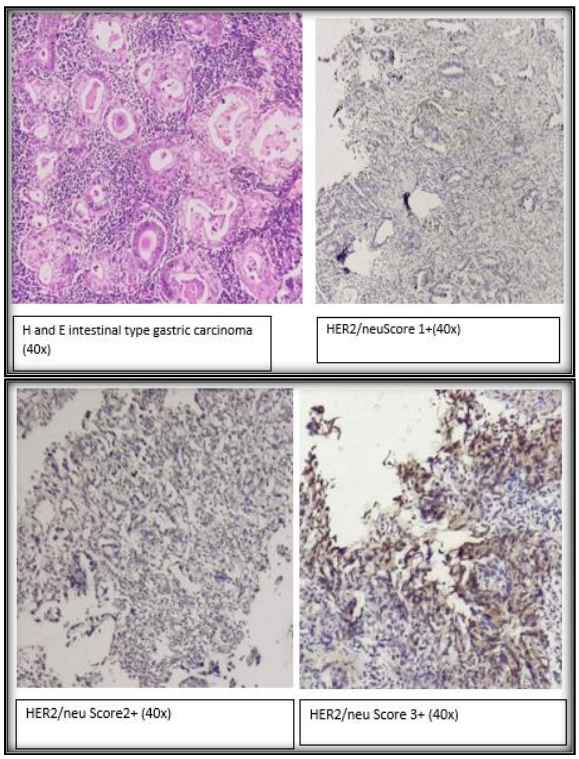


Micoscopic picture of urothelial carcinoma

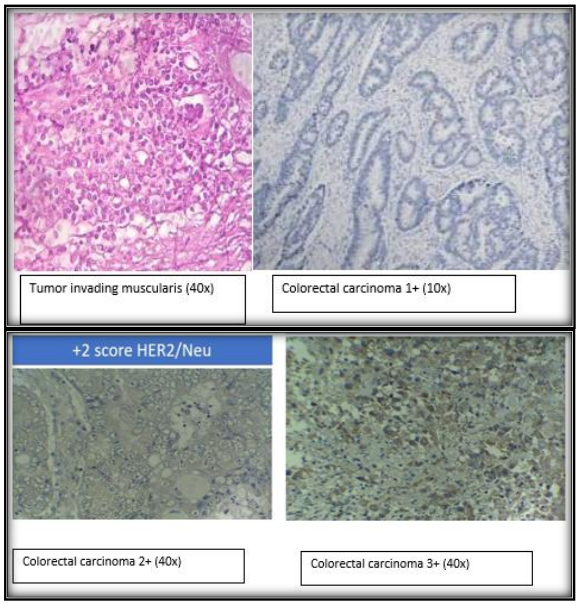




Micoscopic picture of gastric carcinoma



Poorly differentiated colorectal carcinoma



DISCUSSION

In Endometrial carcinomas HER2/NEU expression is strongly positive in high grade endometroid carcinomas and serous carcinomas.

In Gastric carcinomas HER2/NEU expression is normally strongly positive in intestinal type of carcinomas than diffuse carcinomas but in my study diffuse is strongly positive than intestinal type.

In Colorectal carcinoma HER2/NEU positivity is significant in signet ring cell carcinomas

HER2/NEU expression and associated genes

HER2/NEU gene amplification is more common than protein overexpression in endometrial, gastric, urothelial carcinomas but in colorectal carcinomas protein over expression is more common than amplification.[4,5]

Associated genes:

ERBB2: Amplification or mutation can lead to HER2/NEU over expression in all types of carcinomas.[6]

Endometrial carcinoma TP 53 Mutations and loss of PTEN are seen. Gastric cancer TP53, PIK3CA mutation, overexpression VEGF noted. Urothelial carcinomas TP53, PIK3CA mutation, overexpression or mutation of FGF present. Colorectal carcinomas Wild type KRAS, BRAF and mutations in PIK3CA. HER2/NEU overexpression and associated gene alterations may impact prognosis and treatment response.[7-11]

Limitations of the Study

The present study is conducted only in endometrial, gastric, urothelial and colorectal carcinomas

Eventhough HER2/NEU expression is significant in breast, esophagus, ovarian epithelial carcinoma and lung adeno carcinoma. These cancers were not included in the present study

CONCLUSION

1) HER2/NEU is a excellent PROGNOSTIC BIOMARKER in endometrial carcinomas, in gastric and urothelial carcinomas its significance is equivocal but in colorectal carcinoma HER2/NEU expression significance is very low.In all 4 types grade is statistically significant for HER2/NEU expression but stage is significant in endometrial and gastric carcionoma, muscle invasion is significant in endometrial and urothelial carcinomas

2) 2) It is PREDICTIVE BIOMARKER in endometrial carcinoma. Most of the patients shows good response with Herceptin therapy.

3) CORRELATING WITH OTHER PROGNOSTIC MARKERS

The impact of HER2/NEU expression on prognosis can vary depending on the specific tumor type, grade, stage, muscle invasion and treatment

4) INTENSITY OF HER2/NEU EXPRESSION

Higher expression intensity associated with improved response to HER2- targeted therapies and potentially worse prognosis if left untreated. Lesser expression intensity may benefit from alternative therapies such as chemotherapy or hormone therapy for potenatially better prognosis. Mutation in PIK3CA if present in HER2/NEU positive tumors, Potentially contributing resistance to HER2 targeted therapies in all types of carcinomas.

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