



## Original Article

# Immunohistochemistry study for HER2/neu expression in pre-neoplastic and neoplastic lesions of uterine cervix

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## Abstract

**Objective:** To assess immunohistochemistry for HER2/neu expression in preneoplastic and neoplastic lesions of uterine cervix and its correlation with histological type, grade and stage.

**Methods:** Total 50 cases was included during a period from 2017 to 2018. It was a cross-sectional study including both preneoplastic and neoplastic lesion of uterine cervix, immunohistochemistry for HER 2/neu expression was performed in all the cases.

**Results:** HER2/neu expression was seen in 56% cases. Out of 50 cases, 10 was preneoplastic (CIN) and 40 was neoplastic (SCC and adenocarcinoma) lesion. HER2 /neu expression was seen in 3 cases of CIN III, 20 cases of SCC and 5 cases of Adenocarcinoma. Among 35 cases of squamous cell carcinoma, 6 cases were negative for HER2/neu(17%), 9 cases scored 1+(25%), 14 cases 2+(40%) and 6 cases were 3+ (17%). HER2/neu expression was about 50 % in well differentiated SCC, 50% in moderately differentiated and 86 % in poorly differentiated type. Out of 5 cases of adenocarcinoma, HER 2/neu expression was seen in all the cases, of which 3 cases (60%) showed 1+positivity and 2 cases (40%) showed 2+ positivity. 9 cases showed lymph node metastasis positive and out of which 7cases showed HER2/neu positivity (77.77%) and all of them belonged to SCC. Among 14 cases of parametrial extension, 9 cases were positive for HER2 /neu marker. Out of 9 cases 7 cases were of moderately squamous cell carcinoma, 1 was of poorly differentiated SCC and 1 cases of adenocarcinoma.

**Conclusion:** This study shows HER 2/neu expression in cervical carcinoma correlates with higher clinical stage. HER 2/ neu expression correlates with lymph node metastasis and with parametrial extensions.

**Keywords:** Uterine cervix, preneoplastic and neoplastic lesions, Immunohistochemistry, HER 2/neu.

## Introduction

Carcinoma cervix is most common cancer among female population next only to breast cancers, is responsible for about 5% of all deaths due to malignancies worldwide (WHO, 2006). The estimated incidence of cervical cancer is approximately 4.5 lacs every year and remains leading cause of morbidity and mortality worldwide (Sankaranarayanan and Ferlay, 2006). Histologically, WHO has classified invasive tumors as epithelial, mesenchymal, mixed epithelial and mesenchymal, melanocytic, miscellaneous lymphoid and hematopoietic and secondary, which are sub classified further. The relative proportions of these different carcinoma varies but in general approximately 60-80% are classified as CIN I (Cervical Intraepithelial Neoplasia), CIN II, CIN III. CIN I comprises LSIL (Low grade Squamous Intraepithelial Lesion) and CIN II and CIN III comes under HSIL (High grade Intraepithelial Lesions) (Kumaran, 2002; Tavassoli and Deville, 2003).

The role of oncogenes in the development and prognosis of various cancers is a subject of intense investigation. The c-erbB-2 proto oncogene also called neu and HER2/neu (HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2) is a gene located on chromosome 17q21 that encodes a growth factor receptor like molecule with tyrosine kinase activity and has a structure similar to that of epidermal growth factor receptor and has 1255 amino acids. Its expression has been detected in several human cancers and is believed to be associated with poor prognosis, aggressive biological behaviour and metastatic potential (Vaidyanathan et al, 2010).

Over expression leads to constitutive activation of tyrosine kinase residues. The epidermal growth factor receptor (EGFR/HER) family of receptors has been associated with aggressive biological behaviour and metastatic potential. The expression of HER family members in gynaecological cancers and their relationship with disease stage, grade and response to treatment is not well established. (Reyes et al, 2014).

The aim of this study is to assess immunohistochemistry for HER2/neu expression in preneoplastic and neoplastic lesions of uterine cervix and its correlation with histological type, grade and stage.

## Material and Methods

This was a cross-sectional study from a period of 2017 to 2018, conducted in the Department of Pathology, HIMS, Barabanki. It included all preneoplastic and neoplastic lesion of cervix. Ethical approval for the study was obtained from the Institutional Ethical Committee.

Cervical biopsies and hysterectomy specimens was fixed in a 10% buffered formalin solution, processed and embedded in paraffin, these tissue blocks were cut into 4-5 micron sections on a microtome and placed on glass slides further Hematoxylin and Eosin staining was done. The slides was studied under light microscopy and then the sections were further subjected to Immunohistochemical staining with HER 2/neu antibody giving golden brown colour membrane and cytoplasmic staining was taken as a positive reaction. Intensity of HER2/neu expression was graded according to ASCO guidelines.

Staining Pattern	Score	HER-2/neu
No staining or weak membrane staining in < 10% of tumor cells	0	Negative
Weak membrane staining in >10% of tumor cells	1	Negative
Moderate membrane staining in > 10% of tumor cells	2	Positive
Strong membrane staining in > 10% of tumor cells	3	Positive

## Statistical analysis

Statistical analysis of data was performed using SPSS version 17.0. HER2/neu expression and its correlation with various factors was calculated using Pearsons Chi-square test. *P* value <0.05 was taken as statistically significant.

**Results**

Among 50 cases, 3 cases were CIN I (6%), 4 cases were CIN II (8%), 3 cases were CIN III (6%), 35 cases of Squamous cell carcinoma (70%) and 5 cases of adenocarcinoma (10%).

The incidence of HER2/neu was found to be 56%.

The expression of HER 2/ neu was seen in 3 cases of CIN III, 20 cases of SCC and 5 cases of adenocarcinoma while CIN I, CIN II remain negative (Table-1).

In preneoplastic lesions all CIN III cases showed positivity but HER2/neu score was 1+, so according to the ASCO guidelines all the preneoplastic lesions were considered negative for HER 2/neu.

Out of 20 HER2 /neu positive cases of squamous cell carcinoma, 12cases (50%) were of Moderately Differentiated SCC, 6 cases (85.7%) of Poorly Differentiated SCC and 2 cases (50%) of Well Differentiated SCC (Table-2).

Out of 5 cases of adenocarcinoma, HER 2/neu expression was seen in all the cases, of which 3 cases (60%) showed 1+ positivity and 2 cases (40%) showed 2+ positivity.

The distribution of HER2/neu positive cases in relation to various clinical staging was done which

showed stage III cases had increased HER2/neu expression of about 80% positivity. On applying chi square test, the P value was found to 0.033, and the association was significant.

Of the total 50 cases 9 cases showed positive lymph node metastasis. Among 9 cases,7 cases showed HER2/neu expression (77.77%) all of were SCC, moderately differentiated 6 cases and 1 case of poorly differentiated SCC.. Based on the chi square test, p value was (0.106) significant and so a correlation exists between HER2/neu expression and lymph node metastasis in neoplastic lesions of cervix (Table-3)

There were about 14 cases showing parametrial extension. 10 cases of SCC and 4 cases of adenocarcinoma. Out of 10 cases of squamous cell carcinoma showing parametrial extension, 7 were of moderately differentiated carcinoma (70%), 2 of poorly differentiated carcinoma (20%) and 1 case of well differentiated carcinoma(10%). Out of which 9 cases were HER 2/neu positive (64.2%). Among 14 cases, 8 positive for HER 2/neuoncoprotein (64.2%) and all were squamous cell carcinoma. P value was significant 0.028 thus showing association of HER2/neu with parametrial extension. (Table -4)

**Table-1:** Association of incidence of HER-2/neu with histological type

Histological type	No. of patients		HER-2/neu				p-value <sup>1</sup>
			Positive		Negative		
	No.	%	No.	%	No.	%	
CIN I	3	6.0	0	0.0	3	100.0	NA
CIN II	4	8.0	0	0.0	4	100.0	
CIN III	3	6.0	3	100	0	0.0	
Adenocarcinoma	5	10.0	5	100	0	0.0	
SCC	35	70.0	20	57.1	15	42.8	

Chi-square test, NA-Not applicable as >one 0s in a column

**Table-2:** Distribution of HER 2/neu expression in grades of squamous cell carcinoma

Grades of SCC	HER 2/ neu positive cases (n=20)	Percentage
W.D. SCC (n=4)	2	50%
M.D. SCC (n=24)	12	50%
P.D. SCC (n=7)	6	85.7%

Chi square value -2.91[p value -0.23] not significant



**Table-3:** Distribution of HER2/neu expression in clinical staging

Clinical staging	Total cases	HER 2/neu positive cases
STAGE I	18	05 (27.7%)
STAGE II	19	07 (36.8%)
STAGE III	11	09 (81.8%)
STAGE IV	02	01 (50.0%)

Chi-square test value 8.73 [ p value -0.033] the result is significant

**Table-4:** Correlation of HER 2/neu expression with lymph node metastasis in cervix

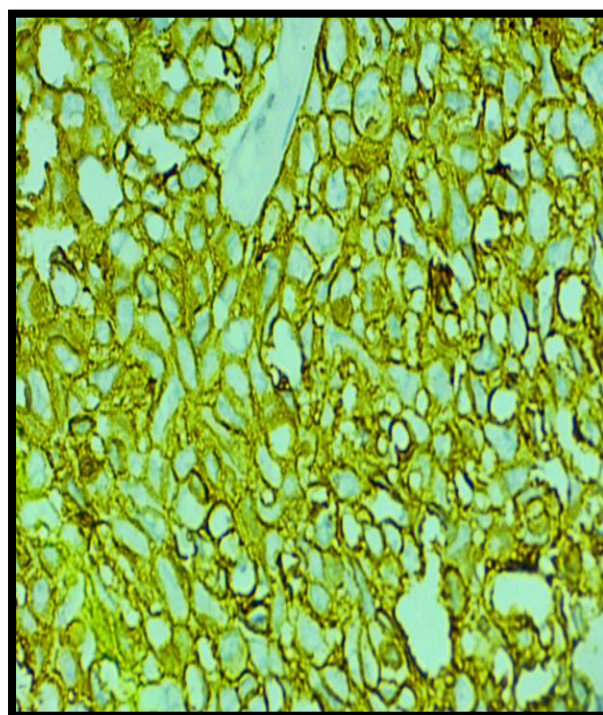
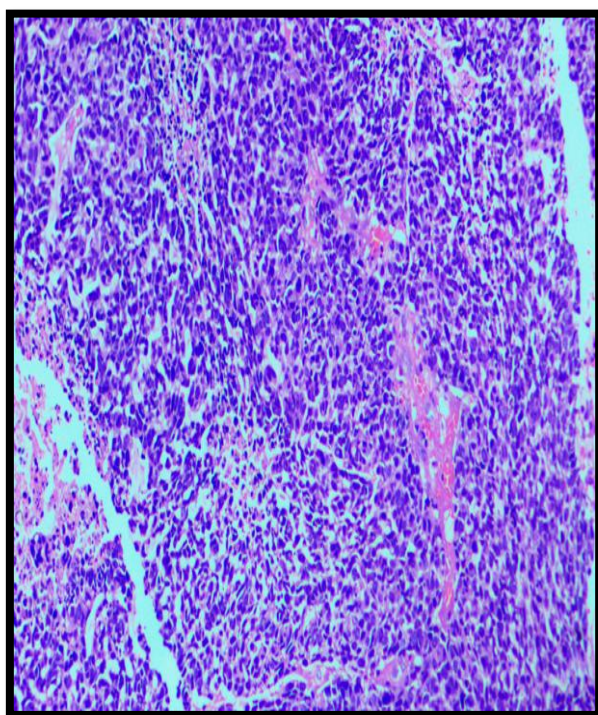
Lymph node metastasis	Total cases	HER 2/neu positive cases	HER 2/neu Negative cases	P value
Present	9	7(77.77%)	2 (22.2%)	0.106
Absent	41	13(31.7%)	28 (68.2%)	

Chi-square test value 6.52 [ p value -0.106 ] the result is significant p<0.05

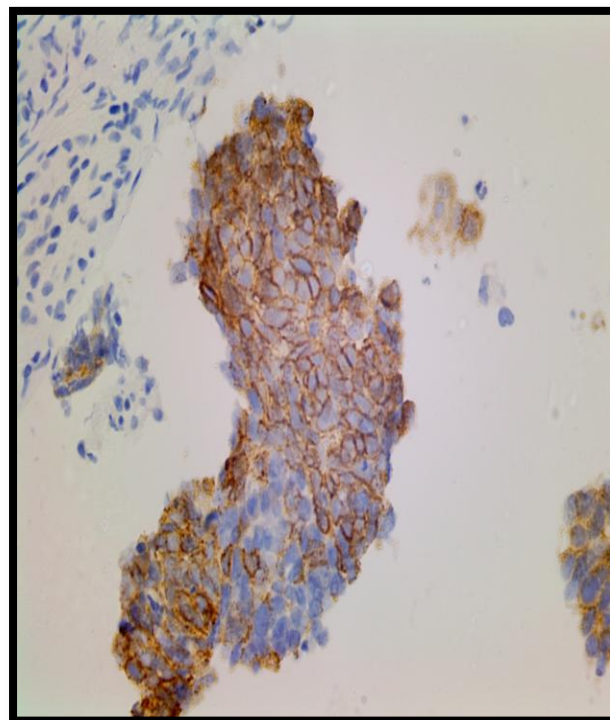
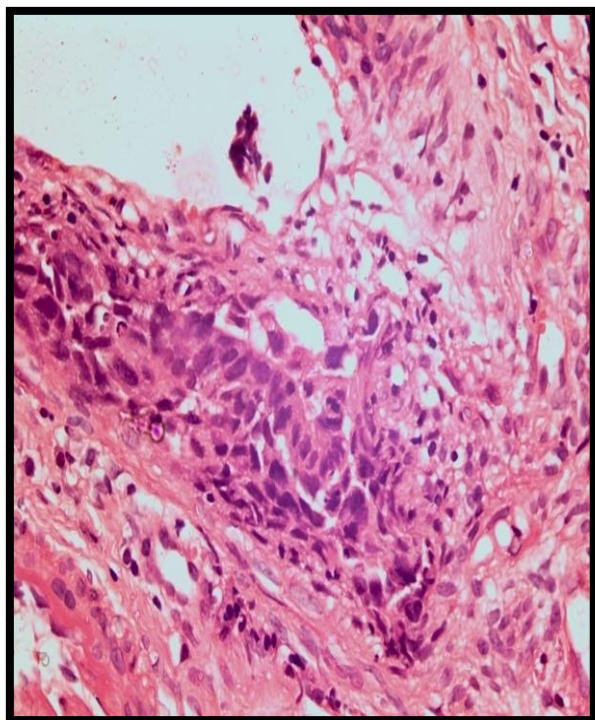
**Table-5:** Correlation of HER 2 / neu positivity in parametrial extension cases of carcinoma cervix

Parametrial extension	No. of cases	HER 2 / neu positive	HER 2 / neu Negative	P value
Present	14	9(64.2%)	5(35.7%)	.028
Absent	36	11(30.5%)	25(69.4%)	

chi square test value -4.77 [ p value-.028] the result is significant



**Photomicrograph H&E & IHC:** Poorly differentiated squamous cell carcinoma (40X), HER 2/neu score 3+ ; neoplastic squamous cell shows strong membranous staining (40X)



**Photomicrograph H&E and IHC: adenocarcinoma (40x), HER 2/neu score 2+ in case of adenocarcinoma moderately differentiated**

### Discussion

The present study was conducted in the Department of Pathology, Hind Institute of Medical Sciences, Barabanki with the objective to assess immunohistochemically the expression of HER 2/neu in preneoplastic and neoplastic lesions of uterine cervix and its correlation with histological type, grade and stage of cervical malignancy.

A total of 50 cases of preneoplastic and neoplastic lesions of uterine cervix were obtained as either cervical biopsies or hysterectomy specimens in this study.

Among the 50 cases, 3 cases were CIN I (6%), 4 cases were CIN II (8%), 3 cases were CIN III (6%), 35 cases were Squamous cell carcinoma (70%) and 5 cases were adenocarcinoma (10%).

In our study SCC cases (70%) outnumbered the adenocarcinoma (10%) cases which was in concordance with World Health Organization too which states that Squamous Cell Carcinoma accounts for approximately 70% -80% of cervical cancer while Adenocarcinoma accounts for 15%-20%.

In the present study the HER2/neu expression was seen in 56% cases while 44 % cases did not show any positivity for HER2/neu. Comparing the HER2/neu positivity with other studies, it was seen that about 63% of cases showed positivity for HER2/neu in Gupta et al (2009). The positivity rate in the present study is close to the study by Sharma et al (2016) and Sarwade et al (2016) who showed 52% and 44% positivity respectively.

In this study the premalignant lesion showed HER 2 expression score upto 1+only , while there were none of the premalignant cases showing score of 2+ and 3+ .Higher score of HER 2/neu was seen only in malignant cases .

Higher expression of HER 2 /neu among malignant cases as compared to premalignant lesion in our study is in agreement with the findings of Sarwade et al (2016) and Carreras et al (2007) and indicated the possibility of gradual progression in HER2/neu expression from premalignant to malignant cases although several previous studies do not endorse the same in terms of positivity alone.

HER2/neu positivity was 30% in the premalignant lesion in this study and was only of 1+type. In



comparison to the present study HER2 expression was noted only in 37.5% of CIN cases by Li et al (2013) while 60% of CIN cases showed HER2 positivity in a study by Gupta et al (2009). Lakshmi et al (1997) noticed HER-2 expression in 86.25% of CIN cases and this was found to be statistically significant. Joseph et al (2015) encountered 10 cases of CIN and found 7 to be HER2/neu (70%) positive.

The reason for discordance between the studies could be due to the fact that less number of cases was analyzed in the present study.

In the present study expression of HER 2/neu in cervical carcinoma was seen to be 44%. Costa et al (1995) reported HER-2/neu expression in 77% of cervical carcinomas while Lakshmi et al (1997) reported HER-2/neu expression in 96.8% of squamous cell carcinomas of cervix. Ndubisi et al (1997) observed HER-2/neu expression in 34 cases out of 150 (22%).

According to various studies expression of HER 2/neu in cervical carcinoma varied from 12.1% to 96.8%. This variability may be attributed to the difference in the number of cases analyzed, variation in stage of tumor and in the experimental procedure followed.

In this study only two types of carcinoma were included in which SCC formed the largest group with 35 cases. Of this 20 (57%) were positive for HER2/neu. There were 5 cases of adenocarcinoma. Of this 2 (40%) were positive for HER2/neu. The 2 positive adenocarcinoma (40%) for HER2/neu expression showed score of 2+ while the rest 3 (60%) was 1+.

Joseph et al (2015) showed 100 % positivity for both adenocarcinoma as well as squamous cell carcinoma. While in the study by Gupta et al (2009) who reported 54.1% squamous cell carcinoma and 84.6% for adenocarcinoma and higher proportion of IHC scores 2+ and 3+ for adenocarcinoma as compared to SCC (43.8%).

The findings of present study, thus does not show harmony with any of the previous studies except some resemblance with the study of Sharma et al (2016) who reported none of the

adenocarcinoma strongly positive for HER2/neu. All the 3 cases showed 1+ positivity. Kihana et al (1994) studied 44 cases of adenocarcinoma and found 1+ and 2+ positivity in 34 cases. In the study conducted by Hale et al (1992) 5 out of 6 adenocarcinoma (83%) showed definite membranous positivity.

In fact, all the studies show different trends, thus indicating that these trends need to be followed further using larger sample sizes.

Many studies on cervical lesions are of the opinion that HER2/neu over expression is directly linked to advanced grades and poorly differentiated tumour having bad outcome.

In the present study there were 35 cases of squamous cell carcinoma forming the largest group. Of this 20 were positive for HER 2/neu. Among the SCC cervix, maximum number of cases belonged to moderately differentiated 24(68.6%), followed by poorly differentiated 7(20%), well differentiated were only 4 cases (11.4%). On performing immunohistochemistry, HER 2/neu positivity rate showed an incremental trend from well differentiated (50%) to poorly differentiated (85.6%). On applying the chi square, p value was 0.23. Hence no significant association could be proved between HER2/neu positivity and grades of squamous cell carcinoma. In the study by Sharma et al (2016) total 18 cases of SCC. Of which 11(61%) were positive for HER2/neu. But there was no significant association between HER2/neu expression and histological grades of SCC (p value -0.52). Brumm et al (1990) reported a high rate (75%) of expression of HER2/neu in SCC cervix. Gupta et al (2009) states that out of 48 cases of squamous cell carcinoma 7 cases (14.5%) showed 2+ staining and 14 cases (29.2%) showed 3+ staining. Therefore, 21/48 (43.7%) cases were positive for HER2/neu. Joseph et al (2015) in their study reported 100 % positivity rate for all histopathological grades, however, with respect to IHC score, they also reported an increasing trend of higher scores (3+) increasing from 0% well differentiated and 27% moderately differentiated

to 72.7% in poorly differentiated histopathological grades respectively but did not find any relation between HER2/neu expression and grades of SCC.

Sarwade et al (2016) in their study reported SCC belonging to moderately and poorly differentiated carcinomas showed 2+ and 3+ positivity where as well differentiated carcinoma showed only 1+ positivity. Of 3 cases with 3+ positivity 2 cases (66.6%) belonged to moderately differentiated and 1 case (33.3%) belonged to poorly differentiated. But no correlation was established between HER2/neu and histological grades of SCC (p value 0.93).

Thus, the findings of present study are in agreement with the literature and show that with increasing loss of differentiation, the HER 2/neu IHC expression rate shows an incremental trend.

In the present study it was found that higher intensity of HER2/neu expression among cases under stage III (81.8%) and stage IV (50%). A statistically significant relationship was established between HER 2/neu expression and stage of the tumour (pvalue-0.033).

Similar to our study Ndubisi et al(1997) and Gupta et al (2009) found a significant correlation between HER-2/neu expression and higher stage of cervical carcinoma. Ndubisi et al (1997) had studied HER-2/neu expression in 150 cases of cervical carcinoma while Gupta et al(2009) had analyzed 65 cases of cervical carcinoma. In study by Gupta et al (2009) positivity was 48% (14/29) in stage I. In stage II 13/18 (72%) cases showed HER2/neu positivity. In stage III this positivity was increased upto 72% (13/18). 2 cases were there in stage IV, both of which were positive for the IHC marker.

Contrary to this Joseph et al(2015) and Sarwade et al (2016) did not find any relation between HER-2/neu expression and higher stage of cervical carcinoma. Joseph et al (2015) studied HER-2/neu expression in 24 cases of cervical carcinoma while Sarwade et al (2016) studied HER2/neu expression in 30 cases of cervical carcinoma.

The conflicting result may be due to difference in institutional treatment standards and due to varied subjective interpretation of staining intensity and distribution between centers. Because staining intensity is judged on a continuum differences in institutional “cut off” for positivity which is likely to also effect correlation with histologic results.

In the present study lymph node metastasis was found in 9 cases out of which 8 belongs to squamous cell carcinoma and 1 cases of adenocarcinoma. HER 2/ neu positivity was seen only in 7 cases of squamous cell carcinoma. It showed statistical significance between HER2/neu expression and the lymph node metastasis (pvalue -0.106).

Mandai et al (1995) and Yong et al(1998) analyzed HER-2/neu expression in 39 and 74 cases of cervical adenocarcinoma respectively and reported that a significant correlation existed between HER-2/neu expression and lymph node metastasis. Yong et al found the expression of c-erbB-2 in 34 cases.

Contrary to our study Joseph et al (2015) in his study among carcinoma cases found that 4 cases (16.7%) had no parametrial or lymph node involvement, 11 cases (45.8%) had only parametrial involvement and 9 cases (37.5%) had involvement of both. On analyzing variation in intensity of HER-2 staining with lymph node and parametrial involvement it was found that among 9 cases with 2+ positivity, 2 cases had no lymph node or parametrial involvement, 4 cases had only parametrial involvement and 3 of the cases showed both. Out of 13 cases with 3+ positivity, 2 cases had no lymph node or parametrial involvement, 5 cases had only parametrial involvement and remaining 6 cases had involvement of both. Even though cervical carcinoma cases with involvement of lymph node and parametrium showed stronger HER-2 staining a statistically significant correlation between these variables could not be established (p=0.577).

In a study by Gupta et al (2009) out of 14 cases of lymph node metastasis, squamous cell carcinoma

(11 cases) and adenocarcinoma (three cases) showed c-erbB-2 positivity rate of 90.9% and 100% respectively.

There were 14 cases of parametrial extension, which comprises of 10 cases of squamous cell carcinoma (71.4%), 4 cases of adenocarcinoma (28.5%). Among these 9 (64.2%) showed increased expression of HER2/neu oncoprotein. Out of which 8 cases (88.8%) was squamous cell carcinoma and 1 case (11%) was adenocarcinoma. It showed statistical significance between HER2/neu expression and parametrial extension (pvalue-0.028).

Similar to our study Gupta et al (2009) analyzed HER-2 expression in 65 cases of cervical carcinomas and stated that intensity of staining correlated with presence of parametrial extension. Contrary to our study Sarwade et al(2016) and Joseph et al(2015) they state that there is no significance between parametrial extension and HER 2/neu expression .

There was a significant correlation between positive HER2 expression and higher clinical stage of presentation. HER 2 expression was significantly higher in lymph node positive cases than the lymph node negative cases .There was also significantly high expression in cases with parametrial involvement.

Other than histological types, result correlated well with other similar studies.

In the literature, there are reports in favour of increased expression of HER 2 oncoprotein and also reports saying that there is only rare over expression of HER 2/neu.

Thus, there are contradictory reports on expression of HER2/neu and prognosis in various uterine lesions which may either due to heterogeneity of lesions or technical problem with antigen retrieval. HER2/neu has a complex activation pathway and its expression is controlled not only by the degree of gene amplification but also by several other factors like gene receptor alteration and rate of gene transcription , which help in tyrosine kinase activation leading to cellular transformation.

One of the limitations of this study is the sample size, hence further studies on larger sample size are recommended.

### Conclusion

Expression of HER 2 /neu is relatively lower in cervical lesions. With shift from well to poorly differentiated lesions, the HER2/neu expression rate shows incremental trend. This study shows HER 2/neu expression in cervical carcinoma correlates with higher clinical stage. HER 2/ neu expression correlates with lymph node metastasis and with parametrial extensions. Immunohistochemical verdict of HER2/neu expression do not distinguish subgroups of patients at higher risk of recurrence of disease. Hence HER2/neu oncogene may not represent a future target for monoclonal antibody directed therapy for cervical cancer. Therefore further studies on various subtypes and their prognostic significance are needed.

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