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## Original Research Article

## Role of HER2/neu expression in premalignant and malignant lesions of uterine cervix

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## ABSTRACT

Many research studies on various biomarkers were done, in analysing the prognosis and in evaluation of therapeutic target strategies which improves the survival rate in carcinoma of cervix. Of these, one of the important biomarker is HER-2/neu.

**Objectives:** To correlate histomorphology of cervical lesions, various clinicopathological parameters with HER-2/neu.

**Materials and Methods:** The present study conducted during the period from June 2017 to May 2019 in department of Pathology, Madurai Medical College, Madurai. 200 cases were selected for study. Among those, 50 cases were selected for immunohistochemical studies with HER 2.

**Results:** Out of 50 cases included, higher HER 2 positivity was observed in HSIL as compared to LSIL. In malignant lesions, positive immunostaining was observed in 71.05% cases. Positivity was seen in 70% of cases of squamous cell carcinoma and 75% of cases of adenocarcinoma cases.

**Conclusion:** Progression of clinical spectrum of the lesion is associated with overexpression of HER 2, suggesting HER 2 can be considered as one of poor prognostic factor. Malignant lesions expressed greater positivity than premalignant lesions. Also, overexpression of HER 2 is associated with progressing grade and advanced stage of cervical carcinoma.

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## 1. Introduction

Worldwide, Cervical carcinoma is the fourth most common cancer affecting women and ranks fourth in cancer-related death in females.<sup>1</sup> The peak age of incidence of cervical carcinoma is 55- 59 years. Premalignant lesions of cervix progress over a period of years to invasive carcinomas. There are many significant pathologic prognostic factors for cervical carcinoma. They include age of patient, HPV status, tumor size, depth of the stromal invasion, nodal status, vaginal and parametrial involvement, FIGO stage, lymphovascular invasion etc.

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HER-2/neu, (human epidermal growth factor receptor) also called as cerbB-2, is a proto-oncogene with 1255 amino acids. HER-2/neu is located on Chromosome 17q21 and it codes for a growth factor receptor-like molecule, present on cell membrane surface with tyrosine kinase activity.<sup>2</sup> HER-2/neu exhibits its function by multiple signal transduction pathways and is involved in regulation of cell growth, proliferation, its survival and differentiation.<sup>3</sup> HER-2 expression is correlated with aggressive metastatic potential.

In our study, we analyse the histomorphology of premalignant and malignant lesions of cervix and expression of the biomarkers – HER 2 in these lesions. The present study also evaluates the expression of HER 2 in

pre-malignant and malignant lesions of cervical carcinoma and its association with parameters like stage, tumor size, vaginal and parametrial involvement, nodal status and with the histological grade of tumor.

## 2. Materials and Methods

The present study is a retrospective descriptive study in pre-malignant and malignant lesions of cervix biopsies and hysterectomy specimens, conducted during the period from June 2017 to May 2019 in Department of Pathology, Madurai Medical College, Madurai.

50 cases including pre-malignant and malignant lesions of cervix were selected randomly and are included in study for histopathological analysis were selected for immunohistochemical studies with HER 2. Pre-malignant lesions included were CIN 1 and CIN 2 each with 3 cases and CIN 3 with 6 cases. Out of 38 malignant neoplasms, 30 were Squamous and 8 were adenocarcinoma. 10 Cases of Well, Moderately and poorly differentiated squamous carcinoma were selected for the study.

Control Carcinoma of breast was taken as internal control for determining HER 2 expression and to avoid false negative results.

## 3. Observation and Results

### 3.1. Interpretation and scoring system

Antibody treated slides were analysed for presence or absence of reactivity, localization (cytoplasmic membrane) and percentage of cells stained and intensity of expression.

**Table 1:** 2014 ASCO/CAP HER 2 scoring guideline

HER 2/neu expression	Staining character
0	Lack of staining or weak membrane staining in less than 10% of tumor cells
+1	Weak membrane staining is observed in greater than 10% of tumor cells
+2	Moderate membrane staining is seen in greater than 10% of tumor cells
+3	Strong membrane staining is seen in greater than 10% of tumor cells

In present study, out of 50 selected cases in which immunohistochemistry was done, 11 cases (22%) showed 1+ positivity, 14 cases (28%) showed 2+ positivity, 8 cases (16%) showed 3+ positivity and other cases were negative.

On comparing the expression of HER 2 in pre-malignant and malignant lesion of cervix, HER 2 was expressed higher in 26 cases of malignant lesion compared to 6 cases in pre-malignant lesions

When HER 2 expression was compared with histopathological subtype of cervical carcinoma, it was observed that overexpression of HER 2 was seen in

squamous cell carcinoma (63.58%), than in adenocarcinoma (18.18%).

In our study, when tumor size and expression of HER 2 were compared, it was observed that larger tumors showed greater expression, when compared to smaller tumors. The correlation between tumor size and expression of HER 2 was found to be statistically significant with a p value of less than 0.001. Hence, it may be suggested that similar to the tumor size, expression of HER 2 can also be considered as a prognostic factor.

When HER 2 expression was compared with parametrial and vaginal involvement, no significant correlation was found.

On comparing the nodal status with HER 2 expression, it was observed that all of the case with enlarged lymph node showed HER 2 expression. Out of 33 HER 2 positive cases, 13 cases (39.39%) showed enlarged lymph nodes detected radiologically.

On comparing the tumor stage with expression of HER 2, expression of HER 2 is upregulated in advanced stages. However, no statistically significant correlation was made in our study.

**Table 2:** Correlation between histological subtypes of carcinoma and HER 2 expression

Squamous cell carcinoma -Grades	HER 2		
	1+	2+	3+
Well differentiated	3 (30%)	3 (30%)	4 (40%)
Moderately differentiated	2 (20%)	4 (40%)	3 (30%)
Poorly differentiated	1 (10%)	4 (40%)	2 (20%)

**Table 3:** Correlation between tumor size and HER 2 expression

HER 2	Tumor Size			
	<0.5 cm	0.5 -4 cm	>4 cm	Nil
Positive (33)	0	18 (54.54%)	10 (30.3%)	5 (15.15%)
Negative (17)	7 (41.17%)	3 (17.64%)	3 (17.64%)	4 (23.5%)

**Table 4:** Correlation between nodal status and HER 2 expression

HER 2	Nodal status	
	Positive	Negative
0	2 (13.33%)	9 (39.13%)
1+	1 (6.67%)	5 (21.74%)
2+	6 (40%)	7 (30.43%)
3+	6 (40%)	2 (8.69%)

## 4. Discussion

Cervical carcinoma is the most prevalent neoplasm of women in India and is one of the major cause of mortality

and morbidity among women. Cervical carcinoma is unique as it can be detected early in course by several screening programmes, which includes Pap smear, VIA, VILI, HPV screening, colposcopy and cervix biopsy.

Researches had been studied in role of HER 2 as a therapeutic target and as a prognostic marker in several tumors such as breast, stomach. Various results had been published in relation to role of HER 2 in cervical lesions.

#### 4.1. Role of HER 2 immunostaining in various aspects of cervical pathology

Out of 12 cases of premalignant lesion, 6 cases (50%) showed HER 2 immunostaining. Out of 3 cases of CIN 1, one showed +1 expression. Out of 3 cases of CIN 2, 2 cases showed +1 expression. 3 cases did not stain with HER 2 and 3 cases showed 1+ positivity. In CIN3, out of 6 cases in which immunohistochemistry of HER 2 was done, 3 cases of did not stain for HER 2, one case showed 3+ positivity, another case showed 2+ positivity and another showed positivity for 1+. The p value was found to be >0.05, hence it was found to be non-significant. In a study published by Protrka et al, 2007, expression of HER 2 in LSIL was found in 56.3% of cases and in HSIL it was reported in 81.8% of cases.<sup>4</sup> In a study by Joseph et al. (2015), 70% of cases with CIN showed HER 2 positivity.<sup>5</sup> In a study conducted by Gupta et al. (2009), 60% of CIN cases showed positivity of HER 2, most of them were of 1+ and 2+ positivity, none of them expressed 3+ positivity.<sup>6</sup> In a study by Li et al. (2013), HER 2 expression was seen only in about 37.5% of cases of CIN positivity.<sup>7</sup>

In malignant cases, the expression of HER 2 was found in 27 cases out of 38 malignant cases (71.05%). In our present study, overexpression of HER 2 was found in malignant lesions compared to premalignant lesions. In a study by Joseph et al. (2015), it was observed that the expression of HER 2 was higher in malignant lesions when compared to the premalignant lesions.<sup>5</sup> They reported that progression of expression of HER 2 was gradual, when the spectrum of the lesion moves higher. In studies reported by Gupta et al. (2009),<sup>6</sup> and Lakshmi et al. (1997)<sup>8</sup> similar findings were observed.

Among 30 squamous cell carcinoma, in which immunohistochemistry was done, 21 cases (70%) showed immunostaining and other 9 cases (30%) did not stain for HER 2. Out of 21 cases, 1+ was observed in 9 cases (30%), 2+ in 11 cases (36.67%) and 3+ in 4 cases. In the study done by Joseph et al, 2015, all cases of squamous cell carcinoma showed HER 2 expression, with 1+ positivity in 10% of cases, 2+ positivity in 35% of cases and 3+ positivity in 55% of cases.<sup>5</sup> In a study by Hale et al. (1992), it was reported that HER 2 expression was found in 38% cases of squamous cell carcinoma, findings are quite similar to our study.<sup>9</sup> Gupta et al. (2009), reported that 53.17% of cases of Squamous cell carcinoma showed HER 2 positivity.<sup>6</sup>

In their study it was observed that 1+ positivity was found in 10.42% cases, 2+ positivity in 14.58% cases and 3+ positivity in 9.17% cases.

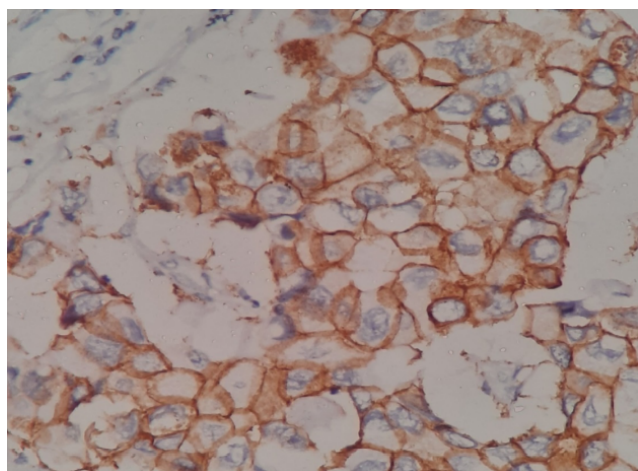
Immunostaining was done in 8 cases of Adenocarcinoma of cervix. Out of 8 cases, 2 cases (25%) did not stain for HER 2 and were considered as negative. Positive staining was observed in 6 cases (75%). Out of 6 cases, 2+ positivity was seen in 2 cases (25%) and 3+ positivity was seen in 4 cases (50%). Adenocarcinoma showed greater and more positivity, when compared to squamous cell carcinoma. But, the p value on comparing Her 2 expression in adenocarcinoma with squamous cell carcinoma was >0.05, hence it was statistically non-significant.

In a study by Joseph et al. (2015), out of 4 cases of adenocarcinoma, 2+ positivity was seen in 2 cases (50%) and 3+ positivity was seen in 2 cases (50%), which was also statistically non-significant (5). In a study by Lee et al. (2004), it was published that overexpression of HER 2 in adenocarcinoma was statistically significant.<sup>10</sup> Gupta et al. (2009), concluded that adenocarcinoma was positive in 84.61% of cases, out of which 1+ positivity 80 was seen in 23.08% cases and 2+ and 3+ positivity was seen in 30.77% cases.<sup>6</sup> In a study by Costa et al. (1995), cervical carcinoma with glandular differentiation showed overexpression of HER 2.<sup>11</sup> Mandai et al. (1995), concluded that HER 2 can be suggested as a prognostic marker in adenocarcinoma.<sup>12</sup> Gupta et al. (2009), suggested that various grades of differentiation of SCC show varied intensity score of HER 2 immunostaining [118]. Poorly differentiated carcinoma showed more positivity (80% cases). In their study all cases of well differentiated grade of SCC were negative with HER 2 immunostaining and moderately differentiated grade of SCC showed positive staining in 54.55% of cases.

In present study, among 10 cases of well differentiated grade of SCC, 4 cases (40%) did not stain. Positivity was seen in other 6 cases (60%). Among 6 positive cases, 1+ positivity was seen in 3 cases (30%), 2+ positivity was seen in 3 cases. None of the case expressed 3+ positivity.

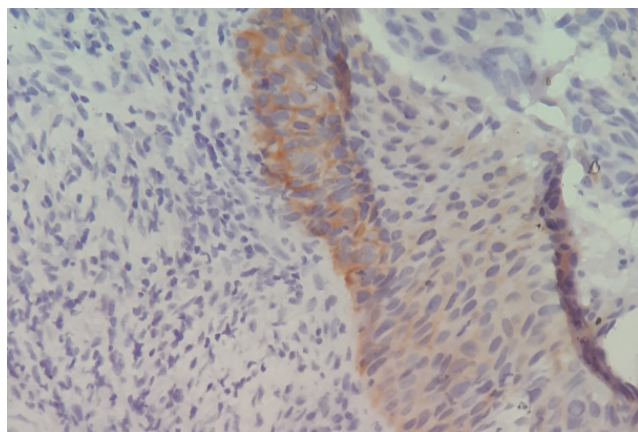
Among 10 cases of moderately differentiated grade of SCC included in our study, 3 cases (30%) did not stain for HER 2. Positive staining was seen in 7 cases (20%). Among 7 positive cases, 1+ positivity was seen in 2 cases (20%), 2+ positivity was seen in 4 cases (40%) 3+ positivity was seen in rest 1 case (10%).

Among 10 cases of poorly differentiated grade of SCC, 2 cases did not stain for HER 2. Positive staining was observed in 8 cases (80%). Among 8 positive cases, 1+ positivity was seen in one case (10%), 2+ positivity in 4 cases (40%) and 3+ positivity in 3 cases (30%). On comparing HER 2 expression with squamous cell carcinoma grade, p value was found to be 0.05, hence it was found statistically non-significant. Gupta et al, 2009, in their study quite similar finding was reported.<sup>6</sup> This study suggested in stage III and stage IV cervical carcinoma greater expression

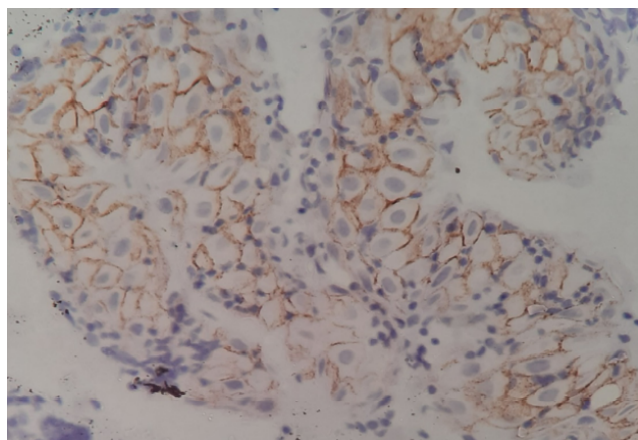


**Fig. 3:** HER 2 3+ positivity in poorly differentiated squamous cell carcinoma

of HER 2 is seen. In a study by Joseph et al, (2015), the correlation between HER 2 positivity and stage of cancer was not statistically significant.<sup>5</sup>



**Fig. 1:** HER 2 2+ positivity in CIN -3



**Fig. 2:** HER 2 2+ positivity in moderately differentiated squamous cell carcinoma

Overall in our study, “Role of her 2 expression in premalignant and malignant lesions of cervix”, it was found that progression of clinical spectrum of the lesion is associated with overexpression of HER 2, suggesting HER 2 can be considered as one of poor prognostic factor. Malignant lesions expressed greater positivity than premalignant lesions. Also, overexpression of HER 2 is associated with progressing grade and advanced stage of cervical carcinoma. Higher positivity was observed in enlarged lymph nodes.

## 5. Conclusion

Worldwide, Cervical cancer is the fourth most common cancer in females, and seventh overall. In India, it ranks second in causing cancer-related deaths, next to breast carcinoma. Various studies, including our present study have suggested the consideration of HER 2 as a poor prognostic factor for carcinoma of cervix. An effective and easier method for determination of prognostic factors in early course of disease is immunohistochemistry. This allows the patients to be categorised and appropriate management to be decided. We as a surgical pathologists, our duty does not end up just in diagnosing carcinoma or subclassifying it, but it is our whole responsibility to help clinicians in determining appropriate treatment for the patients. In this modern era of targeted therapy, many research studies should be done to find out appropriate therapeutic markers, there by targeted therapy can be applied effectively against common killer disease – THE CERVICAL CARCINOMA.

## 6. Source of Funding

None

## 7. Conflicts of Interest


The authors declare that there are no conflicts of interest.

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