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Original Research Article

HER-2 IN CERVICAL CARCINOMA AS A POOR PROGNOSTIC FACTOR– A RETROSPECTIVE STUDY

vijayalakshmi M[1], Sharmila Thilagavathy N[2] , Vijayalakshmi A[3]

[1]Assistant Professor, Department of Pathology, Sivagangai Medical College, Sivagangai, Tamilnadu, India
[2]Professor and Head of the Department, Department of Pathology, Sivagangai Medical College, Sivagangai, Tamilnadu, India.
[3]Associate Professor, Department of Pathology, Sivagangai Medical College, Sivagangai, Tamilnadu, India.

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Corresponding Author:
Dr. Vijayalakshmi M,
Email: drvijayalakshmi1483@gmail.com

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Abstract

Background: Of all the studies done on various biomarkers of cervical carcinoma, only a few have discussed about the biomarker is HER-2/neu and its association with other clinical and histopathological parameters. This will help in analyzing the prognosis and framing therapeutic target strategies to improve the survival rate of patients with Carcinoma of cervix. The objective is to analyze the histopathological parameters of cervical lesions and their association with HER-2. **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 immuno histochemical studies with HER 2. **Result:** Out of 200 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. HER-2 positivity was observed among more number of patients of 51-60 years age group and post-menopausal women. 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 if HER 2, suggesting HER 2 can be considered as one of poor prognostic factor. Advanced tumor stages and nodal involvement expressed greater positivity.

INTRODUCTION

Cervical carcinoma is the fourth most common cancer affecting women worldwide. Cervical carcinoma is diagnosed every year in approximately 569,847 women and accounts for about 311,365 deaths annually.[1] In India, cervical cancer accounts for about 16 % of all cervical cancer cases and 15.2% of total cervical carcinoma deaths occurring globally.[2]

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.[3] Recently, many studies on various biomarkers were done to analyze the prognosis and for targeted therapeutic strategies which in turn improves the survival rate in carcinoma of cervix.[4]

One such biomarker is HER- 2/neu.

HER-2/neu, (human epidermal growth factor receptor) also called as c-erbB-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. It is involved in regulation of cell growth, proliferation and differentiation.

HER-2 expression is believed to be associated with the aggressive biological behavior and metastatic potential of cervical carcinomas.

In this study, we analyze 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 and its association with factors like age of patient, menstrual status, stage and nodal status of the tumor.

MATERIALS AND METHODS

The present study is a retrospective study among premalignant and malignant lesions of cervix biopsy

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and hysterectomy specimens received at the Department of Pathology, Madurai Medical College, Madurai during the period from June 2017 to May 2019. Of all the 518 cervical specimens received, 200 samples were selected randomly which included premalignant and malignant lesions. They were subjected to Histopathological analysis and Immunohistochemical studies with HER 2. Out of 38 malignant neoplasms, 30 were Squamous and 8 were adenocarcinoma. Control Carcinoma of breast was taken as internal control for determining HER 2 expression and to avoid false negative results.

RESULTS

Of all the samples, 8 (4%) cases of hysterectomy and 192 (96%) cases of cervix biopsies were included. Among 200 specimens, 15 (7.5%) were of LSIL, 21 (10.5%) were HSIL, 148 (74%) were squamous cell carcinoma,14 (7%) cases were adenocarcinoma and 2 (1%) case of adenosquamous carcinoma. It was observed that lesions were predominantly malignant (82 %). Among premalignant lesions, the most common one was HSIL. The most common type of cervical malignancy was Squamous Cell Carcinoma (74%), followed by Adenocarcinoma (7 %).

Table 1: Histopathological spectrum of cervical lesion.

HPE diagnosis	Frequency (%)
LSIL	15 (7.5%)
HSIL	21 (10.5%)
SCC	148 (74%)
Adenocarcinoma	14 (7%)
Adeno squamous	2 (1%)
Total	200 (100%)

Squamous cell carcinoma of cervix was categorized based on HPE as well, moderate and poorly differentiated histological grades. Moderately differentiated squamous cell carcinoma was most common histological grade (58.2%) followed by well differentiated grade (25.3%).

Table 2: Histological grading of cervical carcinoma

HPE diagnosis	Frequency (%)
Well differentiated	37 (25.3%)
Moderately differentiated	85 (58.2%)
Poorly differentiated	26 (17.8%)
Total	146 (100%)

In our study, the mean age of cervical carcinoma was found to be 52.51 years, with total of 108 cases (52.51 %) in age group of 41-60 years. The mean age for premalignant lesions of cervix was found to be 39.97 years with major number of cases diagnosed in the age group of less than 40 years (26 cases, 72.22 %).

Table 3: Age wise distribution lesions based on Malignancy status.

Lesions vs Age(in years)	< 40	41 - 50	51 - 60	> 60
Premalignant HSIL & LSIL (36)	26 (72.22%)	4 (11.11%)	3 (8.3%)	3 (8.3%)
Malignant lesions (164)	23 (14.02%)	45 (29.43%)	63 (38.41%)	33 (20.12%)

Poorly differentiated carcinoma was seen in older female of age group greater than 50 years. This correlation was found to be statistically significant with p value less than 0.05.

Table 4: Age wise distribution of malignant squamous cell carcinoma based on HPE diagnosis.

	Age group			
Squamous cell carcinoma differentiation	< 40	41 - 50	51 - 60	> 60
Well differentiated	7 (18.91%)	9 (24.32%)	14 (37.83%)	7 (18.91%)
Moderately differentiated	15 (17.24%)	26 (29.88%)	34 (39.08%)	12 (13.79%)
Poorly differentiated	0	7 (29.16%)	8 (33.33%)	9 (37.5%)

Table 5: Association between Age group and HER-2 expression

HER -2	Age			
	< 40	41 - 50	51 - 60	> 60
Positive (33)	4 (12.12%)	9 (27.27%)	12 (36.36%)	8 (24.24%)
Negative (17)	2 (11.76%)	3 (17.64%)	9 (52.9%)	3 (17.64%)

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Among patients who showed positivity for HER -2, majority (36.36%) belonged to 51-60 years age group followed by 41-50 years age group (27.27%).
When comparing expression of HER-2 and menstrual status, it was observed that over expression of HER-2 was seen in postmenopausal female in 27 cases (81.82%). Only 6 cases (18.18%) showed Her-2 positivity in menstruating female. The association between menstrual status and her-2 expression was not statistically significant.

Table 6: Correlation between menstrual status and her-2 expression

HER -2	Menstrual status	
	Menstruating	PMP
Positive (33)	6 (18.18%)	27 (81.82%)
Negative (17)	3 (17.64%)	14 (82.35%)

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

Table 7: Association between Nodal status and HER-2 expression

HER -2	Nodal			
	Positive	Negative	Nil	Total
Positive	13 (39.39%)	14 (42.42%)	6 (18.18%)	33
Negative	0	11 (52.9%)	6 (35.29%)	17

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 8: correlation of tumor stage and intensity of HER-2

HER 2			stage	
	I	II	III	IV
0	9 (34.61%)	2(28.57%)	0	0
1+	5(19.23%)	1(14.28%)	0	0
2+	8(30.53%)	2(28.57%)	2(66.66%)	1(50%)
3+	4(15.38%)	2(28.57%)	1(33.33%)	1(50%)

DISCUSSION

Cervical carcinoma is the most prevalent neoplasm of women in India and is one of the major cause 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.[5] Various results had been published in relation to role of HER 2 in cervical lesions.
In the study, 200 cases which includes 8 cases of hysterectomy and 192 cases of cervix biopsies were selected. Out of 200 cases, 36 cases were premalignant lesions and others were malignant lesion. In premalignant lesions, LSIL was diagnosed in 15 cases (7.5%) and HSIL was diagnosed in 21 cases (10.5%) similar to a study by Corneanu et al. (2011).[6]
Out of 164 cases of malignant lesion included in our study, squamous cell carcinoma with 148 cases (74%) contributed the major type followed by adenocarcinoma with 14 cases (7%) and then least commonly by adenosquamous carcinoma with 2 cases (1%). Similar findings was published in a study by Watson et al (2008).[7] Squamous cell carcinoma was histologically graded into well differentiated grade (I), moderately differentiated grade (II) and poorly differentiated grade (III). In our present study, 85 cases (42.5%) were moderately differentiated type contributing the major grade, followed by 37 cases (18.5%) of well differentiated grade. Least common with 26 cases (13%) were poorly differentiated grade. The most common lymph nodes to be involved frequently are external iliac lymph node, paracervical and obturator lymph nodes. (Lifshitz et al (1980).[8]
In our present study, overall 42 malignant cases (21%) showed enlarged lymph nodes detected radiologically.
In our present study, among 38 malignant cases in which HER 2 immunohistochemistry was performed, 15 cases showed enlarged lymph node and other 23 cases were negative for lymph node. Out of 15 cases, 2 cases (6.67%) did not stain for HER 2, 1+ positivity was seen in a case and 2+ immunostaining in 6 cases (40%) and rest 6 cases (40%) showed 3+ immunostaining. Among 23 cases of lymph node negative carcinoma, in which immunohistochemistry was done, 39.13% of cases did not stain,[9] 1+ immunostaining was seen in 21.74% of cases,[5] 2+ staining was seen in 30.43% of cases,[7] 3 + staining was seen in 8.69% of cases.[2] P value was found to be <0.05, hence statistically significant correlation was made out similar to studies by Joseph et al, 2015 and Gupta et al. (2009).[9,10]
In present study among 26 cases of cervical carcinoma - Stage I, in which HER 2 immunohistochemistry was done, 34.62% of cases

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did not stain for HER,[9] 1+ positivity was seen in 5 cases (19.23%), 2+ positivity was seen in 8 cases (30.77%), and 3+ positivity was seen in 4 cases (15.38%). Among 7 cases of cervical carcinoma - Stage II, on which immunohistochemistry was done, 2 cases did not stain,1+ positivity was seen in 1 case (14.29%), 2 + positivity was seen in 2 cases (28.57%), 3+ positivity was seen in other 2 cases (28.57%). Among 3 cases of cervical carcinoma - Stage III, 2+ immunostaining was seen in 2 cases (66.67%) and 3+ immunostaining was observed in 1 case (33.33). Among 2 cases of cervical carcinoma - Stage IV, 2+ immunostaining was seen in 1 case (50%), and 3+ immunostaining was seen in 1 case (50%). The p value was >0.05, hence it was found statistically non -significant. Gupta et al, 2009 and Joseph et al, (2015) showed quite similar findings.

CONCLUSION

Cervical cancer being the fourth most common cancer in females worldwide, it ranks second in causing cancer-related deaths, next to breast carcinoma. In concurrence with many others studies on HER-2, this study also showed presence of HER-2 in advanced stages of tumor with extensive nodal involvement. Thus strengthens its association with poor prognosis. This will help in formulating gene targeted intervention strategies against advanced stages of cancer.

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