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Indian Journal of Pathology and Oncology

Journal homepage: www.innovativepublication.com

Original Research Article

Her-2 neu expression in cervical intraepithelial neoplasia and carcinoma of cervix

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ARTICLE INFO

Article history:
Received 19-10-2019
Accepted 27-01-2020
Available online 25-05-2020

Keywords:
Her-2 neu
CIN
Carcinoma cervix
Immunohistochemistry
IHC

ABSTRACT

Background and Objectives: Currently radiotherapy, cisplatin based chemo-radiation and surgery are used in combination for treating cervical cancer according to stage of the tumor. Patients with advanced disease stage have limited treatment options with median overall survival of less than one year. Therefore, there is increasing interest in using targeted therapy as a treatment modality. There are controversial views of various authors regarding role of Her-2 neu targeted therapy in cervical carcinoma. The present study was conducted to evaluate the expression of Her-2 neu in Pre-malignant and Malignant lesions of cervix and attempt its correlation with histological type, grade and stage of the tumor.
Materials and Methods: A cross-sectional observational study was conducted from January 2017 to January 2018 including a total of 55 patients with either pre-malignant and malignant lesions of cervix. Rabbit monoclonal Antibody to Her2/ErBb2 from BioGenex was used for staining. Intensity of Her-2 neu expression was graded according to the 2014 ASCO/CAP guidelines for Her-2 reporting.
Results: There was higher expression of Her-2 neu expression in HSIL then LSIL. There was significant correlation between Her-2 neu expression and histological types of malignant lesions. There was no significant correlation between Her-2 neu expression and pre-malignant lesions, stage of cervical carcinoma and grades of squamous cell carcinoma.
Conclusion: Her-2 neu has a role in higher grade of cervical lesions but studies with larger cohorts are needed to comment upon its definite role in targeted therapy.

1. Introduction

Among women, Carcinoma Cervix is the fourth most common cancer with an estimated 570,000 new cases in 2018 which amounts to 6.6% of all cancers in females. 90% of deaths in low and middle-income countries is attributable to cervical cancer.[1] The mortality due to cervical cancer can be decreased by proper screening of 'at risk' population, early diagnosis and effective treatment in the form of surgery and chemoradiation. Several tissue markers have been studied in cervical carcinoma paving the pathway for targeted therapy and treatment for advanced stages of carcinoma cervix. Recently there has been interest in the use of targeted therapies for the treatment of cervical cancer.[2]

The tissue markers which have been studied includes p27, p53, Ki67, HIF alpha, VEGF, Cyclooxygenase-2, signal transducer and activator of transcription (STAT) proteins family member p-Stat3, bcl2 apoptotic family of proteins and EGFR family Her2 neu.[3] Her-2 neu, also known as c-erbB-2, CD 340 and p185, stands for "Human Epidermal Growth Factor Receptor 2". It is a cell membrane surface bound receptor tyrosine kinase and is involved in signal transduction pathway leading to cell growth and differentiation.[4,5] It is encoded by proto-oncogenes Her-2 neu located on long arm of human chromosome 17 (17q21q22) and plays a crucial part in malignant transformation and carcinogenesis by

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https://doi.org/10.18231/j.ijpo.2020.054

interacting with the other members of the HER family to potentiate intracellular signaling.[6,7] Its amplification and overexpression has been detected in 15-30% breast cancer, 10-30% of gastric/esophageal cancers and others like ovary, endometrium, urinary bladder, lung, colon, and head & neck.[8] This has led to the development of anti-HER2 antibody, trastuzumab (Herceptin TMR), for breast cancer and has shown significant improvement in survival of Her-2 neu expressing breast tumors.[9,10]

There are variable reports on expression of Her-2 neu in cervical carcinoma. Some studies suggested that it is associated with poor clinical outcome,[11,12] whereas others have shown no prognostic effect,[13,14] or even a positive effect on survival.[15] The present study was conducted to evaluate the immunohistochemical expression of Her-2 neu in pre-malignant and malignant lesions of the uterine cervix, its pattern of expression and correlation with histological type, grade of tumor and clinical stage, wherever possible.

2. Materials and Methods

This was a cross-sectional study, conducted over a period of one year from January, 2017 to January, 2018. All the benign tumors, tumors of non-epithelial origin and inadequate or suboptimal biopsies were excluded from the study. Patient information was collected through a structured, pre-designed proforma. The study was carried out after obtaining clearance from the institutional ethical committee. A total of 55 cases were studied over a period of one year which met the inclusion and exclusion criteria. Routine hematoxylin and eosin stained slides were screened and the section for immunohistochemistry with Rabbit mono-clonal Antibody for HER-2 neu antibody was selected.

For Her-2 neu immunohistochemistry, the following procedure was followed:

1. 3-4 microns thick sections were taken on poly-L-lysine coated slides and incubated for 37°C for one day and then further incubated at 58°C for overnight.
2. Then the sections were deparaffinized with two changes of xylene of 15 minutes.
3. Rehydrated by immersing in descending levels of alcohol 100%, 90% and 80%.
4. Rinsed in distilled water for 5 minutes.
5. Antigen retrieval was done by heat using microwave oven.
6. Sections were cooled to room temperature and then rinsed in distilled water for 5 minutes.
7. Washed in Phosphate Buffer saline (PBS) and treated with peroxidase block for 15 minutes to block nonspecific reaction with the other tissue antigens.
8. Treated with primary antibody for Her-2 neu for 30 – 60 minutes to identify the tumor markers by antigen-antibody reaction.
9. Washed in PBS and treated with super enhancer.
10. Washed in PBS.
11. Treated with secondary antibody for 30 minutes.
12. Washed in PBS.
13. Incubated with diaminobenzidine solution for 5-8 minutes to give brown color to the antigens.
14. Rinsed in PBS and washed in running tap water.
15. Counterstaining was done with Harris hematoxylin.
16. Sections were then washed in tap water for 5 minutes to wash excess stain.
17. Dehydrated in graded alcohols.
18. Clearing was done in xylene and mounted with dibutyl phthalate polystyrene xylene (DPX).

A golden-brown membrane and cytoplasmic staining were taken as a positive reaction. Intensity of HER-2/neu expression was graded according to the 2014 ASCO/CAP guidelines.[16]

Statistical analysis was performed using SPSS version 23. Pearson's Chi Square test and Fisher's exact test were used for comparison of data and p-value of < 0.05 was considered significant.

3. Results

The age range of patients with Pre-Malignant lesions ranged from 45-71 years with mean age at diagnosis of 59.1 years. The age range of patients with Malignant lesions was 30-70 years with a mean age of 53.73 years.

Out of 55 cases, 10 cases (5.5%) were of CIN and 45 cases (94.5%) were of carcinoma cervix. Among 10 cases, 6 cases (60%) were of HSIL and 4 cases were of LSIL (40%). Among 45 malignant cases, 40 cases (88.9%) were of squamous cell carcinoma, 3 cases of adenocarcinoma (6.6%) and 2 cases of adeno-squamous carcinoma (4.5%).

Out of the total 55 cases, Her-2 neu expression was noted in 20 (36.4%) cases and remaining 35(63.6%) cases were negative (Table 1). Among pre-Malignant lesions Her-2 neu expression was found to be significantly higher in HSIL than LSIL but there was no significant correlation between intensity of Her-2 neu expression and Pre-Malignant lesions. (p= 0.898) (Table 2). Among malignant lesions maximum intensity of +3 was noted in only 2 cases of squamous cell carcinoma. There was significant correlation between malignant lesions and Her-2 neu expression (Table 3). There was no significant correlation (p=0.552) between grades of SCC and intensity of Her-2 neu expression (Table 4). There was no significant correlation (p= 0.472) between stage of cervical carcinoma and Her-2 neu expression (Table 5).

4. Discussion

Cervix is a hollow cone with the inner surface, i.e. cervical os, lined by squamous epithelium and endocervix by columnar epithelium. The former consists of several layers

Table 1: Distribution of Her-2 neu expression

Her-2 neu Expression (Intensity)	Frequency (n=55)	Percentage
0	35	63.6
1	15	27.4
2	2	3.6
3	3	5.4

Table 2: Distribution of various histological types of Pre-Malignant lesions with respect to Her-2 neu expression

Pre-Malignant type	Intensity of Her-2 neu expression				Total (%)	p-value
	0(%)	1+ (%)	2+ (%)	3+ (%)		
LSIL	3 (60.0)	1 (33.3)	0 (0.0)	0 (0.0)	4 (40.0)	
HSIL	2 (40.0)	2 (66.7)	2 (100.0)	0 (0.0)	6 (60.0)	0.898
Total	5 (100.0)	3 (100.0)	2 (100.0)	0(0.0)	10 (100.0)	

HSIL = High-grade squamous intraepithelial lesion; LSIL = Low-grade squamous intraepithelial lesion

Table 3: Distribution of various histological types of malignant lesions with respect to Her-2 neu expression

Malignant	Intensity of Her-2 neu expression				Total (%)	p-value
	0(%)	1+ (%)	2+ (%)	3+ (%)		
Squamous Cell Carcinoma	27 (60.0)	10 (22.2)	1 (2.2)	2 (4.4)	40 (88.9)	
Adenocarcinoma	2 (4.4)	1 (2.2)	0 (0.0)	0 (0.0)	3 (6.7)	0.0068
Adeno-Squamous carcinoma	1 (2.2)	0 (0.0)	1 (2.2)	0 (0.0)	2 (4.4)	
Total	30 (66.7)	11(24.4)	2 (4.4)	2 (4.4)	45 (100.0)	

Table 4: Distribution of Her-2 neu expression on the basis of Grade of SCC

Grade of Squamous Cell Carcinoma	Intensity of Her-2 neu expression				Total (%)	p-value
	0(%)	1+ (%)	2+ (%)	3+ (%)		
Well Differentiated	4 (10.0)	2 (5.0)	0 (0.0)	0 (0.0)	6 (15.0)	
Moderately Differentiated	18 (45.0)	6 (15.0)	0 (0.0)	1 (2.5)	25 (62.5)	0.552
Poorly Differentiated	5 (12.5)	2 (5.0)	1 (2.5)	1 (2.5)	9 (22.5)	
Total	27 (67.5)	10 (25.0)	1 (2.5)	2 (5.0)	40 (100.0)	

Table 5: Distribution of Her-2 neu expression on the basis of FIGO stages of tumor

FIGO stage of Tumor	Intensity of Her-2 neu expression				Total (%)	p-value
	0(%)	1+ (%)	2+ (%)	3+ (%)		
Stage I	2 (6.7)	1 (9.1)	1 (50.0)	0 (0.0)	4 (8.9)	
Stage II	23 (76.7)	6 (54.5)	1 (50.0)	2 (100.0)	32 (71.1)	
Stage III	1 (3.3)	2 (18.2)	0 (0.0)	0 (0.0)	3 (6.7)	0.472
Stage IV	4 (13.3)	2 (18.2)	0 (0.0)	0 (0.0)	6 (13.3)	
Total	30 (100.0)	11 (100.0)	2 (100.0)	2 (100.0)	45 (100.0)	

FIGO = The International Federation of Gynaecology and Obstetrics

Table 6: Comparison of various histological types of carcinoma cervix in different studies

Study Name	Squamous Cell Carcinoma	Adenocarcinoma	Adenosquamous
Keith et. al.[17] (2002)	90.40%	9.10%	0.50%
Raza et. al.[18] (2010)	86.80%	3.80%	0.00%
Siddiqa et al.[19] (2014)	91.50%	2.10%	6.40%
Sharma N. et al.[20] (2016)	72.00%	12.00%	16.00%
Gul et al.[21] (2015)	58.90%	41.10%	0.00%
Present Study	88.90%	6.60%	4.50%

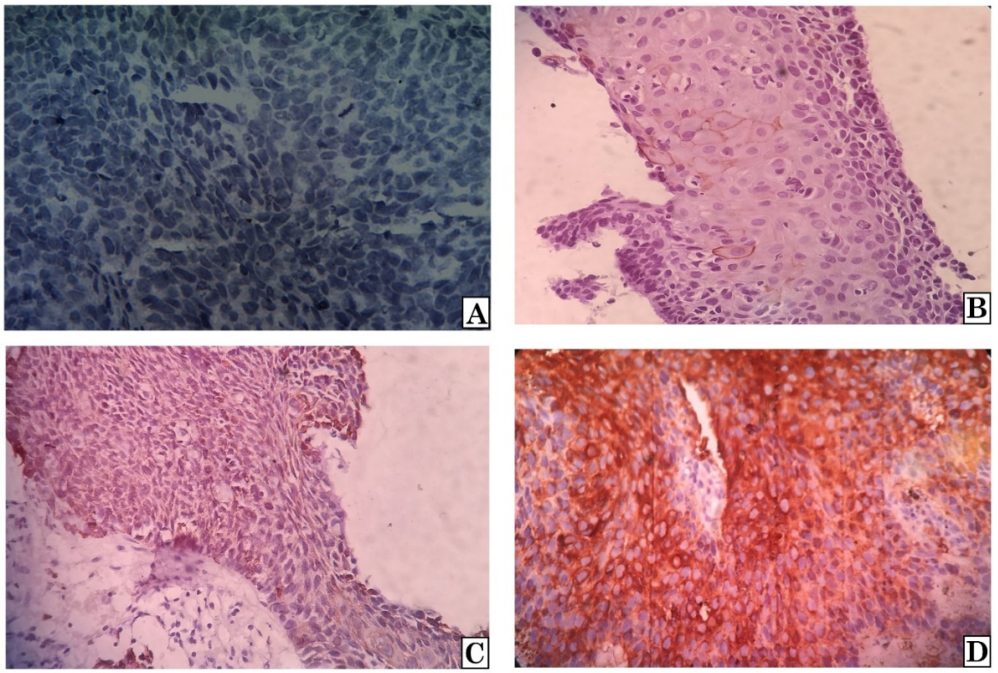

Fig. 1: Her-2 neu staining of cervical malignant lesions; **A):** Negative; **B):** Faint Membranous Positivity; **C):** Equivocal; **D):** Strongly Positive

Table 7: Comparison of Her-2 neu expression in CIN between various studies by IHC

Study Name	Her 2 neu expression (%)
Lakshmi et al.[22] (1997)	86.25%
Z. Protrka et al.[23] (2007)	66.00%
Gupta N et al.[20] (2009)	60.00%
Li et al.[24] (2013)	37.50%
Joseph T. and Raghuveer C.V.[25] (2015)	70.00%
Bajpai S. et al.[26] (2017)	14.80%
Present Study	50.00%

Table 8: Comparison of Her-2 neu expression in cervical carcinoma between various studies by IHC

Study Name	Her 2 neu expression (%)
Gupta N et al.[20] (2009)	63%
Joseph T. and Raghuveer C.V.[25] (2015)	100%
Sharma N. et al.[20] (2016)	52%
R J Hale et al.[12] (1992)	38.7%
Ndubisi et al.[13] (1997)	22%
Bajpai S. et al.[26] (2017)	48.80%
Present Study	33.20%

Table 9: Grades of SCCs with Her-2 neu expression

Study Name	p-value
Gupta N et. al.[20] (2009)	<0.05
Joseph T. and Raghuveer C.V.[25] (2015)	0.165
Sarvade P et al.[27] (2016)	0.935
Sharma N. et al.[20] (2016)	0.52
Bajpai S. et al.[26] (2017)	0.014
Present Study	0.552

Table 10: Correlation of stage of cervical carcinoma and Her-2neu expression

Study Name	p-value
Gupta N et al.[20] (2009)	<0.05
Joseph T. and Raghuveer C.V.[25] (2015)	0.71
Sarvade P et al.[27] (2016)	0.073
Sharma N. et al.[20] (2016)	<0.05
Present Study	0.472

of squamous cells with short cubic cells in the basal layer. The latter contains only one layer of columnar cell. The border area between the squamous epithelium and columnar epithelium is called transitional zone[28] or transformation zone.[29]

Immortalization of the cervical cell is necessary for progression of CIN to invasive cancer. Integration of viral DNA to the host genome that enables expression of viral oncogenes E6 and E7 is a necessary step in immortalization and probably does not occur without the presence of

cofactors. In vitro and animal studies using cell cultures immortalized by HPV have, with few exceptions, failed to demonstrate progression to invasive cancer, but only to CIN.[30]

Her-2 neu has been studied in cervical carcinoma from a long time. RJ Hale et al.[12] (1993) investigated the pattern of epidermal growth factor receptor expression and its prognostic value in 62 cases of cervical carcinoma and found correlation between epidermal growth factor expression and mortality. They concluded that immunohistochemical demonstration of epidermal growth factor receptor expression may be useful in identifying those patients with a poor prognosis, particularly those with adenosquamous carcinomas which have not metastasized to the regional lymph nodes. Joseph T. and Raghuveer C.V.[25,31] (2015) did a study of the Her-2 neu expression in 34 cases of cervical intraepithelial neoplasia and cervical carcinoma and concluded that the intensity of HER-2 expression increased progressively as grade of lesion increased and also, with presence of lymph node and parametrial involvement. All the cases under FIGO stage 4 showed strong (3+) HER-2 expression. Martinho O et al[31] (2017) did comprehensive analysis of HER family receptor alterations in cervical adenocarcinoma and they proposed that the use of HER inhibitors in association with glycolysis blockers can be a potentially effective treatment option for HER-positive cervical cancer patients.

In present study, squamous cell carcinoma comprised a total of 88.9% (n=40), followed by 3 cases of Adenocarcinoma (6.6%) and 2 cases of Adenosquamous carcinoma (4.5%). This finding is in concordance with Keith et al.,[17] Raza et al.,[18,19] Siddiqa et al.[19] and Sharma N. et al.[20] (Table 6). Several authors have reported Her-2 neu expression in CIN ranging from 47.2%-86.25%. In the present study, Her-2 neu expression was noted in 50% of CIN cases which is close to 37.5% in Li et al.[24] 60% in Gupta N et al.,[32] and 66% in Z. Protrka et al.[23] In contrast to present study, Her-2 neu expression was noted in 86.25% of CIN cases as reported by Lakshmi et al.[22] (Table 7).

In 45 (81.2%) cases of carcinoma cervix Her-2 neu expression was noticed in 15 cases (36.4%) of cervical carcinoma. 3 (6.6%) cases were strongly positive with a score of +3 (Figure 1D), 2 (4.4%) cases were equivocal with a score of +2 (Figure 1 C), 11(24.4%) cases showed faint membranous positivity with a score of +1 (Figure 1B) and remaining 29 (64.4%) cases were negative with a score of 0 (Figure 1A). A statistical correlation was established between histological types of malignant lesions and intensity of Her-2 neu staining (p=0.006). According to various studies expression of Her-2 neu in cervical carcinoma ranged from 12.1% to 100% as conducted by Gupta N et al,[32] Li et al.,[24] Joseph T. and Raghuveer C.V.[25] and Yong H et al.[33] The positivity rate in present study is close to that reported by R J Hale et al.[12] and Ndubisi et al.[13] who reported positivity rate of 38.7% and 22% respectively (Table 8).

In the present study, SCC formed the largest group with 40 cases. With respect to higher scores of +2 and +3, the proportion of cases with higher scores was significantly higher in poorly differentiated and moderately differentiated group as compared to well differentiated group. None of the cases from well differentiated group showed +2 and +3 positivity. These findings are similar to those of Joseph T. and Raghuveer C.V.[25] and Gupta N et al.[32] The statistical correlation in grades of SCC and intensity of HER-2 neu staining (p=0.552) could not be established. Similar to our study, Sharma N et al.[20] and Joseph T. and Raghuveer C.V.[25] also did not find any correlation between grades of carcinoma and Her-2 neu expression (Table 9). In this study, 3 cases of adenocarcinoma were analyzed and none was found to be strongly positive. Only 1 (2.2%) case had a score of +1. In contrast, Gupta N et al[32] found positivity in 8 cases of total 13 cases (60%) of adenocarcinoma. Kihana et al.[34] studied 44 cases of cervical adenocarcinoma and found +1 and +2 positivity in 34 (77%) cases.

Out of 45 cervical carcinoma cases, higher intensity of Her-2 neu expression was found among cases under stage II. A statistically significant relationship was not established between Her-2 neu expression and stage of the tumor (p=0.472). Contrary to this Sharma N et al.[20] and Gupta N et al[32] found a significant correlation between Her-2 neu expression and higher stage of cervical carcinoma. Similar to present study, Joseph T. and Raghuveer C.V.[25] did not find any relation between Her-2 neu expression and higher stage of cervical carcinoma (Table 10).

5. Conclusion

In our study, higher intensity of Her-2 neu expression was observed in HSIL than LSIL among Pre-Malignant lesions suggesting Her-2 neu expression increases as the lesion progresses suggesting its role in higher grade of lesions. There is statistically significant association between histological types of cervical cancers and Her-2 neu expression suggesting its role in tumorigenesis. However, due to small sample size we cannot definitely comment on their probability of association with Her-2 neu expression. Therefore, this necessitates follow-up studies with a larger sample size to use Her-2 neu as a targeted therapy in cervical cancer.

6. Limitations

The gold standard test (FISH) could not be done, as it was not available in our institution, for confirmation of Her-2 neu over-expression.

7. Conflicts of Interest

None declared.

8. Ethical Clearance

Taken from Institutional Ethical Committee.

References

1. Cervical W. WHO — Cervical cancer ; 2019. Available from: http://www.who.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/.
2. Dueñas-Gonzalez A, Cetina L, Mariscal I, de la Garza J. Modern management of locally advanced cervical carcinoma. *Cancer Treat Rev*. 2003;29(5):389–99.
3. Gadducci A, Guerrieri ME, Greco C. Tissue biomarkers as prognostic variables of cervical cancer. *Crit Rev Oncol Hematol*. 2013;86(2):104–29.
4. Ray A, Naik S, Sharma BK. Distribution of prognostically unfavourable product of c-erbB-2 oncogene and EGF-R in carcinomas of the breast and uterine cervix. *Indian J Physiol Pharmacol*. 2002;46(4):423–33.
5. Popescu NC, King CR, Kraus MH. Localization of the human erbB-2 gene on normal and rearranged chromosomes 17 to bands q12–21.32. *Genomics*. 1989;4(3):362–66.
6. Bargmann CI, Hung MC, Weinberg RA. The neu oncogene encodes an epidermal growth factor receptor-related protein. *Nat*. 1986;319(6050):226–30.
7. Graus-Porta D. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. *EMBO J*. 1997;16(7):1647–55.
8. Iqbal N, Iqbal N. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol Biol Int*. 2014;2014:1–9.
9. Allen L, Lenehan P, Eiseman I, Elliott W, Fry D. Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer. *Semin Oncol*. 2002;29(3):11–21.
10. Slamon D, Clark G, Wong S, Levin W, Ullrich A, McGuire W. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Sci*. 1987;235(4785):177–82.
11. Oka K, Nakano T, Arai T. c-erbB-2 oncoprotein expression is associated with poor prognosis in squamous cell carcinoma of the cervix. *Cancer*. 1994;73(3):668–71.
12. Hale RJ, Buckley CH, Fox H, Williams J. Prognostic value of c-erbB-2 expression in uterine cervical carcinoma. *J Clin Pathol*. 1992;45(7):594–6.
13. Ndubisi B, Sanz S, Lu L, Podczaski E, Benrubi G, Masood S. The prognostic value of HER-2/neu oncogene in cervical cancer. *Ann Clin Lab Sci*. 1997;27(6):396–401.
14. Rosty C, Couturier J, Vincent-Salomon A, Genin P, Fr??neaux P, Sigal-Zafrani B, et al. Overexpression/Amplification of HER-2/neu is Uncommon in Invasive Carcinoma of the Uterine Cervix. *Int J Gynecol Pathol*. 2004;23(1):13–7.
15. Lee CM, Lee RJ, Hammond E, Tsodikov A, Dodson M, Zempolich K, et al. Expression of HER2neu (c-erbB-2) and epidermal growth factor receptor in cervical cancer: prognostic correlation with clinical characteristics, and comparison of manual and automated imaging analysis. *Gynecol Oncol*. 2004;93(1):209–14.
16. Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J Clin Oncol*. 2013;31(31):3997–4013.
17. Lo KWK, Wong YF, Chan MKM, Li JCB, Poon JS, Wang VW. Prevalence of human papillomavirus in cervical cancer: A multicenter study in China. *Int J Cancer*. 2002;100(3):327–58.
18. Raza SA, Franceschi S, Pallardy S, Malik FR, Avan BI, Zafar A, et al. Human papillomavirus infection in women with and without cervical cancer in Karachi, Pakistan. *Br J Cancer*. 2010;102(11):1657–60.
19. Siddiqa A, Zainab M, Qadri I, Bhatti M, Parish J. Prevalence and Genotyping of High Risk Human Papillomavirus in Cervical Cancer Samples from Punjab, Pakistan. *Viruses*. 2014;6(7):2762–77.
20. Sharma N, Kaushik A, Sumanashree, Sharma U. Evaluation of Her- 2 neu over expression in morphological variants of cervical carcinomas using immunohistochemistry: A study of 25 cases. *Ann Appl BioSci*. 2016;3(2):207–13.
21. Gul S, Murad S, Javed A. Prevalence of High risk Human Papillomavirus in cervical dysplasia and cancer samples from twin cities in Pakistan. *Int J Infect Dis*. 2015;34:14–19.
22. Lakshmi S, Nair B, Jayaprakash PG, Rajalekshmy TN, Nair K, Pillai R. c-erbB-2 Oncoprotein and Epidermal Growth Factor Receptor in Cervical Lesions. *Pathobiol*. 1997;65(3):163–8.
23. Protrka Z, Mitrović S, Arsenijević N, Baskić D, Radosavljević G, Stanković M. HER-2 expression in uterine cervix carcinogenesis. *J BUON*. 2007;12(1):91–98.
24. Li G, Yu D, Zhong-Qiu W. Significance of EGFR, HER-2 and VEGF expressions in cervical intraepithelial neoplasia and squamous cell carcinoma. *Cancer Res Clin*. 2013;25(11):750–3.
25. Joseph T, Raghuveer CV. HER-2/neu expression in cervical intraepithelial neoplasia and cervical carcinoma. *Int J Biomed Adv Res*. 2015;6(1):47–52.
26. Bajpai S, Awasthi S, Dutta S, Mittal A, Kumar A, Ahmad F. Role of Her-2/neu in Premalignant and Malignant Lesions of Uterine Cervix. *J Clin Diagnostic Res*. 2017;11(9):1–04.
27. Sarvade P, Patil S, Bindu R. Immunohistochemistry study for HER-2/neu expression in lesions of uterine cervix. *Int J Cur Res Rev*. 2016;8(13):50–7.
28. Reid R. Genital warts and cervical cancer. II. Is human papillomavirus infection the trigger to cervical carcinogenesis? *Gynecol Oncol*. 1983;15(2):239–52.
29. Singer A. The uterine cervix from adolescence to the menopause. *Br J Obstet Gynaecol*. 1975;82(2):81–99.
30. Herrington CS. Human papillomaviruses and cervical neoplasia. II. Interaction of HPV with other factors. *J Clin Pathol*. 1995;48(1):1–6.
31. Martinho O, Silva-Oliveira R, Cury FP, Barbosa AM, Granja S, Evangelista AF. HER Family Receptors are Important Theranostic Biomarkers for Cervical Cancer: Blocking Glucose Metabolism Enhances the Therapeutic Effect of HER Inhibitors. *Theranostics*. 2017;7(3):717–32.
32. Gupta N, Singh S, Marwah N, Kumar S, Chabra S, Sen R. HER-2/neu expression in lesions of uterine cervix: Is it reliable and consistent? *Indian J Pathol Microbiol*. 2009;52(4):482–5.
33. Yong H, Shumo C, Shaoyin Y, Daren S. Expression of c-erbB-2 and PCNA in cervical adenocarcinoma and its signification. *Chinese J Cancer Res*. 1998;10(1):68–70.
34. Kihana T, Tsuda H, Teshima S, Nomoto K, Tsugane S, Sonoda T, et al. Prognostic significance of the overexpression of c-erbB-2 protein in adenocarcinoma of the uterine cervix. *Cancer*. 1994;73(1):148–53.

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Cite this article: Chaudhary S, Pant H, Khandelwal R, Pandey S, Garg N. Her-2 neu expression in cervical intraepithelial neoplasia and carcinoma of cervix. *Indian J Pathol Oncol* 2020;7(2):285-290.