

Immuno Histo Chemistry of P63 Expression in Women Patients with Cervical Carcinoma in Baghdad City

Athraa Zaidan Hassan¹ Hassan Yasir Jaber²

¹Assistant professor, Ph.D of Medical Laboratory Science Technology/ Middle Technical University / Collage of Health & Medical Technology (MTU)/Iraq

²Microbiologist/ Ministry of Health/ Baghdad Health AL-Karkh Directorate/Iraq

Email: dr.azh.mousawi@gmail.com

Abstract

Background and objective :- P63 is a member of the p53 gene family. It plays an essential role in the normal development of the cervix in addition p63 is considered to be an important differentiation regulation transcriptional factor, but the roles of p63 in many epithelial tumorigenesis and metastasis processes are still not clear. This study was designed to investigate the expression of p63 in squamous cell cancer tissues of uterine cervix and determined any associated between presence of high risk of human papilloma virus and expression of p63 in cervical carcinoma among Iraqi women patients. The expression of p63 was assessed in cervical tumor tissue and cervical non tumor by immunohistochemistry. Method: This study was carried out on 30 patients with hisopathologically confirmed primary cervical cancer in addition 20 cervical tissues from control individuals with no cancer as control groups. From each patients and control cervical tissues were proposed for chromogen in situ hybridization (CISH) techniques to investigation the presence of HPV (HPV 16 /18) DNA CISH in cervical tissues and for immunohistochemistry was used to detected expression of p63. Results:P63 expression was found in 22/ 30 (73.3%) tumor sample while negative cases in 8/30 (26.7 %) tumor sample and no expression of p63 in cervical control groups. In this study demonstrated that cervical carcinoma cases which positive for HPV (16/18) which represented 26/30 from the cases also positive for p16 expression in 20 (76.9%) and negative for p63 expression in 6 (23.1%) .Conclusion: High expression of p63 in cervical carcinoma indicated a neoplastic progression In addition, immunohistochemical detection of P63 may be used to differentiate normal from malignant tissue in the clinical setting.

Keywords: Women Patients ; P63 Expression; Carcinoma

1. Introduction

Carcinoma of the uterine cervix is the most frequent malignancy in women worldwide, with an incidence of approximately 456.000 cases per year (15% of newly discovered cancers in women), leading to 200.000 deaths per year (1). In this context, more than 99% of cervical cancers are positive for high-risk human papilloma viruses (HPVs). E6 and E7 genes encode oncoproteins responsible for virus replication, and also for immortalization and transformation of human keratinocytes [2, 3]. The interaction of human papilloma viruses' oncoproteins E6 and E7 with cell cycle proteins leads to disturbances of the cell cycle mechanism and subsequent alteration in the expression of some proteins, such as p53, p63 and Ki-67.

P63 gene is a member of the p53 gene family. In normal tissues, p53 levels are undetectable and only reach significant levels after genotoxic stress or mutational inactivation causing p53 protein stabilization. In contrast , p63 exhibits a strikingly varied expression pattern in normal tissues. It is expressed at high levels in many normal epithelium squamous epithelium including urothelium and prostate .(4)

P63 plays a crucial role in epithelial cell regeneration and renewal It has emerged as a critical player in embryonic development , epithelial cell stem maintenance, and differentiation (5). Upon the maturation of normal stratified squamous epithelium, p63 protein expression gets down-regulated, and p63 protein is rarely detected in upper layers of the normal epithelium. (6) However, upon dysplastic change, above the basal layers may serve to prevent basal cells from differentiating and thereby helps to maintain their basal cell status.(7)

The development of squamous cell carcinoma SCC is a multistep process requiring the accumulation of multiple genetic alterations, influenced by environmental factors including tobacco, alcohol chronic inflammation, and viral infection .(8)

Precancerous lesions usually precede SCC clinically. At the microscopic level, these lesions show varying degrees of epithelial dysplasia, from mild to severe. A higher grade of dysplasia is generally associated with a higher risk of neoplastic transformation.(9) A number of molecular markers have been identified over the years to detect the transition from normal epithelium to the premalignant and malignant epithelium. P63 is helpful in determining the nature of the progression to inflammation or atypical change. High P63 expression indicates a neoplastic progression.(10,11) . SO in this

recent study the expression of p63 in cervical squamous cell carcinoma will be investigated and evaluation correlation it expression with HPV infection.

2. Materials and methods

In present study Cervical tissues were obtained from (30) patients with cervical cancer and (20) cases from individual cervical tissue were proved to be free from any significant pathological changes were considered as a negative control groups. Specimens belong to the period from April 2016 until March 2018. From each patient and control two blocks was taken formalin fixed, paraffin embedded cervical carcinoma

Tumor, control blocks were collected from the archives of histopathology laboratories of Teaching Laboratories of the Medical City/Baghdad and Teaching Alkarmaa hospital, Teaching AlYarmouk hospital, AlWiya hospital for delivery as well as many private laboratories.

The diagnosis of these tissue blocks were based on the obtained pathological records of these cases from hospital files as well as histopathological laboratories records. A confirmatory histopathological re-examination of each obtained tissue blocks was done. 4 µm thick sections were made and adhesion on positively charged slides. Chromogenic in Situ Hybridization (CISH)/Detection system (Zytovisions GmbH, Bremerhaven, Germany) used to target DNA sequences using Digoxigenin- labelled long DNA probe for HPV types 16/18 in addition to Immunohistochemistry kit for detection p63 (Cat. Number AM418-5M, clone 4A4) Primary antibody :, Biogenex, U.S.A). Method was conducted according to the instructions of manufacturing companies leaflet.

positive tissue slide for P63 was pushed from (Biogenex, US) company, They include tissue from cervical squamous cell carcinoma that were previously known to contain the target marker. Quantification p63 protein expression were evaluated under light microscopy at X100, X400, and X1000. The counting of positive cells was performed at X1000.

Evaluation and Interpretation of P63 Immunostaining

P63 was analyzed individually and also in combination with corresponding Hematoxylin and Eosin H and E. stained slides. To determine the location and proportion of positive, the presence of brown-colored end products at the site of the target antigen (nucleus) was considered as positive. The immunostaining of p63 was judged as positive when more than 10% of the cell nuclei showed a strong intensity (14,15). Immunohistochemical reactions were quantified by means of the intensity of the reaction and the percentage of marked cells, establishing a grading score (G score) for P63 marker.

Scoring of p63

The Immunostaining was evaluated range from totally absent (0) to weak (10) cell nuclei stained, and >10 cell nuclei stained. The positive staining intensity was scored as weak but definite positive (1+), moderate (2+), and strong (3+).(15,16) .Weak positive (score 1) >10-25%,moderate positive (score 2) 26-75% and strong positive (score 3) 76-100%.

Statistical analysis

In this study Chi-square test was used to detect the significances between variables. All the statistical analysis was done by SPSS program (version-18). P-value was considered significant when < 0.05.

3. Result

The distribution of cervical carcinoma according to histopathological grades clearly shown in Table (1). The results of present study revealed that moderate differentiated grade in cervical carcinoma cases constituted of (60%) (18 out of total 30 cases) , whereas cases with well and poorly differentiated grades constituted of (30%) (11 out of 30 cases) and (10%) (1 out of 30 cases) respectively. the statistical analysis of grading distribution of cervical carcinoma shown non significant difference (p>0.05) .

Table 1:- Distribution of cervical carcinoma cases according to histopathological grades

p-value	Cervical carcinoma		Histological grades
	%	NO	
0.54 Non Significant	(10.0%)	3	Poorly Differentiated
	(60.0%)	18	Moderate Differentiated
	(30.0%)	9	Well Differentiated
	(100%)	30	Total

In the current study , expression of p63 was detected in (73.3% :22 out of 30) cells with cervical carcinoma , also cervical control group showed non p63 expression . A high percentage (30% : 9 out of 22 cases) was involving cases with cervical cancer that improved as score (II), While (26.7% : 8 out of 22

cases) were found to have score (III) in addition (16.7%: 5 out of 22 cases) have score (I) . Statistically highly significant difference (p<0.001) were found in comparing the results according to score between the group of cervical carcinoma and cervical control group.

Table (2) :- Frequency distribution of immunohistochemistry results of p63 protein according to the signal scoring among study groups.

Study groups	Total p63negative results	Positivity according to signal scoring			Total p63 positiveresults	p-value
		Score I	Score II	Score III		
Cervical carcinoma(30 cases)	8(26.7%)	5(16.7)	9(30%)	8(26.7%)	22(73.3%)	<0.001 Highly Significant
Cervical control (20cases)	20(100%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	

On observing the total results of p63 – IHC in relation with the grading of the studied cases of cervical

carcinoma , we notice in Table (3) that total p36 expression was detected in 22 / 30 (73.3%) informative cervical carcinoma samples . It was detected that (66.6% : 6 out of 9 cases) of cervical carcinoma cases showed immunoreactivity for P36 have well differentiated grade , (77.7%: 14 out of 18

cases) of these tumor showed moderate differentiated grade , lastly (66.6% : 2 out of 3 cases) of these tumor showed poorly differentiated grade . non significant association was detected with different grades of malignant tumors ($p < 0.05$).

Table (3):- Relationship between p63 expression and histological grades among study groups.

Study group		P63expression		p-value
		Negative	Positive	
Cervical carcinoma	Histological grades	Well	3 (33.3. %)	0.66Non Significant
		Moderate	4 (22.2.%)	
		Poorly	1 (33.3%)	
		Total	8 (26.7%)	
			6 (66.6 %)	
			14 (77.7%)	
			2 (66.6%)	
			22 (73.3%)	

Values of p63 immunoreactivity in HPV 16/18 positive and negative cervical carcinoma were demonstrated in Table (4) . It was noticed that p63 overexpression was 20 (76.9 %) in all cervical carcinoma cases which found to be positive for HPV16/18 CISH results , while 2(50%) of the cases which show negative for HPV16/18- CISH results also presented negative immunohistochemistry for p63

and 2(50%) of the cases which found to be negative for HPV16/18 CISH results showed positivity for p16 expression in addition that 6 (23.1%) of the cases which show positive for HPV16/18 CISH results but negative for p63 expression . Statistical comparison of p63 expression in HPV 16/18 positive and negative tumors demonstrated non significant results ($p < 0.05$).

Table 4 :- Relationship between P63 expression and HPV 16/18 CISH results among study groups.

Study groups			P63 expression		Total	P-value
			Negative	Positive		
Cervical carcinoma	HPV	Negative	2 (50%)	2 (50%)	4 (100%)	0.28Non Significant
		Positive	6 (23.1%)	20 (76.9%)		

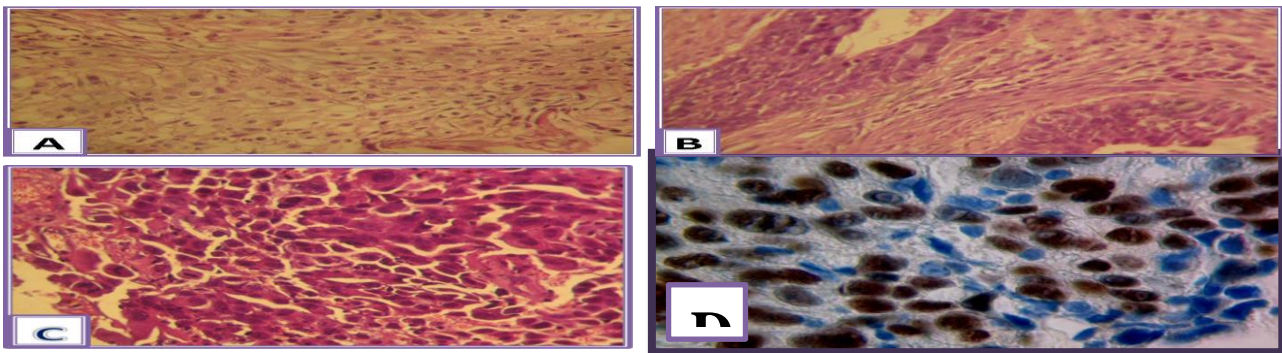


Figure (1) :- Histological Grades Of Cervical Carcinoma Stained With Hematoxyline And Eosin. (40x)

- A :- Well Differentiated Grade (I)
- B :- Moderate Differentiated Grade(II)
- C :- Poorly Differentiated Grade(III)
- D:- Positive P63 – IHC Reaction With High Score And High Intensity Signal (40x)

4. Discussion

Cervical cancer is the third most common cancer and the second most common cause of death in women worldwide. The number of cervical cancer is expected to rise 46% by 2030 (12) . Histological grading is important part in planning cervical cancer treatment and can also be used to help in estimation the prognosis . (13) . In addition , it had been reported that CIN2/CIN3 lesion may developed rapidly following a high – risk HPV infection leaving only very limited time for preceding CIN1 lesion. (14) . The results of our investigation show that moderate differentiated grade in cervical carcinoma cases constituted of (60%) whereas cases with well and

poorly differentiated grades constituted of (30%) and (10%) respectively as show in Table (1) Our findings is compatible with other study which demonstrated that (12.3%) were classified as grade I and (67.7%) of them were classified as grade II were as (20%) of them found to be in grade III. (15) . According to the IKechebelu et al., 2010(16)who observed that only (11.5%) of cervical cases were classified as poorly differentiated ,while Moderate and well differentiated grade were made (58.9%) and (29.4%) respectively. Those results showed agreement with the results obtained in current study. Pannayana and co-workers., 2014(17) also found that (17.5%) of cases were classified as grade 1 while (54.7%) and (25%) of them were found to be grade II and grade III, respectively.These findings showed compatibility with our results. Our investigation unlike to some extent with another study which demonstrated that poorly differentiated grade (III) comprises (42%) among cervical carcinoma cases ,while well and moderate differentiated grade

(I&II) comprises (39%) and (30%), respectively.(18).The relatively low number of cases may possibly explain this variation with our study .

P63 is the precursor of p53 and stains the basal cells, being a useful marker of squamous neoplasms within the cervix. Based on RT–PCR and western blot analysis in cervical cancer cell lines, beta isoform of p63 (possibly DeltaN) may be considered as an important marker in uterine cervical squamous cell carcinogenesis (19).

In the current study , it was found that (73.3%) of cervical carcinoma cases show positively expression for p63 protein as appear in table (2) which is compatible with other study (20) which detect p63 expression in (78.8%) of cervical carcinoma patients In this respect , Vosmik et al .,(2014) analyzed 70 patients with cervical squamous cell carcinoma and found that 94.29% had positive expression of p63 (21) In (2001) Wang et al .(22) detected expression of P63 positivity in 79% of squamous cell carcinoma .This results show agreement with the results of the present study. Filho et al., 2003 (23) showed good sensitivity when detecting squamous cell carcinoma with a positive rate of 92.6% .

Study in Iraqi by Yusra Abdulkhaliq .,2020 (24) who showed higher p63 score expression in all cases of squamous cell carcinoma . The expression of p63 has been demonstrated in squamous cell carcinomas of the cervix. This emphasizes the role of p63 in cervical tumorigenesis, which is in parallel to other studies.(25,26,27).

According to histological grade our investigation show that 77.7% of moderated grade (CII) demonstrated positive p63 expression . these results compatible some extent with Yusra Abdulkhaliq who detected that P63 positivity in 65% of cases with moderate grade . in this respect , Many Reviewers agree that p63 is of great value in the distinction between CIN I, CIN II and CIN III (28 , 29).

Study by Zhou et al., 2011 (30) who demonstrated that cervical carcinoma cases which positive p63 showed 29% well differentiation while 5 % moderate differentiation and only 1% poorly differentiation also, histological grades and clinical stages showed a significant correlation with p63 expression level ($P < 0.05$). these results incompatible with our study . these variation due to the difference in sample size, and the differences in the immunohistochemical staining patterns of expression P63 between the CIN 1 and normal epithelium was less clear than those observed between high-grade CIN or cervical cancer and the normal epithelium. This may have limited our ability to detect significant differences.

Persistent infection with high-risk human papillomavirus (HRHPV) is closely associated with cervical cancer (31) and HR-HPV can bind to their receptors specifically expressed in cervical basal cells (32-33).

Integration of high-risk HPV DNA into the host-cell genome results in elevated expression levels of E6 and E7, the early HPV proteins that contribute to

tumor progression by inactivating cellular tumor suppressor proteins p53 , retinoblastoma and P63, and thus altering cell cycle control during tumorigenesis .(30) .In the current study , It was noticed that p63 expression was (76.9%) in cervical carcinoma cases which found to be positive for HPV16/18 CISH results. Our study findings show compatibility with [Shirendeb et al., 2009](#) (34) who observed that 70% of cervical carcinoma cases showed expression of p63 also positive for HPV16 .Moreover, Wang et al.2001(35) reported that p63 expression was positive in 94% of HPV16 and 50% of HPV18-positive cases in cervical SCC. On the other hand , our investigation appeared that non significant association observed between p63 expression and HPV16/18 presence (P value = 0.28). Our results were in accordance with Kim et al., 2011(20) . Study by Eldakhakhny et al., 2018 (36)Who demonstrated that HPV16 and HPV18 E7-induced p63 expression significantly . these results unlike with our data may be due to the limited sample size may prevent achievement of a (otherwise possible) statistical difference between P63 expression and HPV infection .

However, the function of p63 in the carcinogenesis of HPV-positive cervical cancer is not well understood yet.

Well,lusion :- High expression of p63 in cervical carcinoma indicated a neoplastic progression and P63 may be used to differentiate normal from malignant tissue.

5. References

- 1- Crum C. P., The female genital tract. In: KUMAR V., FAUSTO N., ABBAS A. (eds), Robbins & Cotran Pathologic Basis of Disease, 7th edition, Elsevier–W. B. Saunders Press, 2005, 1098–1099.
- 2- Phelps W. C., Yee C. L., Munger K., Howley P. M., The human papillomavirus type 16 E7 gene encodes transactivation and transformation functions similar to those of adenovirus E1A, Cell, 1988, 53(4):539–547.
- 3- Spitkovsky D., Aengeneyndt F., Braspenning J., Von knebel Doeberitz M. p-53-independent growth regulation of cervical cancer cells by the papillomavirus E6 oncogene, Oncogene, 1996, 13(5):1027–1035.
- 4- Koyuncuer A. Immunohistochemical expression of p63, p53 in urinary bladder carcinoma. Indian J Pathol Microbiol 2013; 56(1):10–5.
- 5-Inoue K, Fry, EA. Alterations of p63 and p73 in human cancers. SubcellBiochem2014;(85)17–40.
- 6- Abilasha R, Ramani P, Sherlin H J, Premkumar P, Natesan A. Immunohistochemical evaluation of oral epithelial dysplasia using cyclin-D1, p27 and p63 expression as predictors of malignant transformation. Nat Sci Biol Med 2013;4(2):349–58.
- 7- Sharada P, Swaminathan U, Nagamalani B R, Vinodkumar K, Ashwini B K, Lavanya V. Semicquantitative analysis of immunohistochemical expression of p63, Ki-67, Cyclin-D1, and p16 in common oral potentially malignant disorders and oral squamous cell carcinoma. Journal of Dr. NTR University of Health Sciences 2018; 7(2):120 –8.
- 8- Shetty S, Krishnapillai R, Prabhu S. Assessment and

- comparison of p53 and p63 expression in oral epithelial dysplasia and squamous cell carcinoma. *SRM Journal of Research in Dental Sciences* 2014; 5(3):149–54.
- 9- Mohite DP, Hande AH, Gupta R, Chaudhary MS, Palit S, Gawandi M. Immunohistochemical evaluation of expression pattern of P53, P63 and P73 in epithelial dysplasia. *Journal of Data Meghe Institute of Medical Science University* 2018; 13(3):122–9.
- 10- Jacob AA, Sundaram A. P16, Ki67 and P63 staining pattern in squamous metaplasia, CIN and cervical cancer. *Int J Res Med Sci* 2018; 6(3):882.
- 11- Saritha VN, Veena VS, Krishna J, Somanathan T, Sujathan K. Significance of DNA Replication Licensing Proteins (MCM2, MCM5 and CDC6), p16 and p63 as Markers of Premalignant Lesions of the Uterine Cervix: Its Usefulness to Predict Malignant Potential. *Asian Pacific Journal of Cancer Prevention* 2017; 19(1):141–58.
- 12- Ferlay J, Shin H R, Bray F, et al. Estimates of world wide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* .2010 Dec 15 ; 127 (12) : 2893-917.
- 13- Sobin LH , Wittekind C.(Ed). (2002). TNM Classification of malignant tumors. (16 th Edition) .New York: Wiley–Liss.
- 14- Snijders pd, Steen RD, Heidewan DA, et al. HPV-mediated cervical carcinogenesis : concepts and clinical implication .*J pathol* 2006; 208: 152-64.
- 15- Vaida A, Algidas B, Adrijus K, et al. Diffusion–weight magnetic resonance imaging of cervical cancer .*Acta Medica lituanica* .2011.vol .18, No 4; p139-146.
- 16- Ikechebelu JI, Onyiaorah TV, Ugboaja JO, et al. Pthological analysis of cervical cancer seen in tertiary health facility in Nnew: South East Nigeria. *Journal of obstetrics and Gynaecology* 2010, 30(3): 229-301.
- 17- Pannayana P, Shuresh S, Raju K, et al.(2014). Clinico pathological correlation of cervical carcinoma : Atertiary Hospital Based study. *Asian pac J cancer prev*, 15(4),1671-1674.
- 18- Ahmed Ibrahim. Cervical cancer;(2013). Risk factors and feasibility of visual inspection with Acetic acid screening method in Khartoum state, Sudan publication of the unite for health promotion Reasearch, series A; No 6.
- 19- Lin Z., Nan Y., Zhang X., Zhao Y., Kim C., Kim I., Reverse transcription-polymerase chain reaction and western blotting analysis for detection of p63 isoforms in uterine cervical cancers, *Int J Gynecol Cancer*, 2006, 16(4):1643–1647.
- 20- Su Mi Kim, MD1, Jeong Uee Lee, MD2, Dae Woo Lee, MD1, Min Jung Kim. The prognostic significance of P16, Ki-67, P63, and CK 17 expression determined by immunohistochemical staining in cervical intraepithelial neoplasia 1 *Korean J Obstet Gynecol* 2011;54(4):184-191.
- 21-Vosmik M, Laco J, Sirak I, Beranek M, Hovorkova E, Vosmikova H, Drastikova M, Hodek M, Zoul Z, Odratzka K, et al. Prognostic significance of human papillomavirus (HPV) status and expression of selected markers (HER2/neu, EGFR, VEGF, CD34, p63, p53 and Ki67/MIB-1) on outcome after (chemo-) radiotherapy in patients with squamous cell carcinoma of uterine cervix. *Pathol Oncol Res*. 2014;20(1):131–137.
- 22- [T Y Wang](#) , [B F Chen](#) , [Y C Yang](#) , [H Chen](#) , [Y Wang](#) , [A Cviko](#) , [B J](#) , [D Quade Sun](#) , [A Yang](#) , [F D McKeon](#) , [C P Crum](#) . Histologic and immunophenotypic immunophenotypic classification of cervical carcinomas by expression of the p53 homologue p63: a study of 250 cases. *Hum Pathol* . 2001 May;32(5):479-86.
- 23- Reis-Filho JS, Simpson PT, Martins A, Preto A, Gartner F, Schmitt FC. Distribution of p63, cytokeratins 5/6 and cytokeratin 14 in 51 normal and 400 neoplastic human tissue samples using TARP-4 multi-tumor tissue microarray. *Virchows Arch*. 2003;443(2):122–132.
- 24- Yusra Abdulkhalik Qasim. . P63 expression profile in uterine cervical lesions . *Zanco J. Med. Sci.*, Vol. 24, No. (2), August, 2020.
- 25- Abilasha R, Ramani P, Sherlin H J, Premkumar P, Natesan A. Immunohistochemical evaluation of oral epithelial dysplasia using cyclin-D1, p27 and p63 expression as predictors of malignant transformation. *Nat Sci Biol Med* 2013; 4(2):349– 58.
- 26- Shetty S, Krishnapillai R, Prabhu S. Assessment and comparison of p53 and p63 expression in oral epithelial dysplasia and squamous cell carcinoma. *SRM Journal of Research in Dental Sciences* 2014; 5(3):149–54.
- 27- Jacob AA, Sundaram A. P16, Ki67 and P63 staining pattern in squamous metaplasia, CIN and cervical cancer. *Int J Res Med Sci* 2018; 6(3):882.
- 28- Mitildzans A, Arechvo A, Rezeberga D, Isajevs S. Expression of p63, p53 and Ki-67 in Patients with Cervical Intraepithelial Neoplasia. *Turk Patoloji Derg* 2017; 33:9–16.
- 29- Kim SU, Lee JU, Lee DW, Kim MJ, Lee HN. The prognostic significance of P16, Ki-67, P63 and CK 17 expression determined by immunohistochemical staining in cervical intraepithelial I. *Korean J Obstet Gynecol* 2011; 54(4):184–91
- 30- Ying Zhou , Qianqian Xu, Bin Ling , Weihua Xiao, et al. Reduced expression of ΔNp63α in cervical squamous cell carcinoma. *Clin Invest Med* 2011; 34 (3): E184-E191.
- 31- Woodman CB, Collins SI, Young LS: The natural history of . cervical HPV infection: unresolved issues. *Nat Rev Cacer* 2007, 7(1):11-22.
- 32-Letian T, Tianyu Z: Cellular receptor binding and entry of human papillomavirus. *Viro J* 2010, 7:2.
- 33- Yoon CS, Kim KD, Park SN, Cheong SW: alpha(6) Integrin is the main receptor of human papillomavirus type 16 VLP. *Biochem Biophys Rev Commun* 2001, 283(3):668-673.
- 34- [Ulziibat Shirendeb](#), [Yoshitaka Hishikawa](#), [Shingo Moriyama](#), [Ne Win](#), et al. Human Papillomavirus Infection and Its Possible Correlation with p63 Expression in Cervical Cancer in Japan, Mongolia, and Myanmar. [Acta Histochem Cytochem](#). 2009 Dec 29; 42(6): 181–190.
- 35- Wang T. Y., Chen B. F., Yang Y. C., Chen H., Wang Y., Cviko A., Quade B. J., Sun D., Yang A., McKeon F. D., Crum C. P. Histologic and immunophenotypic classification of cervical carcinomas by expression of the p53 homologue p63: a study of 250 cases. *Hum. Pathol*. 2001;32:479–486.
- 36- Sahar Eldakhakhny, Qing Zhou, Emma J. Crosbie & Berna S. Sayan. Human papillomavirus E7 induces p63 expression to modulate DNA damage response [Cell Death & Disease volume 9, Article number: 127\(2018\)](#).