Original Research Paper

Volume - 13 | Issue - 03 | March - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pathology

# IMMUNOHISTOCHEMICAL EXPRESSION OF COX-2 IN CARCINOMA CERVIX AND ITS RELATION WITH GRADE AND STAGE OF TUMOUR

| | |
|---|---|
| **Dr. Anmol Dubey** | PG Resident,Department of Pathology, Sri Aurobindo Medical college and P.G. institute,Indore ,Madhya Pradesh,India |
| **Dr. Garima Malpani*** | Professor,Department of Pathology, , Sri Aurobindo Medical college and P.G. institute,Indore ,Madhya Pradesh,India*Corresponding Author |
| **Dr. Amit V. Varma** | Professor,Department of Pathology, , Sri Aurobindo Medical college and P.G. institute,Indore ,Madhya Pradesh,India |

**ABSTRACT** **Background:** Worldwide cervical cancer is fourth most frequent among women.COX-2 plays role in the onset and progression of malignancies and is considered as a marker of tumour aggressiveness. **Aim:**To study the expression patterns of COX-2 in cases of carcinoma cervix and find its relation with histopathological grade & stage.

**Objectives:**

1. To study immunohistochemical expression of COX-2 in Normal, dysplasia and carcinoma cases and score as per Allred scoring system.
2. To compare the expression score of COX-2 among listed cases.
3. To identify relation of COX-2 with age, menopausal status, histopathologicaland FIGO staging.

**Methods:**

Clinical details of 60 histopathological proven cervical carcinoma were retrieved. Cases were classified as per WHO classification. Grading,staging and IHC reporting were done.

**Results:**

In the present study total 60 cases were included , 13 were Total Hysterectomy specimen and 47 were cervical biopsy. Commonest age group was 40-60 years (36 cases-60%) with a mean age group of around 55.62 years. Most cases were of postmenopausal women(34 cases-56.7%). Pre menopausal had post coital bleeding(10 cases-16.6%) and postmenopausal had PMB(11 cases-18.3%) as the commonest clinical symptom. Clinical staging II was most prevalent which comprised of 12 cases (20%) Followed by stage IV and III comprising of 11 cases (18.3%) each. Among various histological subtypes MDSCC(28 cases-70%)was commonest followed by inflammatory(10 cases-20%) and WDSCC(6 cases-13%) cases. Chi square test was applied and the association between cox2 and age, menopausal status, clinical stage, histological subtypes and was found to be significant with histological subtypes (p value- 0.00) . Chi square test was applied and the association between menopausal status and clinical findings was found to be statistically significant. (p value- 0.01) **Conclusion:** Present study points towards the possibility of considering COX2 as a poor prognostic marker for cervix carcinoma. IHC is an easier and effective method for identification of prognostic markers, early in the course of disease to decide appropriate treatment protocol.

**KEYWORDS :** COX2, cervical carcinoma,prognostic marker.

## INTRODUCTION

Worldwide, fourth most frequent cancer in women is cervical cancer with an estimated 604 000 new cases and 342 000 deaths in 2020 [(1)]India accounts for one-fourth of all cervical cancer deaths worldwide, with 60,078 deaths and 96,922 new cases reported in 2018[(2,3).]

The usual 10- 20 years of natural history of progression from mild dysplasia to carcinoma cervix makes this cancer as relatively early preventable disease and provides the rationale for screening[(4).] During this transformation period, many important markers of tumour progression are expressed; one of them is COX-2.

Two distinct forms of COX exists – COX-1 and COX-2[(5).] COX-1 is known as the housekeeping gene and has constant levels of expression in all cells.COX-2 plays a role in the onset and progression of malignancies one of them, is cervical carcinoma and it is considered as a marker of tumour aggressiveness[(6).]

## MATERIALS AND METHODS

The cross sectional study was conducted after the approval of institutional ethics committee in the Department of Surgical Pathology, Sri Aurobindo Medical College & PG Institute (SAMC & PGI), Indore.

The Prospective study period was from April 2021 to September 2022 . Total 60 cases were included in the study.

**Inclusion Criteria:**

1.All cervical biopsies and hysterectomy specimens of cervical carcinomas and cervical dysplasia received in the department of surgical pathology in the study period

2.Ten cases of cervical biopsies/hysterectomy specimens reported normal will be included in the study

**Exclusion Criteria:**

1. Very small biopsies with inadequate tissue for further processing to apply immunohistochemistry.
2. All other tumour diagnosed histopathologically other thancarcinoma cervix.

**METHODS OF EVALUATION:**

**Clinical parameters:**

Clinical details pertaining to age, clinical features, pv findings, menopausal status, site of tumor, HPE Diagnosis were noted.Cervical carcinoma cases were classified as per WHO classification.
Histological grading and TNM Staging and grading of tumor were done.

The cases that were reported were further studied for Immunohistochemical staining by COX 2 antibody.

**Protocol of Staining[7]:**

1. To minimize the non-specific staining (due to action of endogenous peroxidase) each slide was treated with methanol containing 4%hydrogen peroxidase for 10 minutes.

2. After rinsing, the slides were placed in 0.05M-Tris – HCL buffer pH 7.4 for 10 minutes. Excess buffer was removed by wiping of the slides.

3. Sections were covered with adequate amount of primary antibody in the specified dilution and incubated for 1 hour 20 min in a humid chamber at room temperature for COX2. Primary antibody (was obtained from (Diagnostic BioSystems and Biogenex, USA respectively) in dilution 1:50 for COX2.

4. The slides were washed three times in 0.05M Tris-HCL buffer pH

5. 4 followed by incubation at room temperature for 25 minutes for

COX2 after covering with biotinylated secondary antibody of anti-rabbit antiglobulins in phosphate buffer saline (PBS) containing carrier protein and Sodium Azide ( 15mMOL/l) large volume (Diagnostic BioSystems USA kit).

6. After 3 washings (5 minute each) in Tris-HCL buffer, Horse Radish peroxidase (HRP) conjugated Streptavidin was used to cover the slides at room temperature for COX2 and incubated for30minutes.

7. After finishing of the above steps, slides were again rinsed thrice in 0.05MTris- HCL buffer PH 7.4 for 5 minutes each. Slides were then covered with substrate chromogen solution freshly prepared by dissolving 1mg of 3,3- diaminobenzidine tetra hydrochloride (DAB) in 1ml of 0.05M Tris- HCL buffer PH 7.4 containing 1µl of $H_2O_2$. Then the slides were incubated at 22°C for 10 minutes for COX 2 till development of optimum brown colour peroxidase product.

8. After rinsing in distilled water, sections were counterstained with Harris Haematoxylin and then mounted with coverslip using DPXas mounting media.

9. Precautions were taken to avoid drying of tissue at any step of processing.

Each batch of slides was immunostained with appropriate positive controls of sections for COX2 .Accounting to the percentage of positive cells, COX2 was graded Allred grading system.

**Table 1-Scoring for COX 2 marker Expression of COX 2 based on cytoplasmic staining-**

| Proportion | Score (PS) | Intensity Score (IS) | |
|---|---|---|---|
| Value | Significance | Value | Significance |
| 0 | None | 0 | negative |
| 1 | <1% | 1 | weak |
| 2 | 1-10% | 2 | intermediate |
| 3 | 10-33% | 3 | strong |
| 4 | 33-66% | | |
| 5 | >66% | | |

| TS(Points) | Grading of Expression |
|---|---|
| 0 | 0 |
| 2-4 | 1 |
| 5-6 | 2 |
| 7-8 | 3 |

- All the statistical analysis was done using Microsoft Excel.
- Pearson Chi Square test was applied as test of significance of qualitative data to compare IHC scores with the tumor characteristics: tumor grade, stage of tumor, clinical features, menopausal status, per vaginal findings. P-value of less than0.05 was considered statistically significant.

## OBSERVATIONS AND RESULTS

Total 60 patients who were diagnosed as Inflammatory,Dysplasia and Cervical Carcinoma in Surgical Pathology Department of Sri Aurobindo Medical College & Post Graduate Institute (SAMC&PGI),Indore, Madhya Pradesh, were enrolled into the study. In the present study, total number of 60 cases were included ,out of which 13 were Total Hysterectomy specimen and remaining 47 were cervical biopsy.

The most common age group of patients was 41 to 60 years comprising of 60% cases with a mean age group of around 55 years, followed by above 60 years age group which had 23.3% cases and 16.7% cases fall under 21 to 40 years age group. Out of 60 cases ,26 were premenopausal and rest 34 were postmenopausal .

**Table No.2 Distribution of cases based on Menopausal status and Clinical features**

| S. No. | Clinical Features | Pre menopausal | Post menopausal | Total No. of Cases and % |
|---|---|---|---|---|
| 1 | Heavy Menses | 4 | 2 | 6(10%) |
| 2 | Irregular Bleeding | 5 | 8 | 13(21.6%) |
| 3 | Post menopausal Bleeding | 0 | 11 | 11(18.3%) |
| 4 | Post coital Bleed | 10 | 4 | 14(23.3%) |
| 5 | Something coming out | 1 | 1 | 2(3.33%) |
| 6 | White Discharge | 6 | 8 | 14(23.3%) |
| | Total | 26 | 34 | 60(100%) |

According to table no.2 menopausal status and clinical features were taken into consideration where most common clinical feature among premenopausalwas post coital bleeding(16.6%) and postmenopausal bleeding(18.3%) was the commonest presentation inpost menopausal women. Chi square test was applied and the association between menopausal status and clinical findings was foundto be statistically significant. (p value- 0.01)

Of the 60 cases in our study,most common stage was stage II which comprised 12 cases (20%) Followed by stage IV and III comprising of 11 cases (18.3%) each. Staging was not applicable on 18 cases with include inflammatory, dysplasia, and carcinoma in situ cases.

It was observed that among , prevalent age group of 40-60 years(63.3%), moderately differentiated squamous cell carcinoma was found to be the most common histological subtype(70%)( figure1); followed by inflammatory(20%) and WDSCC(13%) cases. Chi square test was applied and the association between age and histological subtypes was found to be statistically non significant. (p value- 0.91) Age of the patient was correlated with IHC COX2 grading and maximum cases had 3+ grading(63.3%) and were of age group 40-60 years. Chi squared test was applied and the associationbetween age and COX2 status was found to be statistically non significant.(p value-0.98).

Menopausal status of patient was correlated with IHC COX2 grading and it was observed that intensity as well as percentage of COX2 was more in postmenopausal women(56.7%) then in premenopausal women(43.4%).Chi square test was applied and the association between menopausal status and COX2 status was found to be statistically not significant.(p value-0.50)

COX2 grading was correlated to stage of the tumour in which, cases which belong to stage II,III,IV had higher COX2 grading(3+).Chi square test was applied and the association between stage and COX2 status was found to be statistically not significant.(p value- 0.80).

**Table No.3: Case Distribution as per Histopathological subtypes and IHC COX2 grading**

| HPE Subtypes | COX2 Grading | | | | Total |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | |
| WDSCC | 0 | 0 | 0 | 6 | 6 |
| MDSCC | 0 | 1 | 2 | 25 | 28 |
| Poorly Differentiated SCC | 0 | 0 | 1 | 5 | 6 |
| WDADC | 0 | 0 | 0 | 0 | 0 |
| MDADC | 0 | 0 | 0 | 2 | 2 |
| Poorly Differentiated ADC | 0 | 0 | 0 | 0 | 0 |
| Dysplasia | 0 | 0 | 1 | 6 | 7 |
| Inflammatory | 10 | 0 | 0 | 0 | 10 |
| Total | 10 | 1 | 4 | 45 | 60 |

In the table 3,IHC COX2 grading was correlated with histological subtypes .It was observed that maximum cases of grade 3 COX2 were seen in moderately differentiated squamous cell carcinoma( figure 1 and figure2)followed by WDSCC &PDSCC. Chi squared test was applied and the association between histopathological subtypes and IHC COX2 status was found to be statistically significant.(p value-0.00)

Chi square test was applied between Inflammatory and SCC and was found to be significant.

(p value-0.0) Similarly chi square test was applied between

Inflammatory and Adenocarcinoma and Inflammatory and carcinoma in situ and both was found to be significant(p value-0.0)

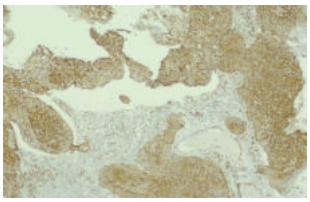

**Figure No.1 : Photomicrograph of MDSCC showing COX2 immunostaining 4x ( Proportion Score-5 and Intensity Score-3.**

**Figure No.2 : Photomicrograph of MDSCC showing COX2 immunostaining 10x ( Proportion Score-5 and Intensity Score-2.**

## DISCUSSION

Among the leading causes of cancer worldwide cervical carcinoma ranks 4th, after breast carcinoma, colorectal carcinoma and lung carcinoma. Cervical carcinoma accounts for the third most common cancer occurring in women and the second leading cancer killer next only to carcinoma breast in developing countries like India.[8]

In this study, the role of COX2 expression as a prognostic marker for carcinoma of cervix was being evaluated.The study was done taking 60 cases in the Department of Surgical Pathology.

In our study, age range of patients was from 25 – 80 years with mean age of 55.62 years. Majority of the patients presented in age group 40-60 years. Study done by Sreedevi A et. al [9] (50-55 years) showed concordance. Similar results were seen in other studies conducted by Afroj et al. [10] (32-57 years), Jain DK et al., [11] (40-70 years),Esmeaili et al., [12]. (60-64 years),Arbyn Marc et al[13] (53-55 years).

In our study group, carcinoma of cervix was found most commonly in post menopausal females (56.6%) then in premenopausal with both having bleeding as the chief clinical complain.The p value between the two variable was found to be significant. Study conducted by Vinneta K et al.[14],Raju k et al.[15] ,Jain DK et al.[11] showed concordance with the present study. Study done by Afroj S et al.[10] ,Patil N et al. [16]showed discordance with higher prevalance seen among premenopausal women presented with postcoital bleed and white discharge respectively.

In our study maximum cases(78%) had carcinoma of stage II followed by III &IV.In the study conducted by Vinneta K et al.[14],showed concordance with maximum cases(77%) of cervical carcinoma in stage II,III,IV).Similar studies done by Raju K et al.[15],Jain DK et al.[11]. Afroj et al.[10] ,Patil N et al.[16]showed prepondance of cases in stage III.

In our study group, the most common histological subtype of carcinoma was squamous cell carcinoma(66%), compared to adenocarcinoma(3.3%).Among SCC ,MDSCC(46%) was most prevalent ,followed by WDSCC& PDSCC(10%) each. Study conducted by Patil et al., R Bandyopadhyay R and Gaikwad SL et al.,[16,17,18]. was concordant with MDSCC being the most prevailing subtype. Study done by Jain et al., ,Raju k et al[11,15]. showed more cases of WDSCC which was discordant with our study.

No significant correlation was found between histological subtypes and age of carcinoma cervix( p – value 0.091).

On comparing the age of the patients with COX2 expression, it was found that the expression of COX2 was lesser in younger females i.e 20-40 years age group (16.6%) when compared to females of older age group i.e age 40-60 years (63.3%) and >60 years (20%).Miaoling H et al[19] ,Ananth K[20] ,Manchana T et al[21] ,Jain P et al [22]also showed a similar incidence. This could be because of higher prevalence of carcinoma in older age group. But in our study no significant correlation was found between age of the patient and COX2 expression.

In the present study, high positivity of cox 2 was noted in both pre and post menopausal women and there was a statistically significant correlation found between the two with p value – 0.50. The study done by Jana D et al, Kim K et al .[23,24] also showed higher cox positivity in post menopausal women.

In the present study, COX2 expression was associated with advanced clinical stage of the disease.Most common age group observed were II (20%)followed by III& IV (18% each) and had high COX2 grading. But this association was not found to be statistically significant. Statistically significant association between COX2 expression and stage were noted in studies by Miaoling H et al ,Jain P et al, Hoellen F et al and Ferrandina G et al.[19,22,,25,26]Other studies like those by Khunamornpong S et al[27]showed no correlation between these two factors and were concordant with our study.

Studies on the expression of cox2 in cervical cancer are relatively few. It has been shown to be expressed in dysplastic epithelium and in invasive carcinomas. The number and intensity of positive COX2 staining has been shown to increase with the severity of dysplasia.

In the present study carcinoma in situ (100%) and invasive carcinoma(80%) both showed good positivity to COX2. It is in concordance with the study done by Farley JH et al.,[28]and Dursan P et al.,[29] Jain P et al.,[22]which showed 25-40% positivity to CIN and 55-80% positivity in invasive carcinoma, which suggests that COX2 may participate in the progression of Cervical cancers.It is in contrast to the study done by BandyopadhyayR[17]showed lower positivity rates to CIN and carcinomas.

**Table4- COX2 expression and histological subtype correlation of different studies.**

| S. No | Study | Year | Histo subtypes | COX2 |
|---|---|---|---|---|
| 1 | Ferrandina G et al.[26] | 2003 | Adenocarcinoma | Positive (High expression) |
| 2 | Jain P[22] | 2020 | Squamous cell carcinoma | Positive (High expression) |
| 3 | Manchana T et al[21] | 2006 | Adenocarcinoma | Positive (High expression) |
| 4 | Bandyopadhyay R et al[17] | 2011 | Adenocarcinoma | Positive (High expression) |
| 5 | Hoellen F et al.[25] | 2016 | Squamous cell carcinoma | Positive (High expression) |

When COX2 expression was correlated with the histopathological subtype of carcinoma, it was seen that higher COX2 expression was seen in carcinoma in situ,squamous cell carcinoma and adenocarcinoma .All were found to be significant when correlated to COX2 using Chi square test(p value-0.00) This is not in concordance with studies by Ferrandina G et al(26) ,Manchana T et al (21)and Bandyopadhyay R et al(17)where higher COX2 expression was noted in adenocarcinoma than in squamous cell carcinoma.( Table 5)The study done by Jain P et al,(22)., and Hoellen F et al.(25) showed higher cox2 positivity in squamous cell carcinoma , whereas in our study higher cox 2 grading was seen in both squamous cell carcinoma and adenocarcinoma.

This variation can be attributed to lesser percentage of cases of adenocarcinoma cases in our study.The results were statistically significant between the control group(inflammatory) and carcinomatous group(carcinoma in situ,SCC,ADC).(p value -0.00)
According to our study, COX2 expression correlated significantly with histological diagnosis and histological subtypes, which are independent prognostic factors of carcinoma of cervix. Hence it can be concluded that positive COX2 expression can be considered as a poor prognostic marker and can aid in determining the treatment options for these patients.

## CONCLUSION

As surgical pathologists, our role does not end merely in diagnosing a malignancy or classifying it, but it is our responsibility to help the clinician in deciding the appropriate treatment for patients. In this era of targeted therapy, more studies should be conducted to detect possible

prognostic markers so that targeted therapy can be implemented effectively against this common killer disease.

## REFERENCES


1. World Health Organization. Cervical cancer.2020[Accessed on 20th october2022].Available from:https://www.who.int/health-topics/cervical-cancer.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 ;136(5):E359-86.
3. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, De Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Asia 2019.
4. Das Gupta A, Naskar NN, Rama R, Deb S. A community based study of the prevalence of risk factor of carcinoma cervix in married women of rural area of West Bengal. Indian J Community Med 2012; 27: 36-9.
5. Rouzer, CA.,&Marnett, LJ. Cyclooxygenases: structural and functional insights. J lipid Res 2009; 50:S29–34.
6. Kim HS, Kim T, Kim MK, Suh DH, Chung HH, and Song YS, Cyclooxygenase-1 and -2: Molecular Targets for Cervical Neoplasia, J Cancer Prev. 2013; 18(2): 123-134.
7. Bancroft JD, Layton C. Manual of Histological Techniques and Their Diagnostic Application. Edinburgh, London, New York, Tokyo : Churchill Livingstone; 1994;173-185.
8. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021:71:209–49
9. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. Int J Womens Health. 2015 Apr 16;7:405-14.
1. Afroj S., Banu M.A., Sultana S., Jahan R., Rahman S., Begum N., Clinicopathological Profile of Cervical Cancer patients attending in a specialized Hospital. J Dhaka Med Coll. 2017; 26 (2) : 117-21
2. Jain D.K., Shukla P., Gupta V., Clinicopathological Survey of Carcinoma Uterine Cervix In Patients Attending Tertiary Care Hospital Of Central Uttar Pradesh. Int J Sci Res (Ahmedabad). 2017; 6 (9) : 63-5
3. Esmaeili H.A., Pourlak T., Ghamari B., Shayan F.K., Sanaat Z., Soltani G.G., Comparison of nuclear P16 immunostaining in atypical and normal endocervical glands: A descriptive analytical study. J Anal Res ClinMed.. 2018; 6 (2) : 66-71
4. Arbyn Marc et al. The Lancer Global Health, Volume 8, Issue 2, e191-e203
5. Kumari, Vineeta, et al. "MENOPAUSE AND CERVICAL CANCER—DESCRIPTIVE STUDY OF PRESENTATION AND MANAGEMENT IN TERTIARY CENTRE OF JHARKHAND, INDIA." Journal of Evolution of Medical and Dental Sciences, vol. 6, no. 86, 26 Oct. 2017, pp. 5970+
6. Raju, K., CV, R., & SR, S. (2019). Clinicopathological correlation of invasive squamous cell carcinoma of uterine cervix: A cross-sectional study. Biomedical Research and Therapy, 6(11), 3443-3451
7. Patil N., Deshmukh V., Rathid A., Jyoti D., Chavan S., Clinicopathological Correlation of Cervical Carcinoma: A Tertiary Hospital-based Study. Int J Sci Stud. 2019; 6 (10) : 1-4 .
8. Bandyopadhyay R, Chatterjee U, Mondal SK, Nag D, Sinha SK. A study on expression pattern of cyclooxygenase-2 ,2011 Oct- Dec;54(4):695-9.
9. Gaikwad S.L., Valand A.G., Agarwal N.U., Clinico-histopathological analysis of lesions of uterine cervix in Ambejogai city of Maharashtra: A 2 year study at tertiary level hospital. Journal of Diagnostic Pathology and Oncology.. 2016; 1 (2) : 32-5 .
10. Miaoling Huang, Qing Chen, Jianpeng Xiao, Changhao Liu and Xiaomiao Zhao Prognostic significance of cyclooxygenase-2 in cervical cancer: A meta-analysis Int. J. Cancer: 132, 363–373
11. Ananth Kumar MARUTHA MUTHU , Phaik-Leng CHEAH, Cing-Chai KOH , ManFong CHEW, Yen-Fa TOH and Lai-Meng LOOI ., Cyclooxygenase-2 (COX2) expression in adenocarcinoma surpasses that of squamous cell carcinoma in the uterine cervix., Malaysian J Pathol 2017; 39(3) : 251 – 255
12. Manchana T, Triratanachat S, Sirisabya N, Vasuratna A, Termrungruanglert W, Tresukosol D. Prevalence and prognostic significance of COX-2 expression in stage IB cervical cancer. GynecolOncol 2006; 100(3): 556-60.
    Jain P, Singh S, Jain M , Ralli M , Sen R, .The expression of cyclooxygenase -2 in carcinoma of uterine cervix. Clin Cancer Investig J 2020;9:69-74
13. Jana D, Sarkar DK, Ganguly S, Saha S, Sa G, Manna AK, Banerjee A, Mandal S. Role of Cyclooxygenase 2 (COX-2) in Prognosis of Breast Cancer. Indian J SurgOncol. 2014 Mar;5(1):59-65
14. Kim K, Jeon YT, Park IA, Kim JW, Park NH, Kang SB et al. Cyclooxygenase-2 expression in cervical intraepithelial neoplasia. In Natural Compounds and Their Role in Apoptotic Cell Signaling Pathways. Blackwell Publishing Inc. 2009. p. 111-115
15. Hoellen F, Waldmann A, Banz-Jansen C, Rody A, Heide M, Köster F, Ribbat-Idel J, Thorns C, Gebhard M, Oberländer M, Habermann JK, Thill M. Expression of cyclooxygenase-2 in cervical cancer is associated with lymphovascular invasion. OncolLett. 2016 Oct;12(4):2351-2356.Goellner J.R., Carcinoma of the cervix. Clinicopathologic correlation of 196 cases. Am J ClinPathol. 1976; 66 (5) : 775-85
16. Ferrandina G, Ranelletti FO et al (2003) Celecoxib modulates theexpression of cyclooxygenase-2, ki67, apoptosis-related marker, and microvessel density in human cervical cancer: a pilot study. Clin Cancer Res 9(12):4324–4331
17. Khunamornpong S, Settakorn J, Sukpan K, Srisomboon J, Ruangvejvorachai P, Thorner PS, et al. Cyclooxygenase-2 expression in squamous cell carcinoma of the uterine cervix is associated with lymph node metastasis. GynecolOncol 2009; 112(1): 241-7.
18. Farley JH, Hickey KW et al (2003) Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early stage, cervical carcinoma. Cancer 97(9):2196–2202
19. Dursun P, Yuce K, Usubutun A, Ayhan A. Cyclooxygenase-2 expression in cervical intraepithelial neoplasia III and squamous cell cervical carcinoma, and its relation with clinicopathologic variables. Int J Gynecol Cancer 2007;17:164-73.