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Original Article

Pathology Section

Role of Proliferative Marker (Ki-67) and ER, PR in Cervical Epithelial Lesions with Clinicopathological Association: A Cross-sectional Study

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ABSTRACT

Introduction: Cervical cancer is the fourth most common cancer affecting women worldwide, following breast, colorectal and lung cancer. India contributes 28% of the cervical cancer mortality burden, with 87,090 deaths due to cervical cancer, making it the second most populous country in the world. Oestrogen Receptors (ER) are located not only in the tissues of the female reproductive tract and breast but also in diverse tissues such as bone, brain, liver, colon, skin and salivary glands. Ki-67 is a nuclear protein expressed during all active phases of the cell cycle and is absent in the G0 phase, making it a potent biomarker of cellular proliferation.

Aim: To study the clinicopathological spectrum of cervical epithelial lesions and their association with cell proliferation (Ki-67) and ER and Progesterone Receptor (PR) status.

Materials and Methods: This was a single-institution-based cross-sectional study in which a total of 202 cases of cervical epithelial lesions diagnosed from May 2022 to May 2024 at the Institute of Post Graduate Medical Education and Research and SSKM Hospital, Kolkata, West Bengal, India were studied. Clinical and demographic data were associated with histological findings. Immunohistochemical staining with Ki-67, ER and PR antibodies was performed and the Ki-67 labelling index and ER and PR status were assessed respectively. Based on the assessment, a master chart was prepared for patients belonging to different age groups with certain medical complaints, and data were organised into tables. Statistical analysis was conducted using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) version 23.0 software.

Results: In this study, 202 patients were evaluated. The patient age ranged from 18 to 68 years, with a mean age of 40.78±10.13 years. Cervical epithelial lesions were most prevalent in the age group of 31 to 50 years (66.8%). Among the 202 cases, 108 (53.5%) were non neoplastic, 10 cases (5.0%) were benign neoplastic, and 84 cases (41.6%) were malignant neoplastic lesions. The difference in proliferative rates, as indicated by the Ki-67 labelling index, between benign neoplasms and malignant neoplasms was statistically significant (p-value <0.001). There was no significant association between the levels of ER and the nature of the lesions in the patients (non neoplastic and neoplastic) (p-value=0.08). Additionally, there was no significant association between the levels of PR and the nature of the lesions in the patients (p-value=0.25).

Conclusion: Malignant neoplasms exhibit a significantly higher proliferative rate than benign neoplasms and non neoplastic lesions. No significant association between ER and PR status and the nature of the lesions was found in the study, although the mean ER score and mean PR score of adenocarcinomas were significantly higher than those of Squamous Cell Carcinoma (SCC) and Cervical Intraepithelial Neoplasia (CIN).

Keywords: Cell proliferation marker, Cervical neoplasm, Hormonal status, Immunohistochemistry

INTRODUCTION

Cervical cancer is the fourth most common cancer in women globally, with around 660,000 new cases and 350,000 deaths in 2022 [1]. In India, cervical cancer is the second most common cancer among women and the second leading cause of cancer deaths. According to the latest data from 2020, cervical cancer accounted for approximately 77,348 deaths in India, constituting about 23% of global cervical cancer deaths [2].

Human Papillomavirus (HPV) infection is a sexually transmitted disease. Infection with high-risk HPV is now viewed as a necessary precondition for the development of all cervical cancer and precancerous intraepithelial lesions, and it is one of the most common sexually transmitted infections worldwide [3]. HPV infection does not always lead to the occurrence of cervical squamous intraepithelial lesions, as the majority of HPV-infected individuals have subclinical or latent viral infections [4]. The progression from HPV infection to cervical squamous intraepithelial lesions depends on the synergistic effect of other factors [5].

The concentration of the ER protein in squamous epithelial cells varies depending on the menstrual cycle. In the early proliferative phase, all layers are negative. In the later proliferative phase, the basal and parabasal layers of the healthy ectocervix begin to show an immunohistochemical staining reaction. Throughout the secretory phase, positive cell nuclei can be found up to the superficial layers. In squamous cell tissue, no positive PR reaction can be detected. In most cases, the adjacent stroma and cervical glands show highly positive PR staining, although there are no changes related to the menstrual cycle [6].

It is well known that ER and PR have been widely used to evaluate the prognosis and guide the therapy of patients with breast and endometrial cancer. The cervix is also hormone-dependent tissue, and various reports have demonstrated that the normal cervix contains steroid receptors; however, their presence in cervical carcinoma has been controversial. Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2, and mitosis) but is not expressed by resting cells (G0). Ki-67 is an excellent marker

for determining the growth fraction of a given cell population. This marker defines the proliferation status of both tumour cells and endothelial cells from tumour blood vessels. During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus, whereas in mitosis, most of the protein relocates to the surface of the chromosomes [7]. The prognostic value of Ki-67 has been investigated in several studies, and its potential as a reliable marker has been demonstrated in cancers of the breast, soft tissue, lung, prostate, cervix and central nervous system [8].

Objectives of study:

1) To examine the clinicopathological spectrum of cervical epithelial lesions in a tertiary care centre.
2) To study the immunohistochemical expression of Ki-67 in cervical epithelial lesions.
3) To study the immunohistochemical expression of ER in cervical epithelial lesions.
4) To study the immunohistochemical expression of PR in cervical epithelial lesions.

MATERIALS AND METHODS

The cross-sectional study was conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology at IPGME&R, SSKM Hospital, Kolkata, West Bengal, India. The study included all hysterectomy and cervical biopsy specimens submitted to the Pathology Department for histopathological confirmation from May 2023 to May 2024, as well as previously diagnosed cases from the previous year (between May 2022 and April 2023). These were assessed by reviewing past records and studying stained sections from stored blocks at IPGME&R and SSKM Hospital. A total of 202 cases of cervical epithelial lesions were included in the study. All procedures performed in the current study were approved by the Institutional Ethics Committee in accordance with the 1975 Helsinki Declaration and its later amendments (the IPGME&R Research Oversight Committee studied and approved this study under Memo No. IPGME&R/IEC/2023/260 dated 18.04.2023).

Inclusion criteria: Women of reproductive and postmenopausal age groups, presenting with abnormal vaginal bleeding, vaginal discharge and dyspareunia to the Gynaecology and Obstetrics OPD. Patients admitted to the inpatient and out patient department of Gynaecology and Obstetrics were included in the study.

Exclusion criteria: Prepubescent females, pregnant women and patients unwilling to give consent were excluded from the study.

Study Procedure

The hysterectomy and biopsy samples obtained in the Pathology Department were fixed in 10% neutral buffered formalin, processed through dehydration, clearing, impregnation and embedding in paraffin, and cut into 3 µm sections using a microtome. Haematoxylin and Eosin (H&E) staining was performed on sections using a standard staining procedure by the regressive method to differentiate nuclear and cytoplasmic components.

Immunohistochemical procedure: For IHC staining, tissue sections underwent antigen retrieval using a heat retrieval cooker and were then incubated sequentially with a primary monoclonal rabbit antihuman Ki-67 antibody from GenomeMe, a secondary antibody, and DAB substrate, followed by haematoxylin counterstaining. Appropriate positive controls (tonsil) and negative controls (all steps same except the primary antibody was omitted) were included. IHC for ER and PR was performed using Zytomed monoclonal rabbit antihuman antibodies on Formalin-fixed, Paraffin Embedded (FFPE) tissue sections, along with appropriate positive controls (breast carcinoma) and negative controls (all steps same except the primary antibody was omitted).

Assessment of IHC stained sections: IHC results were assessed independently by two pathologists. Brown nuclear staining for Ki-67 was considered positive. Ten high-power visual fields were randomly chosen under the microscope, and the positive cell numbers (the intensity of staining was not considered for evaluation) were counted at 400x magnification in 1,000 tumour cells from the 10 fields on each slide. The results were expressed as a percentage of the Ki-67 positive cells [9].

Ki-67 labelling index (LI)=(Number of positive tumour cells/Total number of tumour cells counted)×100

Both microscopical and IHC analysis were performed without any clinical information.

Analysis of staining for ER and PR: In the specimen slide, five high-power visual fields were randomly chosen under the microscope. ER and PR were considered positive if brown granules were present in the nucleus. The IHC grading diagnosis of cervical epithelial lesions was made according to combined grading criteria (similar to Wang H et al.,) [10].

Intensity: The negative staining intensity was rated as 0, weak but stronger than the negative control was rated as 1, clear staining was rated as 2, and strong staining was rated as 3.

The number of positive cells: <10% was rated as 0, 10-30% was rated as 1, 31-60% was rated as 2, and >60% was rated as 3. The above two scores are summed: a total score of 0-1 was considered negative, a score of 2 was considered weak positive, a score of 3-4 was considered medium positive, and a score of 5-6 was considered strong positive.

STATISTICAL ANALYSIS

Statistical analysis was performed with the help of Microsoft Excel and SPSS 23.0 software. Descriptive statistical analysis was conducted to calculate the means along with their corresponding Standard Deviations (SD). The test of proportions was used to determine the Standard Normal Deviate (Z) for comparing the difference in proportions. A t-test was employed to compare two means. One-way Analysis of Variance (ANOVA), followed by Tukey's post-hoc test, was used to compare more than two means simultaneously. The Chi-square test was performed to identify associations. A p-value of <0.05 was considered statistically significant.

RESULTS

In present study, 135 (66.8%) patients were aged between 31 and 50 years, which was significantly higher than in other age groups (Z=7.01; p-value <0.0001). Thus, cervical epithelial lesions were predominantly observed in the age group of 31 to 50 years [Table/Fig-1].

Age (years)	n (%)
11-20	3 (1.5)
21-30	36 (17.8)
31-40	67 (33.2)
41-50	68 (33.7)
51-60	24 (11.9)
>60	4 (2)
Mean±SD	40.78±10.13
Median	40
Range	18-68

[Table/Fig-1]: Distribution of the patients according to their age (N=202).

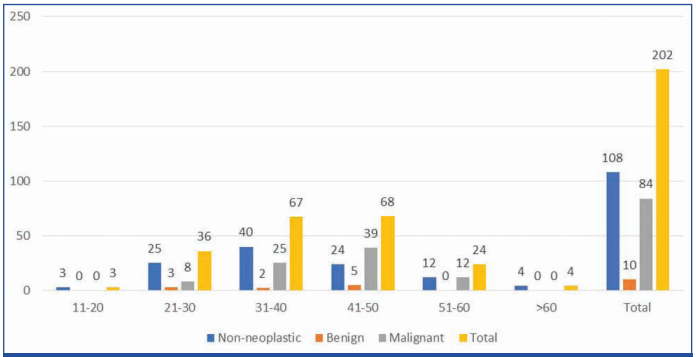
Non neoplastic lesions (53.6%, n=108), followed by malignant neoplasms (41.6%, n=84), were significantly more common

than benign neoplasms (5.0%, n=10) (Z=6.17; p-value <0.0001) [Table/Fig-2].

Nature of lesion	n (%)
Benign neoplasm	10 (5)
Non neoplastic	108 (53.5)
Malignant neoplasm	84 (41.6)

[Table/Fig-2]: Distribution of nature of lesion among all patients (n=202).

Among the 202 cases, the majority of cases were in the age range of 31 to 50 years, which corresponds to the reproductive age. A total of 40 cases of non neoplastic lesions were found in the 31 to 40-year age group, while the maximum number of malignant neoplasms was observed in the 41 to 50-year age group [Table/Fig-3].



[Table/Fig-3]: Association between age and types of lesions of all patients.

The distribution of HPE findings of malignant, benign and non neoplastic are shown in [Table/Fig-4]. One-way ANOVA indicated that there was a significant difference in the mean Ki-67 for different types of HPE findings (p-value <0.0001). The mean Ki-67 for adenocarcinoma, followed by SCC, was significantly higher than the mean Ki-67 for CINs (p-value <0.0001) [Table/Fig-5].

HPE findings	n (%)
Malignant neoplasm	
Squamous Cell Carcinoma (SCC)	48 (23.8)
Adenocarcinoma	1 (0.5)
Adenosquamous carcinoma	1 (0.5)
CIN I	12 (5.9)
CIN II	11 (5.4)
CIN III	11 (5.4)
Benign	
Endocervical polyp	8 (4)
Condyloma acuminatum	2 (1)
Non neoplastic	
Cervicitis	46 (22.8)
Squamous metaplasia	18 (8.9)
Atrophy	15 (7.4)
Nabothian cyst	12 (5.9)
Microglandular hyperplasia	10 (5)
Arias-stella reaction	4 (2)
Endometriosis	2 (1)
Tunnel cluster	1 (0.5)

[Table/Fig-4]: Distribution of histopathological findings among all patients (n=202).
CIN: Cervical intraepithelial neoplasia

ER expression: Among the 108 non neoplastic cases, 17 cases (15.7%) were negative, 28 cases (25.9%) were weak positive, 52 cases (48.2%) were medium positive, and 11 cases (10.2%) were strongly positive for ER status. In the benign neoplasm category, among the 10 cases, two cases (20%) were negative, three cases (30%) were weak positive, and five cases (50%) were medium positive for ER status.

HPE	Mean±SD	F-value	p-value
CIN I	26.56±10.07	184.09	<0.0001[S]
CIN II	42.32±9.10		
CIN III	46.19±8.64		
Squamous Cell Carcinoma (SCC)	64.05±12.34		
Adenocarcinoma	77.70±3.54		
Endocervical polyp	4.01±3.15		
Condyloma acuminatum	6.70±5.52		
Cervicitis	0.62±0.44		
Atrophy	0.40±0.38		
Squamous metaplasia	2.59±3.13		
Microglandular hyperplasia	8.82±7.84		
Arias-stella reaction	8.15±3.30		
Endometriosis	7.00±5.94		
Nabothian cyst	0.73±0.32		
Tunnel cluster	3.50±0.00		

[Table/Fig-5]: Ki-67 Labelling Index (LI) expressions among all histological types of lesions.

Among the 84 malignant cases, 29 cases (34.5%) were negative, 21 cases (25%) were weak positive, 29 cases (34.5%) were medium positive, and five cases (6%) were strongly positive for ER status. The Chi-square test showed that there was no significant association between the levels of ER and the nature of the lesions in the patients (p-value=0.08). Thus, the levels of ER were more or less equally distributed across the patients [Table/Fig-6].

ER	Non neoplastic	Benign neoplasm	Malignant neoplasm	Total
0-1	17	2	29	48
2	28	3	21	52
3-4	52	5	29	86
5-6	11	0	5	16
Total	108	10	84	202

[Table/Fig-6]: Association between the patients' ER levels and the type of lesions.
χ^2=11.26; p-value=0.08; NS: Not significant

PR expression: Among the 108 non neoplastic cases, 31 cases (28.7%) were negative, 30 cases (27.8%) were weak positive, 41 cases (38%) were medium positive, and six cases (5.5%) were strongly positive for PR status. In the benign neoplasm category, among the 10 cases, two cases (20%) were negative, four cases (40%) were weak positive, and four cases (40%) were medium positive for PR status. Among the 84 malignant cases, 37 cases (44.1%) were negative, 17 cases (20.2%) were weak positive, 28 cases (33.3%) were medium positive, and two cases (2.4%) were strongly positive for PR status. The Chi-square test showed that there was no significant association between the levels of PR and the nature of the lesions in the patients (p-value=0.25). Thus, the levels of PR were more or less equally distributed [Table/Fig-7].

PR	Non neoplastic	Benign neoplasm	Malignant neoplasm	Total
0-1	31	2	37	70
2	30	4	17	51
3-4	41	4	28	73
5-6	6	0	2	8
Total	108	10	84	202

[Table/Fig-7]: Association between the patients' PR levels and the type of lesions.
χ^2=7.77; p=0.25; NS: Not significant

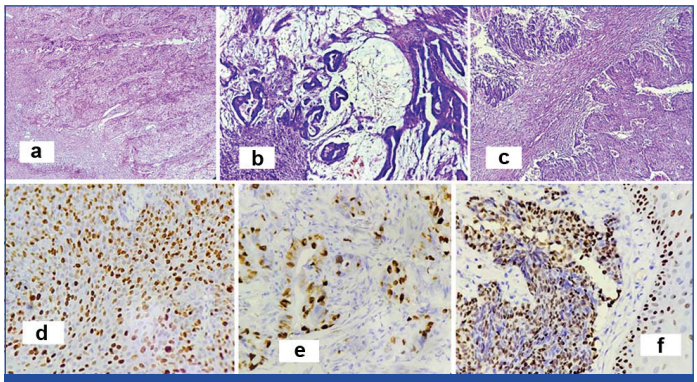
One-way ANOVA showed that the mean ER score of adenocarcinomas was significantly higher than that of other malignant neoplasms (p-value <0.001). Additionally, the mean PR score of adenocarcinomas was significantly higher than that of other malignant neoplasms (p-value <0.001) [Table/Fig-8].

ER/PR score	Type of lesion	Mean±SD	F-value	p-value
ER score	SCC	1.90±1.06	4.119	<0.001^S
	Adeno	5.00±0.00		
	CIN-I	2.67±1.50		
	CIN-II	2.64±1.50		
	CIN-III	2.45±0.93		
	Benign	2.50±1.08		
	Non neoplastic	2.75±1.28		
PR score	SCC	1.73±1.05	3.823	<0.001^S
	Adeno	5.50±0.71		
	CIN-I	2.25±1.22		
	CIN-II	2.45±1.37		
	CIN-III	2.27±1.01		
	Benign	2.30±0.95		
	Non neoplastic	2.30±1.32		

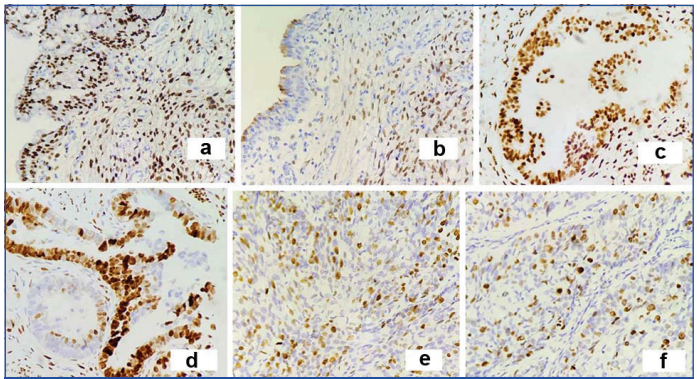
[Table/Fig-8]: Comparison of ER and PR values according to the type of lesions.
NS: Not significant; S: Significant

Photomicrographs of cervical epithelial malignant neoplasms and Ki-67 is shown in [Table/Fig-9].

Photomicrograph of ER, PR expression in cervical epithelial lesions is shown in [Table/Fig-10].



[Table/Fig-9]: a-c) Histopathological images (H&E): (a) SCC (100x); (b) Adenocarcinoma (100x); (c) Adenosquamous carcinoma (100x). Ki-67 expression (d) SCC (400x); (e) Adenocarcinoma; (f) Adenosquamous carcinoma. Dark brown nuclear staining of the tumour cells was taken as positive immunoreactive Ki-67.



[Table/Fig-10]: Photomicrograph of ER expression (original magnification 400 x)- (a) Normal cervix; (c) Adenocarcinoma; (e) Squamous cell carcinoma.
PR expression (original magnification 400X)- (b) Normal cervix; (d) Adenocarcinoma; (f) Squamous cell carcinoma. The expression of ER and PR was localised in the nucleus of tumour cells in case of adenocarcinoma and SCC and also expressed in normal cervix.

DISCUSSION

In the study, 202 patients were evaluated. The age of the patients ranged from 18 to 68 years, with a mean age of 40±10.13 years. In this study, cervical epithelial lesions were predominantly prevalent in the age group of 31 to 50 years, with the maximum number of malignant neoplasms found in the 41 to 50-year age group [Table/Fig-1,3]. Wang H et al., reported a similar average age of 47.49±3.39 years in their study [10]. Raju K et al., reported that the maximum cases of premalignant and malignant cervical lesions were found in the age group of 40 to 49 years [11]. One study concluded that the most common age group involved in carcinoma cervix ranged from 35 to 50 years [12]. Among the 202 cases, there were 108 (53.5%) non neoplastic lesions, 10 (5.0%) benign neoplastic lesions, and 84 (41.6%) malignant neoplastic lesions [Table/Fig-2].

Among the total 202 cases, 48 cases (23.8%) were SCC, one case (0.5%) was adenocarcinoma, one case (0.5%) was adenosquamous carcinoma, 12 cases (5.9%) were CIN grade 1, 11 cases (5.4%) were CIN grade 2, and 11 cases (5.4%) were CIN grade 3. In the benign neoplasm category, eight cases (4.0%) were endocervical polyps, and two cases (1.0%) were condyloma acuminatum. Among the non neoplastic cases, 46 (22.8%) were cervicitis, 18 (8.9%) were squamous metaplasia, 15 (7.4%) were atrophy, 12 (5.9%) were Nabothian cysts, 10 (5.0%) were microglandular hyperplasia, four cases (2.0%) were Aias-stella reaction in the cervix, two cases (1.0%) were endometriosis, and one case (0.5%) was a tunnel cluster [Table/Fig-4]. Raju K et al., reported that about 90% of cervical cancers are SCCs and the remaining 10% are adenocarcinomas [11]. In another study, Kalyani R et al., reported that the majority of cervical carcinomas were histologically SCC, followed by adenocarcinoma [13].

Ki-67 is the gold standard proliferative index and is immunohistochemically detectable throughout the interphase of the cell cycle, reaching its maximal level during mitosis. Immediately after mitosis, the cellular Ki-67 antigen content decreases due to its short half-life and is not detectable in the G0 phase. Ki-67 expression is useful in distinguishing the different grades of dysplasia, though it does not predict their behaviour [14].

In present study, the mean Ki-67 value of 108 cases of non neoplastic lesions was 2.12±3.89%. The majority of non neoplastic cases were cervicitis (n=46), which showed a mean Ki-67 value of 0.62±0.44%. The mean Ki-67 value for 10 cases of benign lesions was 4.55±3.52%. The mean Ki-67 value for 84 cases of malignant neoplasms was 53.84±18.05%. For SCC, the mean Ki-67 LI was 64.05±12.34% (n=48). For adenocarcinoma, the mean Ki-67 LI was 77.70±3.54% (n=2). For CIN, the mean Ki-67 LI values were 26.56±10.07%, 42.32±9.10%, and 46.19±8.64% for grades 1, 2, and 3, respectively. The mean Ki-67 of malignant neoplasms was significantly higher than all others (p<0.0001), and the mean Ki-67 of benign neoplasms was significantly higher than that of non neoplastic lesions. Additionally, the mean Ki-67 of adenocarcinoma, followed by SCC, was significantly higher than the mean Ki-67 of CINs [Table/Fig-5].

Various studies have shown that Ki-67 is an important reference for predicting the development of CIN and cervical cancer. Its expression can reflect the biological behaviour of tumour cells [15,16]. Hebbar A and Murthy VS found that Ki-67 immunostaining was negative in chronic cervicitis cases. In their study, they reported positive expression in 70% of CIN I cases in the basal half of the epithelium, in contrast to 40% of cases of squamous metaplasia with atypia. In cases of CIN II and III, more intense positive staining was observed throughout the full thickness of the epithelium. Invasive carcinomas showed diffuse and strong expression of Ki-67 in all cases. The grade of dysplasia was found to correlate well with Ki-67 expression [17].

Silva-Filho AL et al., found that invasive SCC had a high staining score for Ki-67 [18]. Godoy AEG et al., reported that Ki-67 expression is greater in CIN samples than in normal or metaplastic epithelium, and Ki-67 staining was stronger in high-grade CIN compared to low-grade CIN [19]. Therefore, Ki-67 is usually used to differentiate and grade CIN [19]. Raju K et al., found that the expression of Ki-67 was significantly higher in invasive SCC cases and showed that Ki-67 expression correlates with the histological grade of cervical neoplasia. They also found that all adenocarcinoma cases exhibited high Ki-67 positivity [11].

In present study, all 202 cases were evaluated by IHC staining for ER and PR. Among the non neoplastic cases (n=108), 17 cases (15.7%) were negative, 28 cases (25.9%) were weak positive, 52 cases (48.2%) were medium positive, and 11 cases (10.2%) were strongly positive for ER status. For PR status, 31 cases (28.7%) were negative, 30 cases (27.8%) were weak positive, 41 cases (38%) were medium positive, and six cases (5.5%) were strongly positive.

In benign neoplasms (n=10), 2 cases (20%) were negative, 3 cases (30%) were weak positive, and 5 cases (50%) were medium positive for ER status. For PR status, among the 10 cases, 2 cases (20%) were negative, 4 cases (40%) were weak positive, and 4 cases (40%) were medium positive. Among malignant neoplasms (n=84), 29 cases (34.5%) were negative, 21 cases (25%) were weak positive, 29 cases (34.5%) were medium positive, and 5 cases (6%) were strongly positive for ER status. For PR status, 37 cases (44.1%) were negative, 17 cases (20.2%) were weak positive, 28 cases (33.3%) were medium positive, and 2 cases (2.4%) were strongly positive. No significant association between ER and PR status and the nature of the lesions was found in this study [Table/Fig-6,7].

Nikolaou M et al., found that the majority of the basal cells in normal cervical tissue stained positive for ERα, whereas the percentage of ERα expression decreased in CIN and squamous cervical carcinoma. In contrast, PR expression tends to increase alongside cervical cancer progression [20]. Coelho FRG et al., observed that around 21% of cervical tumour biopsies were ERα positive in the tumour epithelium [21]. In a study by López-Romero R et al., 93.7% ERα expression was detected in the epithelium of normal cervical tissues, but none was found in invasive cervical carcinomas (0%) [22]. In present study, mean ER score and mean PR score of adenocarcinomas were significantly higher than those of other malignant neoplasms (p-value <0.001) [Table/Fig-8].

Immunoreactive Ki-67 positive cells showed dark brown staining in the nucleus. In present study, SCC and adenocarcinoma showed higher means of Ki-67 at 64.05±12.34% (n=48) and 77.70±3.54% (n=2), respectively [Table/Fig-9]. The expression of ER and PR was localised in the nucleus of cells in the normal cervix. In the cases of adenocarcinoma and SCC, ER and PR were expressed in the nuclei of tumour cells [Table/Fig-10].

Limitation(s)

- As the study period was too short, survival analysis could not be conducted, and follow-up was not possible within the limited timeframe. Therefore, no comments can be made on the prognostic role of the markers Ki-67, ER, and PR.
- Being a tertiary care hospital, there was a higher number of complicated and long-standing cases. Simple pathologies, such as condyloma acuminatum, endocervical polyps, and squamous metaplasia, which are evidently benign and non neoplastic, are often managed and treated outside of specialist centres.

CONCLUSION(S)

In conclusion, a higher rate of cellular proliferation was noted in malignant tumours compared to benign ones, indicating its role in the malignant potential and aggressive behaviour of these tumours. Ki-67 immunostaining should be considered an adjunct for grading malignant tumours in addition to histopathological findings. Ki-67 may prove to have a diagnostic role in differentiating benign from malignant lesions in cervical epithelial lesions; however, the cut-off for such discrimination needs to be evaluated in a larger population.

Moreover, further prospective studies with long-term follow-up of patients are warranted to assess the value of this marker as a predictor of survival. No significant association between ER and PR status and the nature of the lesions was found in the study. A detailed study with larger samples is needed, and genetic analysis of these hormone receptors is required for further evaluation.

REFERENCES

[1] Stelzle D, Tanaka LF, Lee KK, Khalil AI, Baussano I, Shah ASV, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health. 2021;9(2):e161-69.
[2] Muthuramalingam MR, Muraleedharan VR. Patterns in the prevalence and wealth-based inequality of cervical cancer screening in India. BMC Womens Health. 2023;23(1):337.
[3] Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32:S16-24.
[4] Raulf N, Lucarelli P, Thavaraj S, Brown S, Vicencio JM, Sauter T, et al. Annexin A1 regulates EGFR activity and alters EGFR-containing tumour-derived exosomes in head and neck cancers. Eur J Cancer. 2018;102:52-68.
[5] Shen C, Chen F, Wang H, Li G, Yu C, Wang X, et al. The Pinx1 gene downregulates telomerase and inhibits proliferation of CD133+ cancer stem cells isolated from a nasopharyngeal carcinoma cell line by regulating Trfs and Mad1/C-Myc/p53 Pathways. Cell Physiol Biochem. 2018;49:282-94.
[6] Mosny DS, Herholz J, Degen W, Bender HG. Immunohistochemical investigations of steroid receptors in normal and neoplastic squamous epithelium of the uterine cervix. Gynecol Oncol. 1989;35(3):373-77.
[7] Cimpean AM, Saptefrati L, Ceausu R, Raica M. Characterization of endoglin and Ki-67 expression in endothelial cells from benign and malignant lesions of the uterine cervix. Pathol Int. 2009;59(10):695-700.
[8] Li LT, Jiang G, Chen Q, Zheng JN. Ki67 is a promising molecular target in the diagnosis of cancer (review). Mol Med Rep. 2015;11(3):1566-72.
[9] Kim KK, Jang TJ, Kim JR. HSP70 and ER expression in cervical intraepithelial neoplasia and cervical cancer. J Korean Med Sci. 1998;13:383-88.
[10] Wang H, Jin Y, Ni C, Tian X, Wang W, Zhao Y. Correlation between ER, PR, P53, Ki67 expression and high-risk hpv infection in patients with different levels of cervical intraepithelial neoplasia. Indian J Pharm Sci. 2020:82(2)Spl issue3;01-07.
[11] Raju K, Punnayanapalya SS, Mariyappa N. Significance of p53, pRb and Ki-67 markers in cervical intraepithelial lesion and malignancy. Biomed Res Ther. 2015;2(10):24.
[12] Aswathy S, Quereshi MA, Kurian B, Leelamoni K. Cervical cancer screening: Current knowledge & practice among women in a rural population of Kerala, India. Indian J Med Res. 2012;136(2):205-10.
[13] Kalyani R, Das S, Bindra Singh MS, Kumar H. Cancer profile in the department of pathology of Sri Devaraj Urs Medical College Kolar: A ten years study. Indian J Cancer. 2010;47(2):160-65.
[14] Carreras R, Alameda F, Mancebo G, García-Moreno P, Mariñoso ML, Costa C, et al. A study of Ki-67, c-erbB2 and cyclin D-1 expression in CIN-I, CIN-III and squamous cell carcinoma of the cervix. Histol Histopathol. 2007;22(6):587-92.
[15] Subramaniam N, Thankappan K, Anand A, Balasubramanian D, Iyer S. Implementing American Joint Committee on Cancer 8th edition for head-and-neck cancer in India: Context, feasibility, and practicality. Indian J Cancer. 2018;55:04-08.
[16] O'Connor M, O'Leary E, Waller J, Gallagher P, Martin CM, O'Leary JJ, et al. Socio-economic variations in anticipated adverse reactions to testing HPV positive: Implications for the introduction of primary HPV-based cervical screening. Prev Med. 2018;23:90-96.
[17] Hebbar A, Murthy VS. Role of p16/INK4a and Ki-67 as specific biomarkers for cervical intraepithelial neoplasia: An institutional study. J Lab Physicians. 2017;9(02):104-10.
[18] Silva-Filho AL, Traiman P, Triginelli SA, Reis FM, Pedrosa MS, Miranda D, et al. Expression of p53, Ki-67 and CD 31 in the vaginal margins of radical hysterectomy in patients with stage IB carcinoma of the cervix. Gynecoloncol. 2004;95(3):646-54.
[19] Godoy AEG, Bazzo KO, De Moura LB, Serafini EP. Expression analysis of p53, Ki-67 and bcl2 in premalignant lesions of cervix. Open J Obstetrics and Gynecology. 2014;4:462-69.

[20] Nikolaou M, Koumoundourou D, Ravazoula P, Papadopoulou M, Michail G, Decavalas G. An immunohistochemical analysis of sex-steroid receptors tumour suppressor gene p53 and Ki-67 in the normal and neoplastic uterine cervix squamous epithelium. Medicinski Pregled. 2014;67:202-07.
[21] Coelho FRG, Prado JCM, Pereira Sobrinho JS, Hamada G, Landman G, Pinto CA, et al. Estrogen and progesterone receptors in human papilloma virus-related cervical neoplasia. Braz J Med Biol Res. 2004;37:83-88.
[22] López-Romero R, Garrido-Guerrero E, Rangel-López A, Manuel Apolinar L, Piña-Sánchez P, Lazos-Ochoa M, et al. The cervical malignant cells display a down regulation of ER-α but retain the ER-β expression. Int J Clin Exp Pathol. 2013;6:1594-602.

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