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Evaluation of p16 expression in carcinomas of the uterine cervix diagnosed only on cervical biopsies

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Abstract. The use of differing diagnostic terms by pathologists in their histopathological reports relating to tumours of the uterine cervix can affect the clinical decision-making of treating physicians or surgeons. A retrospective cross-sectional study was conducted with the aim of evaluating p16 expression in all cervical carcinomas diagnosed solely through cervical biopsies, following a review of their previous diagnoses. Any association between p16 expression and the age of the patient or previous diagnosis was also examined. The mean, median and mode ages in the study were 53 ± 12.4, 60, and 65 years, respectively. In 70 out of 393 cervical biopsies (17.8%) were diagnosed cervical carcinomas. A significant inconsistency in the use of diagnostic terminology by pathologists was observed. Of the 53 cases submitted for p16 immunostaining, 50 cases (94.3%) were p16 positive, and 3 (5.7%) were negative. Moreover, 88.7% of cases were reclassified as squamous cell carcinoma, human papillomavirus-associated, 5.7% as squamous cell carcinoma, human papillomavirus-independent, and 5.7% as Adenocarcinoma, human papillomavirus-associated of the uterine cervix. A mean age at diagnosis of 65 years was not significantly associated; however, the previous categories of large cell non-keratinising and keratinising squamous cell carcinoma showed the highest p16 positivity ($p < 0.001$). The inclusion of p16 status in pathological reports would not only promote uniformity in histopathological reporting but also assist physicians and surgeons in determining the appropriate treatment approach, predictive value, and prognosis

Keywords: human papillomavirus; immunohistochemistry; squamous cell; haematoxylin; eosin

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Introduction

p16INK4A, also known as p16, is considered a surrogate marker of human papillomavirus (HPV) infections in the uterine cervix and other anatomical sites. Two HPV subtypes – 16 and 18 are primarily responsible for pre-cancerous and cancerous lesions of the uterine cervix. Early and accurate diagnosis of cervical tumours offers substantial benefits to patients in terms of timely treatment initiation and improved prognosis. However, it is not uncommon for pathologists to use inconsistent nomenclature or provide incomplete histopathological reports, which can hinder physicians and surgeons in initiating the most appropriate treatment regimen. Multiple factors may contribute to this avoidable situation.

In 2022, cervical cancer ranked fourth in both incidence and mortality among cancers affecting females worldwide. It was the leading cause of cancer-related deaths in women in 37 countries, particularly in sub-Saharan Africa, South America, and South-Eastern Asia [1]. Cervical cancer is most prevalent among women aged 40 to 60 years. However, S. Neumeyer *et al.* [2], in a German study, reported that the incidence in women over 65 years, who constituted 30% of all cases, may be underestimated due to the lack of hysterectomy correction in the data. The World Health Organization (WHO) [3] emphasised the role of HPV infection and has classified squamous cell carcinomas of the uterine cervix primarily into HPV-associated and HPV-independent types. Squamous cell carcinoma, not otherwise specified (NOS), remains a separate entity. Similarly, adenocarcinomas are mainly grouped as HPV-associated or HPV-independent types of the uterine cervix.

There are limited studies available that have examined the different histopathological diagnoses offered by pathologists in biopsy-diagnosed cervical carcinoma cases, based on the latest WHO guidelines. A.K. Höhn *et al.* [4] noted that the 2020 WHO classification of tumours of the lower female genital tract is designed to distinguish between HPV-associated and HPV-independent squamous cell carcinoma. Histopathological morphology alone cannot differentiate between these two forms; therefore, p16 immunohistochemistry is recommended. P.D. Chaganti *et al.* [5], in India, studied 124 cases of cervical cancer diagnosed through cervical biopsies and other hysterectomy specimens, and performed p16 immunohistochemistry on 40 cases only. Based on the results of p16 IHC, they concluded that 90% of the 40 cases were HPV-associated, and 10% were HPV-independent. W.K. Cho *et al.* [6] also applied the 2020 WHO classification to retrospectively review 365 patients with endocervical adenocarcinoma who had undergone hysterectomy, and compared the HPV-associated carcinomas with HPV-independent types in terms of tumour characteristics, patterns of recurrence, and survival outcomes. They observed that 75.3% of cases were HPV-associated, while 24.7% were HPV-independent adenocarcinomas, which were found to have a poorer prognosis and lower survival rates.

Several studies have investigated mixed pre-cancerous and cancerous lesions of the cervix. F.S. Medeiros *et al.* [7], in their study, collected a total of 94 cervical biopsies (62 from cervical lesions and 32 from adjacent areas near the lesions) from 62 Brazilian women and subjected them to p16 IHC. Two pathologists classified the lesions blindly as benign, LSIL, or HSIL. They noted that the intensity of p16 positivity increased with the severity of the lesions: 5% of LSIL and 37% of HSIL cases showed high p16 expression. Z. Zuberi *et al.* [8] also conducted a study in which they collected 145 cervical biopsies from lesions ranging from benign to malignant in Tanzania, to assess p16 and topoisomerase II-alpha (TOP2A) protein expression. Ninety-five biopsies were from malignant lesions. Two independent pathologists also reviewed the slides. They found p16 to be strongly positive in all 83 SCC (100%) and in six adenocarcinomas. R. Ebisch *et al.* [9], in their study, noted that combining H&E and p16 staining in 326 colposcopic cervical biopsy specimens (from lesions ranging from CIN I to carcinoma) led to a change in diagnosis in 27.3% of cases (n = 89), with a decrease in the number of CIN I and CIN II diagnoses, and an increase in the number of CIN III and cancer diagnoses, compared to standard H&E-based CIN diagnosis alone.

As can be seen from the above, there are few studies that have specifically analysed p16 expression in cervical carcinomas diagnosed solely on biopsy specimens. Most existing studies have investigated mixed cervical lesions, ranging from normal to malignant, and some included hysterectomy specimens as well. No studies were identified in which the previous diagnoses of cervical carcinomas were revised and reclassified according to the 2020 WHO Female Genital Tumours (FGT) guidelines, and correlated with HPV association status using p16 IHC. There was a need for a study to address this gap. The present study aimed to analyse the results of p16 immunohistochemistry following a review and reclassification of all previously biopsy-diagnosed cervical carcinomas in accordance with the latest WHO guidelines.

Materials and Methods

A retrospective, descriptive cross-sectional study was conducted to evaluate p16 expression in all cases of cervical carcinoma diagnosed from cervical biopsies received at the Department of Pathology of a tertiary care centre in Eastern part of India over a five-year period, from January 2017 to 31 December 2021. The study was approved by the Institutional Ethics Committee (Application number 155BH/05/IEC/2022) and adhered to the principles of the Declaration of Helsinki [10]. No patient intervention of any kind was involved in the study. Relevant data, including age and previous final diagnosis, were retrieved from histopathological reports and respective histopathology registers. All cases of cervical carcinoma diagnosed on cervical biopsy during the study period were included, provided that Formalin-fixed, paraffin-embedded (FFPE) blocks with adequate residual

tissue were traceable. Cases with untraceable FFPE blocks or blocks with insufficient residual tissue were excluded.

The total number of cervical biopsies received during the study period was recorded, along with the total number of cervical carcinoma cases diagnosed by various pathologists. All H&E-stained slides for each diagnosed case, along with the corresponding FFPE blocks, were retrieved and assessed for staining quality and intensity. In cases where slides were poorly stained or faded, fresh sections were prepared and stained with haematoxylin and eosin. All slides were reviewed independently by two pathologists; in cases of disagreement, a third pathologist provided a final opinion. FFPE blocks with sufficient residual tissue were selected. New 1-2 sections, each 3-4 microns thick, were cut from each block and mounted on poly-L-lysine-coated slides. For p16 immunostaining, both positive and negative controls were used in each batch. A mouse anti-human p16INK4A monoclonal antibody (Clone MX007, manufactured by Vitro Master Diagnostic, Sevilla, Spain) was used with an indirect detection system. p16 expression was considered positive when moderate to strong nuclear and cytoplasmic staining (block positivity) was observed in more than 10% of epithelial cells, and negative when no staining or weak staining was present in less than 10% of epithelial cells. A multi-head Olympus BX53 microscope (Japan) was used to examine both H&E and immunohistochemically stained slides.

Revised histological diagnoses were made in accordance with the 2020 WHO Classification of Female Genital Tumours [3], based on p16 expression, and recorded as either squamous cell carcinoma, HPV-associated or HPV-independent, or adenocarcinoma, HPV-associated or HPV-independent of the uterine cervix, for each case studied. All data were entered into a Microsoft Excel spreadsheet. SPSS software was used for data analysis and statistical testing. Chi-square tests were applied to examine any association between age, previous diagnosis, and p16 expression. A p-value less than 0.05 was considered statistically significant.

Results and Discussion

The 5th edition of the WHO Classification of Tumours [3] was published nearly six years after the previous 4th edition in 2014 [11]. Numerous changes were introduced across nearly all organ systems, with some of the most significant involving the classification of carcinomas of the uterine cervix, vagina, and vulva, due to substantial advances in the understanding of these neoplasms. The WHO has recommended the adoption of a p16-based classification of squamous lesions of the cervix, vagina, and vulva, as well as glandular lesions of the cervix, distinguishing between HPV-associated and HPV-independent carcinomas. The pathogenesis of cervical carcinoma involves the inactivation of the p53 and retinoblastoma protein (pRb) tumour suppressor genes by the HPV E6 and E7 oncoproteins, respectively. Expression of the E7 viral oncoprotein leads to inactivation of pRb, which in turn increases the activity of E2F transcription factors, driving the cell into the S-phase of the cell cycle and resulting in increased p16 expression [12-14].

Of the 17,142 cervical biopsy samples received between January 2017 and December 2021, only 393 were cervical biopsies (i.e. diagnostic samples from the cervix). Of these, 70 were diagnosed as cervical carcinomas. Only 53 FFPE blocks with sufficient residual tissue could be located for analysis. Therefore, the detection rate of cervical carcinoma in this study over a five-year period was approximately 0.17%. Most patients (70%) were over 50 years of age, with squamous cell carcinoma being the most common histological type, accounting for 94% of cases. The mean age (± standard deviation) was 53 ± 12.4 years, with median and mode values of 60 and 65 years, respectively. Different reporting pathologists were involved throughout the study period, which may have contributed to the use of varying diagnostic terminology in the final histopathological reports. There was notable inconsistency in the diagnostic terms used, with a lack of standardisation across pathologists. The previous histopathological diagnoses are summarised in the pie chart shown in Figure 1. p16 immunostaining was performed on 53 cases, as only these had traceable FFPE blocks with adequate residual tissue. The results of the immunostaining are presented in Table 1.

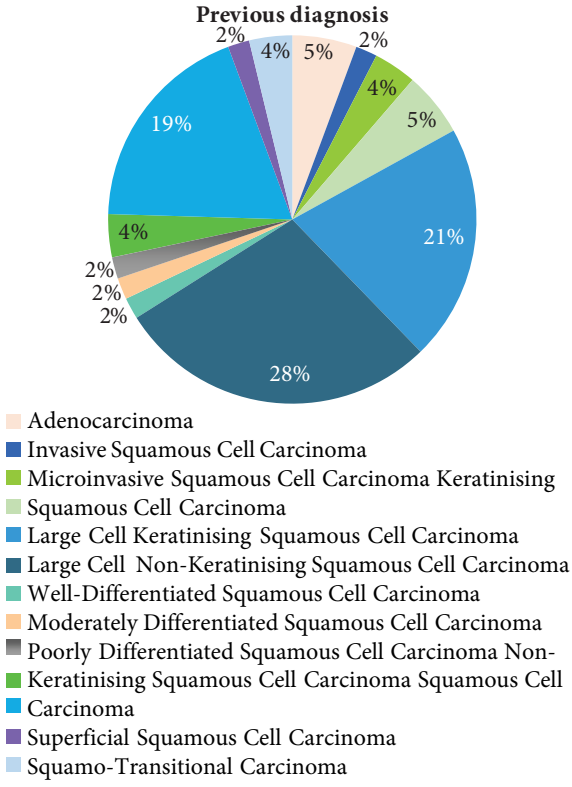

Figure 1. Pie chart showing the distribution of cases according to previous diagnoses

Note: Large Cell Non-Keratinising Squamous Cell Carcinoma (28%), Large Cell Keratinising Squamous Cell Carcinoma (21%), and Squamous Cell Carcinoma (19%) were the most frequently noted categories

Source: compiled by the authors

Table 1. Results of p16 immunostaining

Previous diagnosis	Number of cases (n = 53)	Age ≤50 yr	Age >50 yr	p16 positive	p16 negative	Revised diagnosis according to WHO FGT 2020
SCC	10 (18.8%)	–	10 (27.02%)	7 (14%)	3 (6.7%)	SCC HPV-associated (89%) SCC, HPV-independent (6%) Adenocarcinoma, HPV-associated (5%) (p < 0.001)
Superficial SCC	1 (1.8%)	1 (6.25%)	–	1 (2%)	0	
Invasive SCC	1 (1.8%)	–	1 (2.7%)	1 (2%)	0	
Microinvasive SCC	2 (3.7%)	–	2 (5.4%)	2 (4%)	0	
KSCC	3 (5.6%)	–	3 (8.1%)	3 (6%)	0	
LCKSCC	11 (20.7%)	6 (37.5%)	5 (13.5%)	**11 (22%)**	0	
LCNK SCC	15 (28.3%)	5 (31.25%)	10 (27.02%)	**15 (30%)**	0	
NKSCC	2 (3.7%)	–	2 (5.4%)	2 (4%)	0	
WDSCC	1 (1.8%)	1 (6.25%)		1 (2%)	0	
MDSCC	1 (1.8%)	–	1 (2.7%)	1 (2%)	0	
PDNKSCC	1 (1.8%)	–	1 (2.7%)	1 (2%)	0	
Adenocarcinoma	3 (5.6%)	3 (18.7%)	–	3 (6%)	0	
Squamo-Transitional carcinoma	2 (3.7%)	–	2 (5.4%)	2 (4%)	0	
Total	**53**	**16 (30.1%)**	**37 (69.8%)**	**50 (94.3%)**	**3 (6.7%)**	

Note: SCC – Squamous Cell Carcinoma; KSCC – Keratinising SCC; LCKSCC – Large Cell Keratinising SCC; LCNKSCC – Large Cell Non-Keratinising SCC; NKSCC – Non-Keratinising SCC; WDSCC – Well-Differentiated SCC; MDSCC – Moderately Differentiated SCC; PDNKSCC – Poorly Differentiated Non-Keratinising SCC
Source: compiled by the authors

More than 90% of patients in both age groups – those under and over 50 years – showed p16 expression, while fewer than 5% were p16-negative. Overall, p16 expression was observed in 50 cases (94.3%). All 53 cases were re-classified based on p16 status as squamous cell carcinoma, HPV-associated or HPV-independent of the uterine cervix, and adenocarcinoma, HPV-associated or HPV-independent of the uterine cervix. Eighty-nine per cent of cervical carcinomas diagnosed during the study period were classified as squamous cell carcinoma, HPV-associated, followed by squamous cell carcinoma, HPV-independent (6%) and adenocarcinoma, HPV-associated (5%).

Chi-square tests were performed to evaluate associations between age, previous diagnoses, and p16 expression. While no significant association was observed between age at diagnosis and p16 expression, the highest positivity was noted at 65 years of age (p = 0.483). In contrast, cases previously diagnosed as large cell keratinising and non-keratinising SCC showed the highest p16 positivity, which was statistically significant (p < 0.001). Photomicrographs of different cervical carcinoma subtypes with corresponding p16 immunostaining are shown in Figures 2-4.

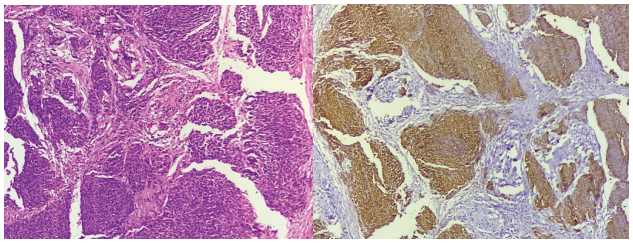

Figure 2. p16-positive in squamous cell carcinomas, HPV-associated, of the uterine cervix (H&E, 10x and IHC, 10x)
Source: compiled by the authors

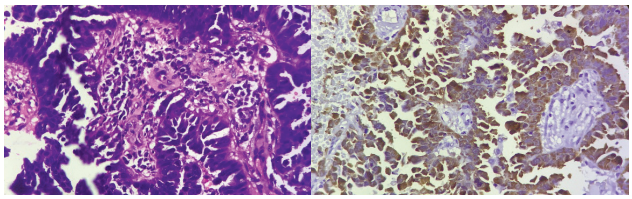

Figure 3. p16-positive in adenocarcinoma, HPV-associated, of the uterine cervix (H&E, 20x and IHC, 20x)
Source: compiled by the authors

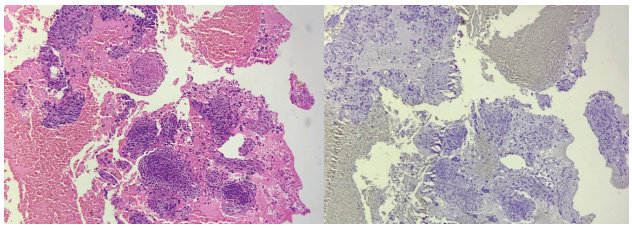

Figure 4. p16-negative in squamous cell carcinoma, HPV-independent, of the uterine cervix (H&E, 10x and IHC, 10x)
Source: compiled by the authors

Most patients in this study were older than 50 years, with a mean age of 53 years. This finding is consistent with the study by C.M. Gnade *et al.* [15], who investigated whether there has been an increase in the age at diagnosis over time, highlighting a shifting age pattern of cervical cancer between 1986 and 2016. They observed that the age at diagnosis increased by 0.2 years per calendar year. In their cohort of 1,019 patients, the average age at diagnosis was 43.7 years in 1986, rising to 49.5 years in 2016. However, among women over 65 years, no significant change was reported over time. Similarly, I. Nicolás *et al.* [16] found a

mean age of 50 years in their study involving 194 women. It is worth noting that while most HPV infections resolve spontaneously, a small proportion may persist and progress to cervical cancer. Although cervical cancer most commonly affects older women, it can also occur in younger age groups. The youngest patient in the current study was 29 years old, and two patients were under the age of 30. B. Gravdal *et al.* [17] used data from the Norwegian Cancer Registry to examine cervical cancer incidence in women from the 1950s onwards. They found that the incidence of cervical cancer among women under 30 years had almost tripled since the 1950s. Among 21,160 cases of cervical cancer (1953-2013), 5.3% were diagnosed in women under 30 years. One possible explanation for this increase is improved detection as a result of expanded cervical screening programmes.

In this study, the majority of patients (89%) showed p16 expression. While age at diagnosis was not significantly associated with p16 status, the highest rate of p16 positivity was observed in women around the age of 65 years. This finding is in line with the study by R.M. Ismail *et al.* [18], who, in their analysis of 95 women with cervical cancer, also found no significant age association with p16 expression. However, they did observe low or absent p16 expression in older women over 60 years of age. In the present study, the higher age at diagnosis among older women could be explained by the possibility that they had been harbouring HPV infections for many years, during which precancerous lesions such as CIN went unnoticed. These women may have been missed by routine screening programmes due to a lack of awareness or due to limited accessibility to healthcare services, especially for the early detection of pre-cancerous cervical lesions.

Regarding diagnosis, it was observed in this study that pathologists used a wide variety of diagnostic terms over time. Despite the availability of the WHO FGT 2014 classification [11] and the more recent WHO FGT 2020 classification [3], which were supposed to guide reporting during most of the study period, Figure 1 clearly indicates a lack of consistency and uniformity in diagnostic terminology among the reporting pathologists. Unlike the FGT 2020, the FGT 2014 classification did not mandate the use of p16 immunohistochemistry, which may explain the absence of p16 testing in the majority of cases diagnosed prior to 2020. In laboratories – particularly those in low- and middleincome countries – the availability of advanced diagnostic tests may be limited. Furthermore, the knowledge and training of pathologists can play a major role in such inconsistencies. In the tertiary care centre where this study was conducted (in Eastern India), the hospital was able to provide p16 testing for all confirmed cervical carcinoma cases at no additional cost to the patients. However, this may not be the case in other facilities, where the p16 test may be either unavailable or financially inaccessible. In such settings, diagnosis relies solely on H&E morphology, potentially contributing to non-uniform and inconsistent reporting.

The most commonly assigned previous diagnosis was large cell non-keratinising squamous cell carcinoma (28%), followed by large cell keratinising squamous cell carcinoma (21%), and squamous cell carcinoma (19%). Diagnostic terms such as well-differentiated, moderately differentiated, and poorly differentiated SCC, or simply SCC, were frequently used. It is evident that this wide range of diagnostic terminology may lead to confusion and a lack of clinical utility for physicians and surgeons when planning patient care and management. Moreover, these diagnoses were not entirely consistent with the 2014 WHO criteria, which categorised cervical tumours into epithelial, mesenchymal, and mixed epithelial and mesenchymal types [9]. Among epithelial tumours, three main categories were identified: squamous tumours, glandular tumours, and other epithelial tumours. The squamous category included squamous cell carcinoma, NOS, its morphological variants, early invasive SCC, CIN III, and SCC *in situ*. Similarly, glandular tumours included adenocarcinoma and its variants, early invasive adenocarcinoma, and adenocarcinoma *in situ*. The term "large cell" was typically used in reference to neuroendocrine tumours.

No studies were identified that examined the association between previous histopathological diagnoses and the revised classification of carcinomas as either HPV-associated or HPV-independent. It is reiterated that, in the present study, cases previously diagnosed with large cell non-keratinising SCC and large cell keratinising SCC showed the highest p16 positivity, which was statistically significantly associated ($p < 0.001$). The finding of 89% p16 positivity in the current study is consistent with findings from several other studies. B. Vedula *et al.* [19] conducted a study assessing p16 expression in both dysplastic and neoplastic cervical lesions in 86 cases over two years, reporting 88% p16 positivity. Similarly, I. Nicolás *et al.* [16] observed 96% p16 positivity in a cohort of 194 cervical cancer patients, in a study evaluating clinicopathological features, HPV genotype correlations, and the prognostic role of p16. R.M. Ismail *et al.* [18] also reported p16 expression in 80% of their 95 patients.

Chemotherapy, immunotherapy, and radiotherapy remain effective treatment modalities for HPV-related cervical carcinomas [20]. Both S. da Mata *et al.* [21] and I. Nicolás *et al.* [16] found that p16 expression is associated with improved survival, although it is not an independent prognostic factor. In the case of p16-positive cervical adenocarcinomas, M. Ishikawa *et al.* [22], in a study involving 82 patients, reported a favourable prognosis and improved overall survival. Conversely, as noted by B. Xing *et al.* [23] and J.-E. Lee *et al.* [24], patients with HPV-negative tumours are more likely to present at an advanced FIGO stage, with a consequently poorer prognosis.

This study observed a lack of consistent implementation of the WHO classification of tumours of the uterine cervix by pathologists over the study period. A significant association was found between previously diagnosed cases of large cell keratinising and non-keratinising squamous cell carcinoma and p16 positivity, whereas age at

diagnosis showed no significant correlation with p16 expression. Among the 53 reclassified cases, 89% were identified as HPV-associated squamous cell carcinoma, 6% as HPV-independent squamous cell carcinoma, and 5% as HPV-associated adenocarcinoma of the uterine cervix.

Conclusions

It can be concluded that in this single-centre study, in which all biopsy-diagnosed cervical carcinoma cases were re-evaluated and reclassified in accordance with the latest WHO guidelines, a wide variation in diagnostic terminology was noted among pathologists over the study period. Some reports included comprehensive information, including p16 status, while others did not. This inconsistency in histopathological reporting may be attributed to several factors, the most prominent being the lack of mandatory p16 IHC in all confirmed cervical carcinoma cases. Additional contributing factors could include insufficient training of reporting pathologists and limited availability of testing kits. p16 immunohistochemistry performed on all 53 cases demonstrated a high positivity rate of 89%, which is comparable to that reported in the literature. While age was not significantly associated with p16 expression, the highest rate of positivity was observed in patients over 65 years of age. This study also investigated the relationship between prior diagnoses and revised classification, finding that cases previously identified as large cell keratinising or non-keratinising squamous cell carcinoma were predominantly p16-positive, with a significant correlation. There is scope for further research, including multicentre studies, to assess how pathologists across different regions or countries classify cervical carcinomas and how their diagnoses align with p16 IHC or HPV genotyping results.

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Conflict of Interest

None.

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Оцінка експресії гену p16 у карциномах шийки матки, діагностованих лише на основі біопсії шийки матки

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Анотація. Використання патологами різних діагностичних термінів у своїх гістопатологічних звітах щодо пухлин шийки матки може впливати на клінічні рішення лікарів або хірургів, які проводять лікування. Було проведено ретроспективне поперечне дослідження з метою оцінки експресії p16 у всіх випадках раку шийки матки, діагностованих виключно за допомогою біопсії шийки матки, після перегляду попередніх діагнозів. Також було досліджено будь-який зв'язок між експресією p16 та віком пацієнтки або попереднім діагнозом. Середній, медіанний та модальний вік у дослідженні становили відповідно 53 ± 12,4, 60 та 65 років. У 70 з 393 біопсій шийки матки (17,8 %) було діагностовано рак шийки матки. Було виявлено значну невідповідність у використанні діагностичної термінології патологами. З 53 випадків, поданих для імунофарбування p16, 50 випадків (94,3 %) були p16-позитивними, а 3 (5,7 %) – негативними. Більше того, 88,7 % випадків було перекласифіковано як плоскоклітинний рак, асоційований з вірусом папіломи людини, 5,7 % – як плоскоклітинний рак, незалежний від вірусу папіломи людини, і 5,7 % – як аденокарцинома шийки матки, асоційована з вірусом папіломи людини. Середній вік на момент діагностики 65 років не мав істотного значення; проте попередні категорії великоклітинного некератинізуючого та кератинізуючого плоскоклітинного раку показали найвищу p16-позитивність ($p < 0,001$). Включення статусу p16 до патологічних звітів не тільки сприятиме уніфікації гістопатологічних звітів, але й допоможе лікарям і хірургам у визначенні відповідного підходу до лікування, прогностичної цінності

Ключові слова: вірус папіломи людини; імуногістохімія; плоскоклітинний; гематоксилін; еозин