Section: Radiation Oncology

Original Research Article

p16^{INK4A} OVEREXPRESSION AS A PROGNOSTIC INDICATOR IN LOCALLY ADVANCED CERVICAL CANCER: A PROSPECTIVE OBSERVATIONAL STUDY

Shashi[1], Arun Kumar Rathi[2], Kishore Singh[3], Shramana Mandal[4], Nitish Kumar[5]

[1]*Senior Resident, Department of Radiation Oncology, Lady Hardinge Medical College and Associated Hospital, New Delhi, India*
[2]*Director Professor and Head, Department of Radiation Oncology, Maulana Azad Medical College and Associated Lok Nayak Hospital, G.I.P.M.E.R and G.N.E.C, New Delhi, India*
[3]*Professor and Head, Department of Radiation Oncology, Subharti Medical College and Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India*
[4]*Professor, Department of Pathology, Maulana Azad Medical College and Associated Lok Nayak Hospital, G.I.P.M.E.R and G.N.E.C, New Delhi, India*
[5]*Senior Resident, Department of Radiation Oncology, Lady Hardinge Medical College and Associated Hospital, New Delhi, India*

Received *: 23/03/2025*
Received in revised form *: 14/05/2025*
Accepted *: 02/06/2025*

Corresponding Author:
Dr. Nitish Kumar,
Senior Resident, Department of Radiation Oncology, Lady Hardinge Medical College and Associated Hospital, New Delhi, India
Email: nitish2kumar@gmail.com

DOI: 10.70034/ijmedph.2025.2.390

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 2166-2172

ABSTRACT

Background: Human papillomavirus (HPV)-associated cervical cancers demonstrate distinct molecular characteristics, with p16INK4a overexpression serving as a surrogate marker for HPV infection. The prognostic significance of p16 expression in locally advanced cervical cancer remains inadequately characterized in Indian populations. The objective is to determine the occurrence of p16 positivity in locally advanced cervical cancer and correlate p16 expression with treatment outcomes following concurrent chemoradiation.

Materials and Methods: A prospective observational study of 22 patients with histopathologically confirmed locally advanced cervical cancer (FIGO stages IB3-IVA) treated at a tertiary care center were evaluated for p16 expression using immunohistochemistry on formalin-fixed paraffin-embedded tissue specimens, and received concurrent chemoradiation followed by brachytherapy. WHO and RECIST 1.1 criteria were used to assess treatment response; chi-square test and Student's t-test were applied.

Results: In total, 90.9% (20/22) patients exhibited p16 positivity, which was associated with a significantly lower mean age compared with p16-negative patients (49.2±10.2 vs 62.5±10.6 years; p=0.0007), higher complete response rates (95% vs 50%, p=0.005), and better treatment response according to both WHO criteria (p=0.0348) and RECIST 1.1 criteria (p=0.005).

Conclusion: The high p16 positivity rate in locally advanced cervical cancer correlates with an improved response to concomitant chemoradiation, supporting its usefulness as a prognostic biomarker for treatment planning and patient counselling.

Keywords: p16^{INK4a}, human papillomavirus, cervical cancer, prognosis, biomarker, chemoradiation.

INTRODUCTION

Cervical cancer is a leading cause of global health burden and represents the fourth most common type of cancer in women worldwide,[1] it disproportionately affects women from low- and middle-income countries where screening and preventive care are not available or are unavailable early enough to prevent advanced-stage presentations.[2] In India, cervical cancer is the second-most commonly occurring female cancers with 123,907 new cases and 77,348 deaths each year.[3]

Persistent infection with human papillomavirus (HPV), especially high-risk subtypes HPV-16 and HPV-18, is a well-established cause of cervical cancer.[4] Oncogenic HPVs can integrate into the host genome and interfere with cell cycle control by expressing viral oncoproteins E6 and E7. The E7 protein binds to the retinoblastoma tumor suppressor

protein (pRb) and inactivates it, thus deregulating the G1/S checkpoint; p16INK4a expression is subsequently overexpressed.[5]

p16INK4a is a cyclin-dependent kinase inhibitor that acts as a tumor suppressor to halt cell cycle progression from G1 to S phase. The loss of negative feedback regulation by pRb leads to the paradoxical overexpression of p16 in HPV-transformed cervical epithelial cells, which has made immunohistochemical expression of p16 a reliable surrogate marker for transcriptionally active HPV infection in cervical neoplasia.[6,7]

Data from recent studies indicate that HPV-positive cervical cancers display different clinical features such as younger patient age at diagnosis, better response to radiotherapy and chemotherapy, and overall better survival compared to HPV-negative tumors,[8] however, there are currently limited data regarding p16 expression patterns and their prognostic significance in locally advanced cervical cancer within the Indian populations.

For locally advanced cervical cancer, concurrent chemoradiation is now the standard of care for treatment, which has shown marked improvements in overall survival and disease-free survival.[9] However, there exists a wide range of treatment response among patients with this type of cancer, which emphasizes the need to identify reliable biomarkers that predict therapeutic efficacy to direct personalized treatment strategies.

Aim & Objectives

Primary Objective

To determine the occurrence and prevalence of p16INK4a positivity in patients with locally advanced cervical cancer.

Secondary Objectives

1. To correlate p16 expression status with treatment response following concurrent chemoradiation and brachytherapy
2. To analyze the association between p16 positivity and baseline clinicopathological characteristics
3. To evaluate the prognostic significance of p16 expression in predicting complete response rates

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted at the Department of Radiation Oncology and Department of Pathology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, over a period of 12 months (November 2019- October 2020). The study protocol has been approved by the institutional ethics committee.

Study Population and Eligibility Criteria

Inclusion Criteria:

- Histopathologically confirmed cancer of the cervix
- Clinical phase FIGO IB3 up to IVA
- Age 18-70 years
- East Cooperative Oncology Group (ECOG) status of performance: <2
- Normal parameters of hematology, liver and kidney function
- Adequate heart function for chemotherapy

Exclusion Criteria:

- Previous history of malignancy or cancer treatment
- Presence of distant metastases
- Immune system disorders
- Prior HPV vaccination
- Uncontrolled medical co-morbidities
- Pregnancy

Sample Size Calculation

The size of the sample was determined by the formula for estimating the proportion of qualitative results:

$$n = \frac{\left(Z_{\frac{\alpha}{2}}\right)^2 . p.(1-p)}{d^2}$$

Where:

- $Z_{\frac{\alpha}{2}}$ = 1.96 (95% confidence level)
- p = 0.94 (expected p16 positivity rate from Arians N et al.[10])

d = 0.1 (10% precision)

This yielded a minimum required sample of 22 participants. While adequate for preliminary analysis, the small cohort size - particularly the limited p16-negative subgroup (n=2) - necessitates cautious interpretation of comparative statistics.

Ethical Considerations: The Institutional Ethics Committee of Maulana Azad Medical College approved this study (IEC No. F.1/IEC/MAMC/70/05/2019/No. 519). Written informed consent was obtained from all participants after detailed explanation of study procedures. Patient confidentiality was maintained through anonymized data handling.

Sampling Methodology: Consecutive eligible patients presenting to the radiation oncology department between (November 2019- October 2020) were enrolled, following the screening process detailed in [Figure 1].

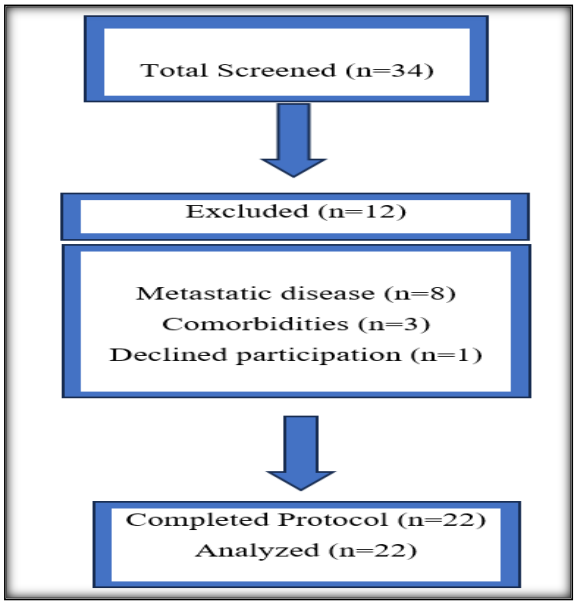

Figure 1: Patient enrolment CONSORT

p16 Immunohistochemistry Protocol

Tissue blocks were formalin-fixed and paraffin-embedded; 4-µm thick sections were stained immunohistochemically for p16INK4a with a monoclonal antibody against p16INK4a using the avidin-biotin peroxidase method with diaminobenzidine (DAB) chromogen.

Scoring System:

The results of p16 expression were scored according to combined nuclear and cytoplasmic staining intensity [Figure 2-5] and extent as follows:[10]

- Grade 0: No staining (negative)
- Grade 1: 1-25 Percent positive cells
- Grade 2: 26-50 Percent positive cells
- Grade 3: 51-75 Percent positive cells
- Grade 4: 76-100 Percent positive cells

Any detectable staining (>1% positive cells) was considered positive for p16 expression. Two pathologists scored p16 expression using the validated quartile system independently and inter-rater reliability was assessed by Cohen's κ coefficient (κ=0.89), with discrepancies resolved by consensus review.

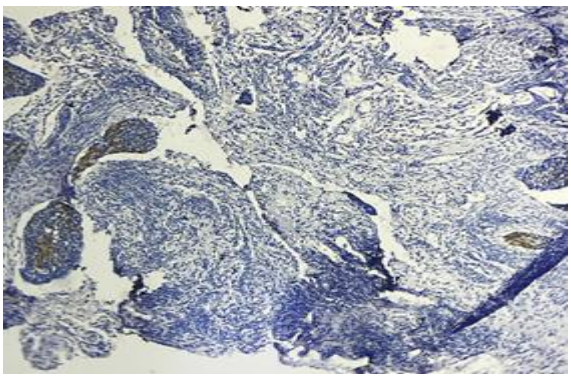

Figure 2: p16 grade 1 (IHC x 200)

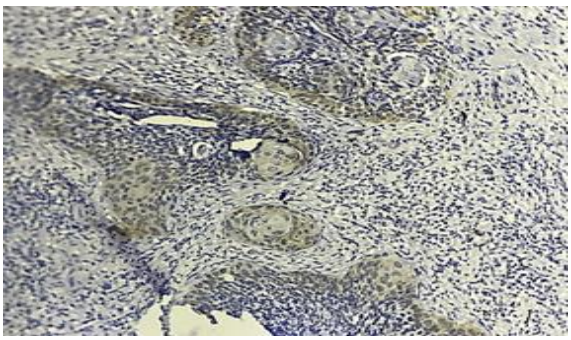

Figure 3: p16 grade 2 (IHC x 200)

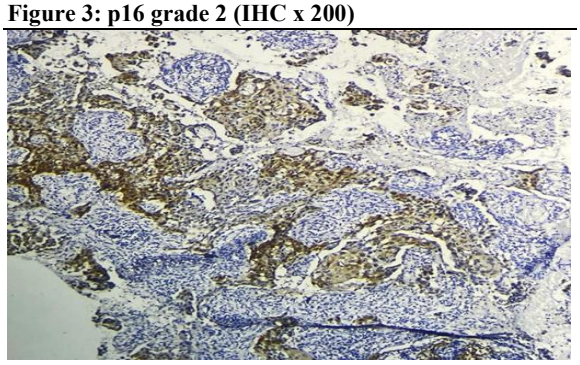

Figure 4: p16 grade 3 on IHC

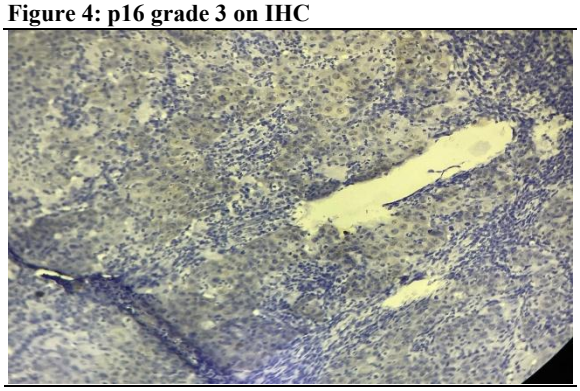

Figure 5: p16 grade 4 on IHC

Toxicity Management

Radiation-related adverse events have been graded according to CTCAE v5.0. There were 4 patients (18.2) who discontinued treatment for >3 days due to toxicity grade ≥3. Missed chemotherapy doses were analyzed using intention-to-treat principles.

Treatment Protocol

All patients received concurrent chemoradiation consisting of:

- External Beam Radiotherapy (EBRT): 50 Gy in 25 fractions over 5 weeks using Cobalt-60 teletherapy unit
- Concurrent Chemotherapy: Weekly cisplatin 40 mg/m² for 5 cycles
- Brachytherapy: High-dose-rate brachytherapy delivering 7 Gy per fraction for 3 fractions to point A (intracavitary, figure 6 & 7) or 5 Gy per fraction for 4 fractions (interstitial, Figure 8 & 9)

Intracavitary brachytherapy

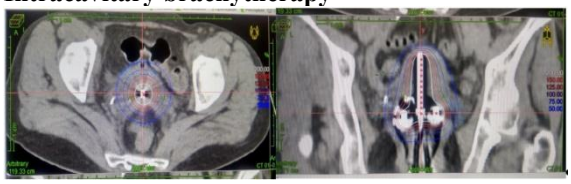

Figure 6 & 7: Intracavitary Brachytherapy planning on TPS with isodose lines

Interstitial brachytherapy

Figure 8: Martinez Universal Perineal Interstitial Template placed in situ in a case of carcinoma cervix

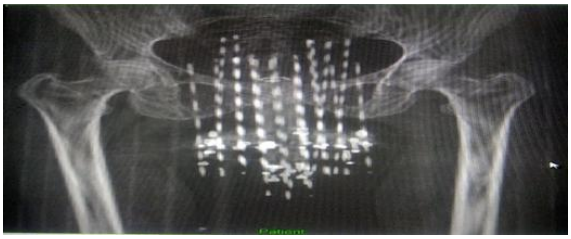

Figure 9: Radiograph showing needles of MUPIT in situ

Response Assessment

Treatment response was evaluated 6 weeks post-completion using:

- Clinical examination
- Contrast-enhanced computed tomography (CECT, [Figure 10 & 11]) or magnetic resonance imaging (MRI)
- Response criteria: World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

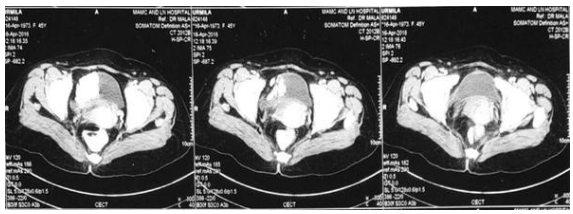

Figure 10: Baseline CECT showing heterogeneously enhancing lesion of 5.3 x 4.3 cm with extension to LUS and upper 1/3rd vagina and abutment of bladder.

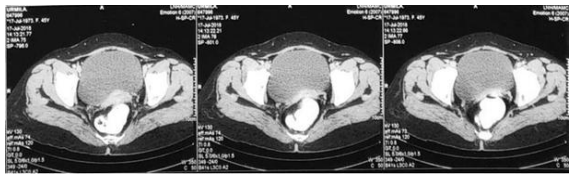

Figure 11: CECT (post-CCRT) shows no enhancement in the region of uterine cervix.

Statistical Analysis: The analysis of the data was conducted using SPSS version 25.0. Continuous variables were described as means with standard deviations and categorical variables were described by frequencies and percentages; chi-square test were run for categorical variables, Student's t-tests or Mann-Whitney U test based on data distribution, and $p<0.05$ set the threshold of statistical significance.

RESULTS

Twenty-two patients with locally advanced cervical cancer were enrolled in the study. While statistically significant differences emerged between p16-positive (n=20) and p16-negative (n=2) groups ($p<0.05$ for response rates), the limited sample size in the negative cohort precludes definitive conclusions. These findings should be considered hypothesis-generating rather than confirmatory. The baseline socio-demographic and clinical characteristics are summarized in [Table 1]. The mean age of the study population was 50.4±11.8 years (range: 32-65 years). The majority of patients (45.5%) belonged to lower socioeconomic status, and 95.5% had ECOG performance status of 1.

Table 1: Baseline Socio-demographic and Clinical Characteristics of Study Participants

Characteristics	Frequency (n=22)	Percentage (%)
Age Groups (years)		
30-39	2	9.1
40-49	8	36.4
50-59	5	22.7
≥60	7	31.8
Socioeconomic Status		
Upper middle	1	4.6
Middle	3	13.6
Lower middle	8	36.4
Lower class	10	45.5
ECOG Performance Status		
1	21	95.5
2	1	4.5
Parity		
<4 children	12	54.5
≥4 children	10	45.5

FIGO Stage		
IIB	10	45.5
IIIB	4	18.2
IIIC1	6	27.3
IIIC2	1	4.5
IVA	1	4.5
Histological Subtype		
Keratinizing SCC	11	50.0
Non-keratinizing SCC	11	50.0

Table 2: Immunohistochemical Grading of p16 Expression Using Nuclear/Cytoplasmic Staining (400× Magnification, DAB Chromogen).

p16 Expression	Frequency (n=22)	Percentage (%)
Overall Expression		
Positive	20	90.9
Negative	2	9.1
Grading Distribution		
Grade 0 (0%)	2	9.1
Grade 1 (1-25%)	1	4.5
Grade 2 (26-50%)	2	9.1
Grade 3 (51-75%)	9	40.9
Grade 4 (76-100%)	8	36.4

Table 2 depicts that p16 positivity was observed in 90.9% (20/22) of patients. High-grade expression (grades 3-4) was noted in 77.3% of cases, indicating intense p16 overexpression in the majority of tumors [Figure 12].

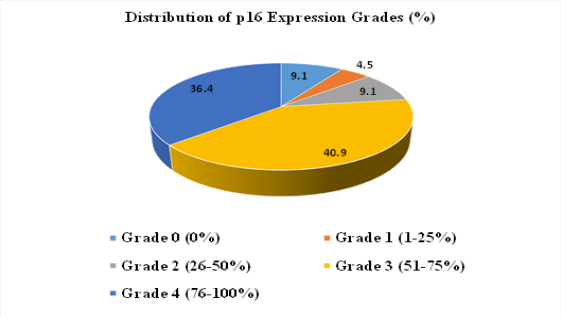

Figure 12: Distribution of p16 Expression Grades

Out of 22 patients in the study, the mean age of the p16 positive group was 49. 2 years and p16 negative group are 62.5 years [Figure 13]. There was no significant difference between two groups in terms of age distribution with p-value of 0.33.

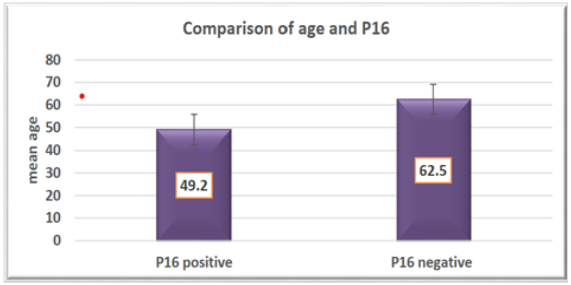

Figure 13: Age Distribution According to p16 Status

Table 3: Association of p16 Expression with Treatment Response

Response Parameter	p16 Positive (n=20)	p16 Negative (n=2)	P-value
Clinical Response			
Complete response	19 (95.0%)	1 (50.0%)	0.005
Partial response	1 (5.0%)	1 (50.0%)	
WHO Criteria			
Complete response	19 (95.0%)	1 (50.0%)	0.0348
Partial response	1 (5.0%)	1 (50.0%)	
RECIST 1.1 Criteria			
Complete response	19 (95.0%)	1 (50.0%)	0.005
Partial response	1 (5.0%)	0 (0%)	
Progressive disease	0 (0%)	1 (50.0%)	

p16-positive tumors demonstrated significantly superior treatment response compared to p16-negative tumors across all assessment criteria as summarized in [Table 3].

The post-treatment clinical examination of p16 positive tumor showed no residual growth in 19 cases and 1 case had residual growth, whereas in p16 negative tumor 1 case had residual growth and 1 case had no residual growth (Figure 14). There was significant difference between the two groups in terms of post treatment assessment according to WHO criteria with p-value of 0.005.

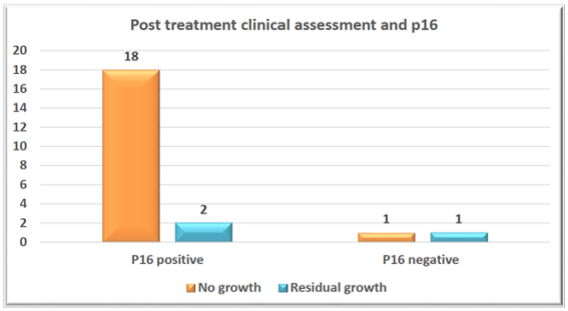

Figure 14: Comparative Treatment Response by p16 Status (WHO Criteria)

Table 4: Comparative Analysis of Tumor Dimensions Pre- and Post-Treatment in p16-Positive Cases

Parameter	Pre-treatment	Post-treatment	P-value
CECT Dimensions (cm)	**Mean ± SD**	**Mean ± SD**	
Craniocaudal	3.7 ± 1.5	0.14 ± 0.47	<0.001
Anteroposterior	3.6 ± 1.0	1.4 ± 0.97	<0.001
Transverse	4.1 ± 1.4	0.15 ± 0.67	<0.001

Significant tumor dimension reduction was observed in all measured parameters following treatment in p16-positive cases as shown in [Table 4].

Treatment Outcomes and Toxicity Profile

Patients underwent the prescribed treatment regimen and the median time to complete therapy was between 7-12 weeks (mean: 9.2±1.3 weeks). Acute toxicity was well-tolerated with primarily grade 1-2 reactions in various organ systems; no treatment-related mortality during the study period.

DISCUSSION

The high rate of p16INK4a positivity (90.9%) seen in this prospective study supports the established role for HPV in cervical carcinogenesis, which is consistent with recent international studies reporting p16 positivity rates ranging from 85-95% in cervical cancers. [11,12]

This association between p16 positivity and superior treatment response is a clinically relevant observation with significant patient management implications as p16-positive tumors had an 95% complete response rate versus 50% in p16-negative tumors (nearly doubled therapeutic efficacy) that most likely reflects the unique molecular characteristics of HPV-associated tumors including intact DNA damage response pathways.[13]

Our results are consistent with previous findings that HPV-positive cervical cancers have better therapeutic responses after definitive chemoradiation [14] due to the following molecular mechanisms: HPV-positive tumors maintain wild-type p53 function allowing an effective DNA damage response and apoptosis upon radiation-induced cellular stress,[15] and E7 oncoprotein causes replication stress and chromosomal instability, which can render the tumor more sensitive to DNA-damaging agents.[16]

The age distribution we observed in present study, with p16-positive patients presenting at a younger mean age (49.2 years) compared to p16-negative patients (62.5 years), is consistent with worldwide epidemiological trends and reflects the natural history of HPV-associated cervical carcinogenesis, in which persistent viral infection usually causes malignant transformation within 10-20 years after initial exposure.[17]

The high-grade p16 expression (grades 3-4 in 77.3% of cases) reflects the strong overexpression seen in HPV-transformed cervical epithelia and reinforces its reliability as a surrogate biomarker for HPV status, especially in settings where molecular HPV testing is not widely accessible.[18]

Objective radiological documentation of this improved treatment response was demonstrated by a significant decrease in tumor size, and complete or near-complete resolution of measurable disease in most p16-positive patients compared with persistent or progressive disease patterns commonly seen in p16-negative tumors.[19]

More recent molecular profiling studies have described unique genomic signatures of HPV-positive cervical cancers characterized by a lower mutational burden, specific methylation patterns, and characteristic gene expression profiles,[20] all leading to better therapeutic response and prognosis for these types of tumors.

These findings may have clinical implications beyond prognostic assessment for decision making regarding treatment. [21]

CONCLUSION

The present study demonstrates the utility of p16INK4a as a favorable prognostic biomarker in locally advanced cervical cancer, where positive expression correlates with better treatment response to concurrent chemoradiation, which is consistent with the high prevalence of p16 positivity (90.9%) due to the predominance of HPV-driven carcinogenesis for this population and thus supports its inclusion as a routine diagnostic test for patients with cervical cancer.

Recommendations

For better treatment of cervical cancer, the inclusion of immunohistochemistry p16 in standard diagnostic tests for prognostic stratification is recommended. This should inform treatment planning, in particular in the case of dose adjustments or adaptive approaches. In addition, risk stratified surveillance strategies should be implemented, which may allow for less intensive monitoring of patients with p16 positive complete responders. Future efforts should be focused on carrying out larger multi-centre studies to confirm these findings and to investigate de-escalation strategies in tumors with p16 positive tumors that have demonstrated an excellent response to treatment. Standardised protocols for interpretation and reporting of p16 immunohistochemistry are also essential to ensure consistency between pathology laboratories.

Limitations of the Study

The following limitations should be considered when interpreting these results: The relatively small sample size (n=22) reduces the power to detect associations with less common clinicopathological variables; the single-center design may limit generalizability to other populations with varied demographic characteristics or HPV prevalence patterns; the lack of molecular HPV testing prohibits correlating p16 expression with specific HPV genotypes, and the short follow-up period precludes assessment of long-term survival outcomes and late treatment-related toxicities.

Relevance of the Study

This study fills an important knowledge gap in p16 expression patterns and prognostic implications in locally advanced cervical cancer among the Indian population, which can support further development of molecular biomarkers into cervical cancer management algorithms for risk stratification and treatment personalization. It adds to the global body of literature on HPV-related cervical cancer characteristics and therapeutic outcomes.

REFERENCES

1. 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.
2. Zuberi Z, Mremi A, Chilongola JO, Semango G, Sauli E. Expression analysis of p16 and TOP2A protein biomarkers in cervical cancer lesions and their correlation with clinico-histopathological characteristics in a referral hospital, Tanzania. Plos one. 2021 Oct 27;16(10):e0259096.
3. Mendaza S, Fernández-Irigoyen J, Santamaría E, Zudaire T, Guarch R, Guerrero-Setas D, Vidal A, Santos-Salas J, Matias-Guiu X, Ausín K, Díaz de Cerio MJ. Absence of nuclear p16 is a diagnostic and independent prognostic biomarker in cancerof the cervix. International journal of molecular sciences. 2020 Mar 19;21(6):2125.
4. Manso L, Ramchandani-Vaswani A, Romero I, Sánchez-Lorenzo L, Bermejo-Pérez MJ, Estévez-García P, et al. SEOM-GEICO Clinical Guidelines on cervical cancer (2023). Clin Transl Oncol. 2024;26(11):2771–2782.
5. Wang YW, Chen M, Shen WT, Xu HP. The clinical practice and dosimetric outcome of the manual adaptive planning during definitive radiotherapy for cervical cancer. J Cancer Res Clin Oncol. 2024;150(5):280.
6. Yao G, Qiu J, Zhu F, Wang X. Survival of Patients With Cervical Cancer Treated With Definitive Radiotherapy or Concurrent Chemoradiation According to Histological Subtype: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2022;9:843262.
7. Albers AE, Qian X, Kaufmann AM, Coordes A. Meta analysis: HPV and p16 pattern determines survival in patients with HNSCC and identifies potential new biologic subtype. Sci Rep. 2017;7:16715.
8. Chahoud J, Zacharias NM, Pham R, Qiao W, Guo M, Lu X, et al. Prognostic Significance of p16 and Its Relationship with Human Papillomavirus Status in Patients with Penile Squamous Cell Cancer: Results of 5 Years Follow-Up. Cancers (Basel). 2022;14(24):6024.
9. Zhao F, Ma D, Wang T, Zhang Y, Dong Y, Zhao J. The Application of Liquid-Based Cytological Detection for p16, Cytologic Evaluation and High-Risk Human Papillomavirus Testing in Cervical Cancer Screening: A Clinical Evaluation. Int J Womens Health. 2022;14:965–973.
10. Arians N, Prigge ES, Nachtigall T, Reuschenbach M, Koerber SA, Debus J, von Knebel Doeberitz M, Lindel K. Overexpression of p16INK4a serves as prognostic marker in squamous cell vulvar cancer patients treated with radiotherapy irrespective of HPV-status. Frontiers in Oncology. 2019 Sep 11;9:891.
11. Rao Q, Han X, Wei Y, Zhou H, Gong Y, Guan M, et al. Novel prognostic nomograms in cervical cancer based on analysis of 1075 patients. Cancer Med. 2023;12(5):6092–6104.
12. Zhang GY, Zhang R, Bai P, Li SM, Zhang YY, Chen YR, et al. Concurrent definitive chemoradiation incorporating intensity-modulated radiotherapy followed by adjuvant chemotherapy in high risk locally advanced cervical squamous cancer: a phase II study. BMC Cancer. 2022;22(1):1331.
13. Feng L, Shi Q, Wang S, Zhao Y, Wu H, Wei L, et al. The outcome of advanced and recurrent cervical cancer patients treated with first-line platinum and paclitaxel with or without indication for immune checkpoint inhibitors: the comparative study. BMC Cancer. 2024;24(1):1267.
14. Kang S, Wu J, Li J, Hou Q, Tang B. Prognostic Significance of Clinicopathological Factors Influencing Overall Survival and Event-Free Survival of Patients with Cervical Cancer: A Systematic Review and Meta-Analysis. Med Sci Monit. 2022;28:e934588.
15. Chang PH, Wang HM, Kuo YC, Lee LY, Liao CJ, Kuo HC, et al. Circulating p16-Positive and p16-Negative Tumor Cells Serve as Independent Prognostic Indicators of Survival in Patients with Head and Neck Squamous Cell Cancers. J Pers Med. 2021;11(11):1156.
16. Teshome R, Yang I, Woldetsadik E, Girma E, Higgins M, Wells J. Survival Status and Predictors Among Women with Advanced Stage of Cervical Cancer. Int J Womens Health. 2024;16:605–617.
17. Liu J, Tang G, Zhou Q, Kuang W. Outcomes and prognostic factors in patients with locally advanced cervical cancer treated with concurrent chemoradiation. Radiat Oncol. 2022;17(1):142.
18. Ang DJM, Chan JJ. Evolving standards and future directions for systemic therapies in cervical cancer. J Gynecol Oncol. 2024;35(2):e65.
19. Xu Y, Qiu Y, Yuan S, Wang H. Prognostic implication of human papillomavirus types in cervical cancer patients: a systematic review and meta-analysis. Infect Agents Cancer. 2020;15(1):66.
20. Xie G, Wang R, Shang L, Qi C, Yang L, Huang L, et al. Calculating the overall survival probability in patients with cervical cancer: a nomogram and decision curve analysis-based study. BMC Cancer. 2020;20(1):833.
21. Meng X, Jiang Y, Chang X, Zhang Y, Guo Y. Conditional survival analysis and real-time prognosis prediction for cervical cancer patients below the age of 65 years. Front Oncol. 2023;12:1049531.