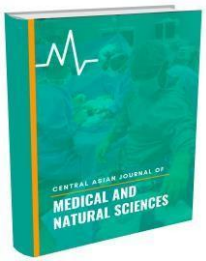

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Article

P16 as a HPV-Related Biomaker: Evaluation Its Correlation with the Proliferation Index (ki67) In Benign/Premalignant and Malignant Laryngeal Lesions

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Abstract: Subsequent to lung cancer, laryngeal carcinoma is considered the second most common carcinoma within the aerodigestive region, representing about 20% of all H&N carcinomas. Laryngeal carcinoma is regarded as the most prevalent head and neck cancer within the Middle Euphrates regions. Recently, HR-HPV infection has been recognized as a potentially contributing factor in promoting LSCC progression. The co-expression of p16 and Ki67, the proliferation index, is considered a characteristic marker of HPV-driven cancers. The cross-sectional study involved 44 laryngeal lesions-benign, premalignant, and malignant-preserved as FFPE blocks that were classified in two main group: A) 21 sample with LSCC and B) 23 samples with benign/premalignant laryngeal lesions. Immunohistochemical analysis for p16 and Ki67, respectively. Statistical associations were evaluated using fisher's exact and Chi square tests. P-value less than 0.05 was regarded as statistically significant. Significant correlation observed between p16 positivity and age, sex, lesion site, diagnosis, and Ki67. P16 immunohistochemical analysis is insufficient as a conclusive biomarker of HPV-driven laryngeal lesions.

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1. Introduction

Laryngeal carcinoma encompasses nearly 20% of all head and neck carcinomas (HNSCC) [1]. Subsequent to lung cancer, it is regarded as the second most prevalent cancer in the aerodigestive tract [2], reporting 12,650 new cases and 3,880 deaths in 2024 in the United States [3]. According to Mjali et al. study [4], laryngeal cancer ranks as the most frequent head and neck malignancy in the Middle Euphrates in Iraq. In spite of therapeutic advancements, laryngeal carcinoma five-year OS rate has stayed nearly 50% [5], [6]. The laryngeal squamous cell carcinoma (LSCC) is the most common type, representing approximately 85% to 95% of all laryngeal malignancies [2]. Several factors can contribute to the LSCC development, including alcohol consumption, smoking, air pollution, sex hormone level, and HPV infection, particularly high-risk HPV, which have been recently identified as a potentially promoting factor in the development of LSCC [7]. However, it remains a subject of ongoing debate. Globally, HPV is the most frequent sexually transmitted disease that has been associated with both anogenital and oropharyngeal malignancies [8]. Several strains of HPV are carcinogenic, leading to malignancy transformation in anogenital and oropharyngeal tissue, including HPV

strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, where HPV 16 and HPV 18 represent the vast majority of HR-HPV strains found in LSCC [9].

As HPV-related tumorigenesis follows a unique molecular mechanism in comparison with HPV-unrelated cases, valid markers are important for differentiating between these groups. Among these, immunohistochemical (IHC) analysis of p16 protein has become a reliable indicator of HPV-derived HNSCC [10], [12].

P16, the gene product of CDKN2A, acts as a tumor suppressor protein by suppressing cyclin D-dependent protein kinase 4 and 6. Thereby the cell cycle is arrested before entering the S phase as a result of blocking retinoblastoma (pRb) phosphorylation [13]. Although p16 is a tumor suppressor, in HPV-associated cancer it is an essential factor for the survival of malignant cells. During HPV infection, a persistent E2F activation occurs as a result of E7-related pRb degradation, ultimately leading to uncontrolled cell proliferation (elevated Ki67 levels). To restrain this uncontrolled proliferation, the cell upregulates p16 expression as a compensatory pathway; however, HPV presence disrupts this cellular response, resulting in a dysfunctional cell exhibiting elevated levels of both p16 and Ki67 [14], a molecular hallmark distinguishing HPV-related from other unrelated cancers [15]. Studies found that Ki67 immunohistochemical analysis is strongly associated with laryngeal premalignant/malignant lesions aggressiveness and worse prognosis [16], [18].

In the current study, we investigated 1) the occurrence of HPV in laryngeal lesions using P16 IHC analysis as a surrogate marker of HPV infection and 2) the correlation between P16 expression and Ki67 (proliferation index) within laryngeal lesions.

2. Materials and Methods

Patients

The cross-sectional study involved 44 formalin-fixed paraffin-embedded (FFPE) archival blocks that were obtained from the department of pathology at Al-Sader Medical City and from various private laboratories in Al-Najaf province over a period of six years (from 2019 to 2024). Clinical information on age, sex, lesion site within the larynx, and final diagnosis approved by the pathologists was obtained based on the archived pathology reports accompanying each FFPE tissue sample. All tissues in the study were suitable for immunohistochemical analysis.

The current study included selected cases of laryngeal lesions that varied to include epithelial cysts, nodules, polyps, papillomas, dysplasia, and LSCC, covering a spectrum of benign, premalignant, and malignant laryngeal lesions. These cases were classified into two primary groups based on the final diagnosis of each case: (1) 21 cases of LSCC and (2) 23 cases of benign/premalignant laryngeal lesions.

Immunohistochemistry

Pre-prepared FFPE tissue blocks were utilized for immunohistochemical analysis. Each tissue block was sectioned at 4 μm and mounted onto two distinct positively charged slides (Thermo Scientific USA). Deparaffination and dehydration of tissue-mounted slides were achieved by immersing in xylene and alcohol gradients after incubation at 60℃ for two hours. Using ImmunoDNA Retriever 20X containing citrate buffer (Bio SB, USA), antigen retrieval was performed for 20 minutes at 95℃ (pH 6.0).

Immunohistochemical detection was conducted using the PolyDetector Plus DAB HRP Kit provided by Bio SB (USA). For stain visualization, an HRP-labeled secondary antibody was applied together with DAB substrate as the chromogen. A ready-to-use Rabbit Monoclonal p16INK4a primary antibody (Clone RM267, Bio SB, USA) and Rabbit Monoclonal Ki67 primary antibody (Clone RM19, Bio SB, USA) were separately applied for 60 minutes each. To prevent nonspecific staining, sections were treated with Peroxidase/AP Blocker (Bio SB, USA) prior to antibody application. Following each step, slides were rinsed with Bio SB ImmunoDNA Washer 20X (USA).

Immunohistochemical analysis

A senior pathologist and experienced microbiologist independently examined the slides in order to validate the reliability of the obtained findings, as follows:

P16: a 70% cutoff value was applied to differentiate between p16+ and p16- cases. P16 positivity was identified by the presence of strong and diffuse nuclear/cytoplasmic immunoreactivity in more than 70% of lesion cells [19], [20], [21], [22], [23], [24], [25].

Ki67: Our finding showed that Ki67 expression was approximately centered at 40% in the analyzed cases; thus, a 20% cutoff value was used to determine the level of Ki67 expression across the sample set [26], as follows:

Score 1: none (negative)

Score 2: 1-20% (low expression)

Score 3: > 20% (high expression)

Cells were considered positive if their nuclei exhibited dark yellow to brown immunostaining. To assess the percentage of immunoreactive cells, cells exhibiting Ki67 positive expression were selected among five distinct regions with the highest density of positive cells; thereafter, a total of one hundred nuclei were quantified under higher-power magnification (200X)[27].

Statistical analysis

Statistical comparisons were performed in SPSS software (version 27). To examine significant association, chi-square or Fisher's exact tests were applied depending on cell count. In larger tables (> 2×2) with low count, Monte Carlo simulation (10,000 iterations) was used to estimate the exact p-values. A $p < 0.05$ was considered as statistically significant.

3. Results

In total, 44 cases (63.63% of the male and 36.36% of the female) were analyzed in the current study. Patients had a mean age of 50.1 years at the time of diagnosis, ranging from 5 to 85 years. The mode of age was 60. The 53-68 age group was the most common, accounting for 40.9% of all cases. The majority of cases are seen in the glottic region (65.9%), followed by supraglottic and subglottic, at 31.8% and 2.27%, respectively. Regarding the lesion types, LSCC was the most common in this study (47.72%); other included types are nodule (25%), dysplasia (9.08%), papilloma (6.81%), polyp (6.81%), and epithelial cyst (4.54%). Among LSCC, moderately differentiated cancers were the most commonly observed (76.2%), followed by well-differentiated cancers, which accounted for 23.8%, as demonstrated in Table 1.

Table 1. clinic-pathological variables

Variable	Categories	No. and %
gender	Male	28(63.63)
	Female	16(36.36)
	Total	44(100)
Age Mean (50.15) Mode (60) Range (5-85)	5-20	1(2.27)
	21-36	8(18.18)
	37-52	13(29.54)
	53-68	18(40.9)
	69-85	4(9.09)
	Total	44(100)
histological site	glottic	29(65.9)
	subglottic	1(2.27)
	supra glottic	14(31.81)
	Total	44(100)
Diagnosis	scc	21(47.72)
	dysplasia	4(9.08)
	epithelial cyst	2(4.54)

	nodule	11(25)
	papilloma	3(6.81)
	polyp	3(6.81)
	Total	44(100)
Differentiation of scc	well	5(23.81)
	moderate	16(76.19)
	Total	21(100)

S: Significant difference at P<0.05, HS: High significant difference at P<0.01

As shown in Table 1, although a slight increase in p16 expression was recorded in the female and 69-85 age groups, P16 positivity showed no significant association with patient sex (P = 0.565), age (P ≈ 0.44), or lesion site (P ≈ 859).

Among malignant laryngeal lesions, 13 cases (61.9%) showed p16 expression and negative expression in eight cases (38.1%). All malignant lesions with moderate differentiation showed positive expression of p16. P16 expression in the benign lesions with papilloma and epithelial cysts were positive in 1/3 and 1/2 of cases, respectively; all polyps were negative for p16 expression, while the majority of laryngeal nodules were p16 positive (7/11), at 63.6%. Among premalignant laryngeal tumors, 3/4 of dysplastic lesions exhibited positive expression of p16, as shown in Figure 1. In total, our findings suggest that the p16-positive percentage was 52.2% across benign and premalignant lesions. Nevertheless, the correlation between p16 positivity and histopathological diagnosis was not statistically significant (P≈0.40).

Table 2. Distribution of P16 expression according to the clinicopathological variables

Variable	**Categories**	**No.**	**P16 result**		**P value**
			Positive (n=25) No. and (%)	Negative (N=19) No. and (%)	
sex	Male	28	15(53.57)	13(46.42)	0.565 (NS)
	female	16	10(62.5)	6(37.5)	
	Total	44	25(56.82)	19(43.18)	
Age	5-20	1	0(0)	1(100)	≈0.44 (NS)
	21-36	8	5(62.5)	3(37.5)	
	37-52	13	9(69.23)	4(30.76)	
	53-68	18	8(44.44)	10(55.55)	
	69-85	4	3(75)	1(25)	
	Total	44	25(56.82)	19(43.18)	
Lesion site	glottic	29	17(58.62)	12(41.37)	≈0.859(NS)
	subglottic	1	1(100)	0(0)	
	supra glottic	14	7(50)	7(50)	
	Total	44	25(56.82)	19(43.18)	
diagnosis	scc	21	13(61.9)	8(38.1)	≈0.401(NS)
	dysplasia	4	3(75)	1(25)	
	epithelial cyst	2	1(50)	1(50)	
	nodule	11	7(63.64)	4(36.36)	
	papilloma	3	1(33.33)	2(66.66)	
	polyp	3	0(0)	3(100)	
	Total	44	25(56.82)	19(43.18)	

Differentiation of SCC	well	5	5(100)	0(0)	0.044(S)
	moderate	16	8(50)	8(50)	
	Total	21	13(61.9)	8(38.1)	

NS: No significant difference at P>0.05, S: Significant difference at P<0.05

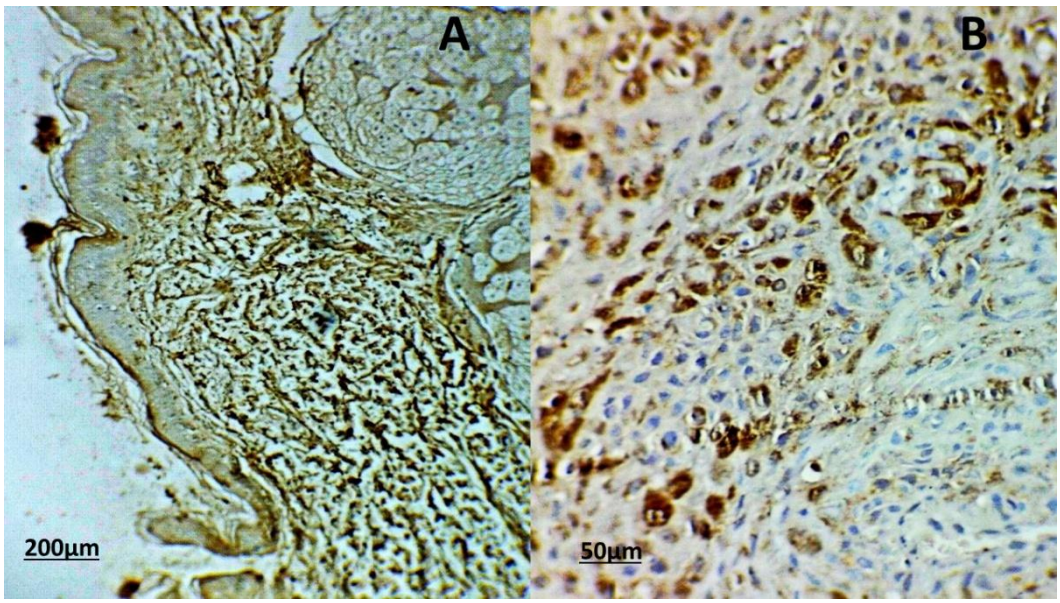

Figure 1. A laryngeal dysplasia exhibiting diffuse p16 expression: A (10X), B (40X).

Of all examined cases, 56.8% were p16-positive, of which 13 (61.9%) were malignant lesions, while 12 (52.2%) were benign/premalignant lesions, reflecting a slightly elevated p16 positivity of malignant lesions, as demonstrated in Table 3.

Table 3. p16 distribution according to the study groups

Study group	**No.**	**P16 result**		**P value**
		Positive (n=25) No. and (%)	Negative (N=19) No. and (%)	
Malignant lesions	21	13 (61.9%)	8 (38.1%)	0.544(NS)
Benign and dysplastic lesions	23	12 (52.2%)	11 (47.8%)	
Total	44	25 (56.8%)	19 (43.2%)	

NS: No significant difference at P>0.05

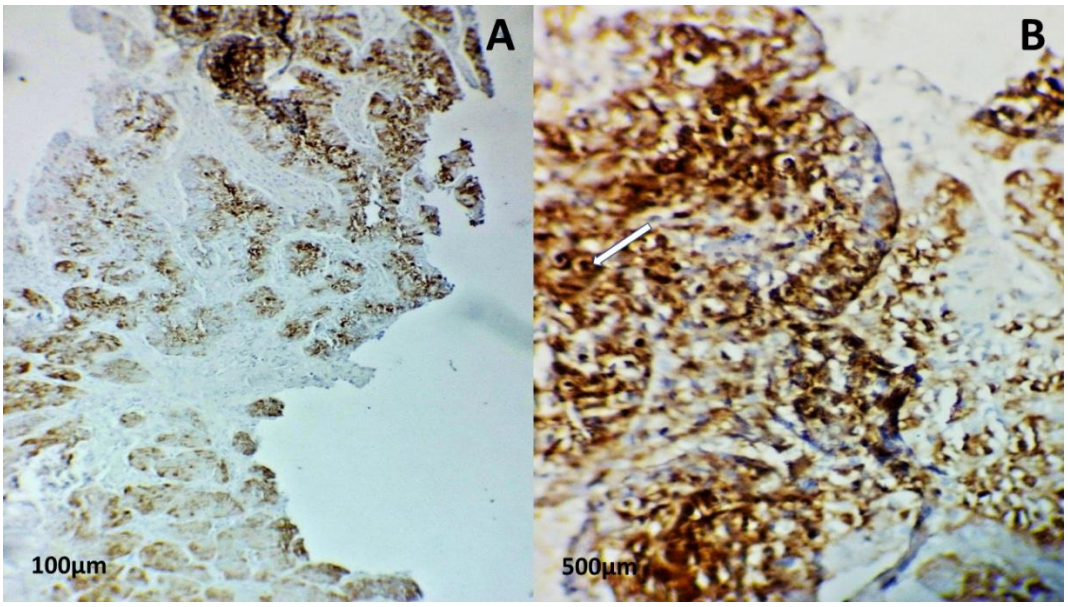

Figure 2. A laryngeal squamous cell carcinoma (LSCC) exhibited focal, non-diffuse p16 staining; A) 10X, B) 40X. The white arrow indicates a p16-positive nucleus.

According to Table 4, there was no significant correlation between p16 expression and the proliferation marker (Ki67) status (Figure 3).

Table 4. Ki distribution According to the P16 outcome

P16 result	No.	Ki result No. and (%) a			P value
		negative	low	High	
Positive	25	10(40)	10(40)	5(20)	0.814(NS)
Negative	19	8(42.10)	6(31.57)	5(26.31)	
Total	44	18(40.9)	16(36.4)	10(22.7)	

NS: No significant difference at P>0.05

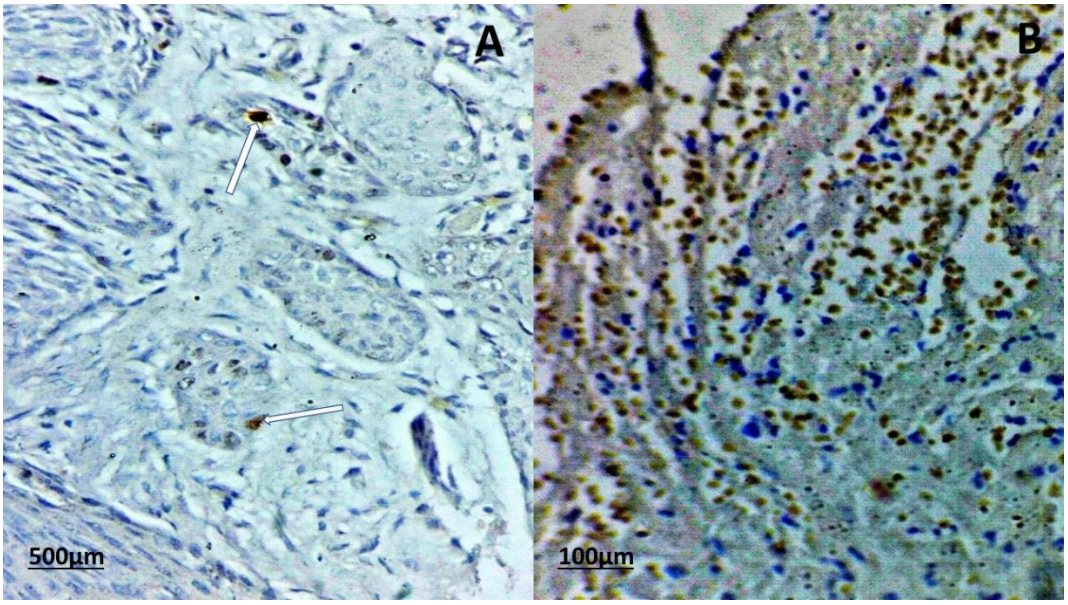

Figure 2. A Laryngeal squamous cell carcinoma (LSCC) shows low expression of Ki67 (40x); B: Laryngeal dysplasia shows high expression of Ki67.

4. Discussion

Accumulated studies have confirmed the essential role of HPV as a causative factor in HNSCC, particularly in OPSCC [28], [29], highlighting the reliability of using P16-IHC as

a surrogate marker of HPV infection [30]. Nevertheless, the involvement of HPV and the diagnostic reliability of P16-IHC in LSCC are yet to be precisely established and remain the subject of ongoing discussion.

Supporting our findings, Liu X et al. study [31] identified no significant correlation between p16 expression and certain clinicopathological parameters (age ($P \approx 0.44$) and lesion site ($P \approx 0.859$)) of patients with malignant laryngeal lesions indicating that these parameters might have no impact on p16 behavior in this regard, whereas significant association was observed with others (differentiation level ($P = 0.044$)), this selective correlation may suggest the elaborate dynamics among viral-driven carcinogenesis, cellular pathways, and tumor tissue features.

Although p16 positivity was observed across all types of laryngeal lesions (benign, premalignant, and malignant), our finding suggested no significant differences were observed between the study groups. Several studies, comprising those employing chromogenic ISH, revealed a relatively moderate correlation between p16 expression and the presence of HR-HPV infection [32], [33], indicating that p16 positivity does not necessarily reflect the presence of HPV infection.

The co-expression of both p16 (tumor suppressor) and Ki67 (proliferation index) within the same cell is regarded as a characteristic molecular feature of HPV-associated carcinomas [15]. Our findings revealed no significant correlation between p16 positivity and the proliferation marker within laryngeal lesions, reinforcing the notion that p16 overexpression, particularly in laryngeal cells, could be attributed to other HPV-unrelated cellular mechanisms [34], [35], including inflammatory responses, genetic alteration, or cellular senescence.

5. Conclusion

The reliability of p16 as a surrogate marker for HPV in LSCC has not yet been definitively established. Although 56.8% of laryngeal lesions in the current study exhibited positive p16 expression, statistical analysis revealed no significant correlation between p16 expression and either the study groups or the proliferation index status, indicating that p16 overexpression may reflect alternative cellular processes and that P16-IHC alone should not be relied upon as a conclusive marker of HPV infection in laryngeal lesions. The lack of significant association could be partly attributed to the small cohort size. Therefore, future studies should involve a larger sample size and apply p16-IHC analysis in conjunction with molecular diagnostics tools, such as PCR or ISH, to support diagnostic accuracy.

REFERENCES

[1] Karatzanis AD, Psychogios G, Waldfahrer F, Kapsreiter M, Zenk J, Velegrakis GA, et al. Management of locally advanced laryngeal cancer. Journal of Otolaryngology-Head & Neck Surgery. 2014;43(1):4.

[2] Megwalu UC, Sikora AG. Survival outcomes in advanced laryngeal cancer. JAMA Otolaryngology–Head & Neck Surgery. 2014;140(9):855–60.

[3] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.

[4] Mjali A, Hassan AK, Nassrullah HAA, Sedeeq AO, Abbas NT, Al-Shammari HHJ, et al. Pattern of Head and Neck Cancers in Karbala Province, Iraq: Data from a Developing Country. Asian Pacific Journal of Cancer Care. 2023;8(4):703–8.

[5] Koontongkaew S. The tumor microenvironment contribution to development, growth, invasion and metastasis of head and neck squamous cell carcinomas. J Cancer. 2013;4(1):66.

[6] Yang QQ, Deng YF. Long non-coding RNAs as novel biomarkers and therapeutic targets in head and neck cancers. Int J Clin Exp Pathol. 2014;7(4):1286.

[7] Yang D, Shi Y, Tang Y, Yin H, Guo Y, Wen S, et al. Effect of HPV infection on the occurrence and development of laryngeal cancer: a review. J Cancer. 2019;10(19):4455.

[8] Scott-Wittenborn N, Fakhry C. Epidemiology of HPV related malignancies. In: Seminars in radiation oncology. Elsevier; 2021. p. 286–96.

[9] Vazquez-Guillen JM, Palacios-Saucedo GC, Alanis-Valdez AY, Huerta-Escobedo A, Zavala-Pompa A, Rivera-Morales LG, et al. p16INK4a and pRb expression in laryngeal squamous cell carcinoma with and without infection by EBV or different genotypes of HPV: a retrospective study. Infect Agent Cancer. 2023;18(1):43.

[10] Machczyński P, Majchrzak E, Niewinski P, Marchlewska J, Golusiński W. A review of the 8th edition of the AJCC staging system for oropharyngeal cancer according to HPV status. European Archives of Oto-Rhino-Laryngology. 2020;277:2407–12.

[11] Bhardwaj S, Gitman M, Ramirez JD, Paniz-Mondolfi A, Westra WH. Reappraisal of p16 for determining HPV Status of Head and Neck Carcinomas arising in HPV hotspots. Am J Surg Pathol. 2024;48(5):581–7.

[12] Tran NH, Sais D, Tran N. Advances in human papillomavirus detection and molecular understanding in head and neck cancers: Implications for clinical management. J Med Virol. 2024;96(6):e29746.

[13] Mahajan A. Practical issues in the application of p16 immunohistochemistry in diagnostic pathology. Hum Pathol. 2016;51:64–74.

[14] Munger K, Gwin TK, McLaughlin-Drubin M. p16 in HPV-associated cancers. Oncotarget. 2013;4(11):1864.

[15] Linxweiler M, Bochen F, Wemmert S, Lerner C, Hasenfus A, Bohle RM, et al. Combination of p16INK4a/Ki67 immunocytology and hpv polymerase chain reaction for the noninvasive analysis of HPV involvement in head and neck cancer. Cancer Cytopathol. 2015;123(4):219–29.

[16] Gioacchini FM, Alicandri-Ciufelli M, Magliulo G, Rubini C, Presutti L, Re M. The clinical relevance of Ki-67 expression in laryngeal squamous cell carcinoma. European Archives of Oto-Rhino-Laryngology. 2015;272:1569–76.

[17] Kleist B, Junghans D, Lorenz G, Bankau A, Poetsch M. The supplementary diagnostic power of selected immunohistochemical, molecular genetic and infective parameters in epithelial hyperplastic laryngeal lesions. Oncology. 2003;65(4):347–54.

[18] Şengiz S, Pabuççuoğlu U, Sarioğlu S. Immunohistological comparison of the World Health Organization (WHO) and Ljubljana classifications on the grading of preneoplastic lesions of the larynx. Pathology-Research and Practice. 2004;200(3):181–8.

[19] Mylly M, Nissi L, Huusko T, Routila J, Vaittinen S, Irjala H, et al. Epidemiological study of p16 incidence in head and neck squamous cell carcinoma 2005–2015 in a representative northern European population. Cancers (Basel). 2022;14(22):5717.

[20] Ribeiro EA, Maleki Z. p16 immunostaining in cytology specimens: its application, expression, interpretation, and challenges. J Am Soc Cytopathol. 2021;10(4):414–22.

[21] Serra S, Chetty R. p16. J Clin Pathol. 2018;71(10):853–8.

[22] Abi-Raad R, Prasad ML, Gilani S, Garritano J, Barlow D, Cai G, et al. Quantitative assessment of p16 expression in FNA specimens from head and neck squamous cell carcinoma and correlation with HPV status. Cancer Cytopathol. 2021;129(5):394–404.

[23] Chung CH, Zhang Q, Kong CS, Harris J, Fertig EJ, Harari PM, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. Journal of clinical oncology. 2014;32(35):3930–8.

[24] Meshman J, Wang PC, Chin R, John MS, Abemayor E, Bhuta S, et al. Prognostic significance of p16 in squamous cell carcinoma of the larynx and hypopharynx. Am J Otolaryngol. 2017;38(1):31–7.

[25] Vazquez-Guillen JM, Palacios-Saucedo GC, Alanis-Valdez AY, Huerta-Escobedo A, Zavala-Pompa A, Rivera-Morales LG, et al. p16INK4a and pRb expression in laryngeal squamous cell carcinoma with and without infection by EBV or different genotypes of HPV: a retrospective study. Infect Agent Cancer. 2023;18(1):43.

[26] Couture C, Raybaud-Diogène H, Têtu B, Bairati I, Murry D, Allard J, et al. p53 and Ki-67 as markers of radioresistance in head and neck carcinoma. Cancer. 2002;94(3):713–22.

[27] Chen W, Lin G, Chen Y, Cheng F, Li X, Ding J, et al. Prediction of the Ki-67 expression level in head and neck squamous cell carcinoma with machine learning-based multiparametric MRI radiomics: a multicenter study. BMC Cancer [Internet]. 2024 Apr 5;24(1):418. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-024-12026-x

[28] Beniwal A, Karwasra I, Parmar A, Beniwal HK, Sakhrani JK. Human Papillomavirus in Head and Neck Squamous Cell Carcinoma. Indian Journal of Surgery. 2018;80:322–6.

[29] Taberna M, Mena M, Pavón MA, Alemany L, Gillison ML, Mesía R. Human papillomavirus-related oropharyngeal cancer. Annals of Oncology. 2017;28(10):2386–98.

[30] GEIßLER C, Tahtali A, Diensthuber M, Gassner D, Stoever T, Wagenblast J. The role of p16 expression as a predictive marker in HPV-positive oral SCCHN–a retrospective single-center study. Anticancer Res. 2013;33(3):913–6.
[31] Liu XY, Hanjing S, Zhang B huang, Luo XY. Expression of p16 and Ki67 in laryngeal squamous cell carcinoma and their clinical significance. Front Oncol. 2024;14:1430830.
[32] Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U, et al. Overexpression of p16INK4A as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer. 2001;92(2):276–84.
[33] Sano T, Oyama T, Kashiwabara K, Fukuda T, Nakajima T. Expression status of p16 protein is associated with human papillomavirus oncogenic potential in cervical and genital lesions. Am J Pathol. 1998;153(6):1741–8.
[34] Laco J, Slaninka I, Jirásek M, Čelakovský P, Vošmiková H, Ryška A. High-risk human papillomavirus infection and p16INK4a protein expression in laryngeal lesions. Pathology-Research and practice. 2008;204(8):545–52.
[35] Dogantemur S, Ozdemir S, Uguz A, Surmelioglu O, Dagkiran M, Tarkan O, et al. Assessment of HPV 16, HPV 18, p16 expression in advanced stage laryngeal cancer patients and prognostic significance. Braz J Otorhinolaryngol. 2020;86(3):351–7.