The prognostic role of HPV status in Penile Squamous Cell carcinoma: A Systematic Review and Meta-analysis

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Abstract

Penile squamous cell carcinoma (PSCC) is a rare but aggressive malignancy that can present as either Human papillomavirus (HPV)-associated or HPV-independent. Currently, there is no consensus on the prognostic value of HPV status in PSCC or its role in guiding treatment strategies. Therefore, in this systematic review and meta-analysis we aim to assess the impact of different methods of determining HPV status on cancer specific survival (CSS) and overall survival (OS) in patients with PSCC.

Databases including MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were systematically searched between 1980 and February 2025. Studies were eligible if they assessed HPV status using any method in PSCC patients and reported CSS or OS with a minimum follow-up of two years. Case reports, narrative reviews, expert opinions, and studies reporting less than 50 participants were excluded. Quality of included studies was assessed using the QUIPS tool.

A total of 31 studies, published between 2001 and 2024, met the inclusion criteria, all of which were of retrospective design. High risk of bias (RoB) was noted for study attrition, prognostic factor measurement, and study confounding. Sample sizes ranged from 57 to 611 participants (median: 152 participants).

HPV-status was assessed through DNA testing in 19 studies and 10 studies used p16 immunohistochemistry (IHC) as a surrogate marker of HPV-driven carcinogenesis. Four studies used both HPV DNA measurements and p16 IHC staining and two articles determined HPV status based on histological subtyping. Median follow-up was 49.9 months (range: 27-107.9 months). We identified 23 studies that reported sufficient data for inclusion in a meta-analysis, encompassing a total of 5291 men with various stages of PSCC. Of these, 1946 (36.8%) had HPV-associated disease. Positive p16 status was associated with improved CSS (HR=0.40, 95% CI [0.20, 0.80], p=0.009) and OS (HR=0.49, 95% CI [0.29, 0.85], p=0.01) in a pooled cohort of 1266 and 1189 patients respectively. HPV DNA positivity was associated with improved CSS (HR=0.54, 95% CI [0.35, 0.83], p=0.005), but not with OS (HR=0.86 95% CI [0.70, 1.07], p=0.17).

In conclusion, p16 and HPV DNA positivity are associated with improved CSS in patients with PSCC. Positive p16 status was related to better OS, while HPV status based on DNA measurements was not. These findings underscore the prognostic value of p16 and HPV status.

Introduction

Penile squamous cell carcinoma (PSCC) affects approximately 1 per 100 000 men in Western countries(1). PSCC is a rare but aggressive disease with involvement of the lymph nodes being the most important prognostic factor, associated with high morbidity and mortality(2–4). The current standard of care primarily involves surgical resection of the primary tumor and, if necessary, malignant lymph nodes, which can lead to considerable decrease in patients' quality of life (5,6). A major challenge in the management of PSCC is the lack of reliable prognostic and predictive markers, which could potentially determine treatment decisions such as de-escalation of therapy.

The World Health Organization (WHO) currently classifies PSCC into HPV-associated (HPV+) and HPV-independent (HPV-) subtypes (7). It is estimated that approximately 50% of PSCC globally are associated with HPV(8). During a persistent HPV infection with a high-risk HPV genotype, the viral genome may integrate into the host cell's DNA, disrupting the viral life cycle. This integration often leads to the constitutive transcription and translation of the viral oncoproteins E6 and E7, which bind to and inactivate the tumor suppressor proteins p53 and retinoblastoma-1 (Rb), driving cellular dysregulation and potential malignant transformation respectively(9). The cyclin-dependent kinase inhibitor 2A (CDKN2A) gene encodes inhibitor of cyclin-dependent kinase 4a p16 ($p16^{INK4a}$), which inhibits cyclin-dependent kinase 4/6 (CDK4/CDK6), preventing phosphorylation of Rb and thereby halting the G1-to-S phase transition in the cell cycle(9). In HPV infection, the E7 oncoprotein degrades Rb, leading to p16 overexpression as a compensatory response(9). p16 immunohistochemistry (IHC) is therefore considered a surrogate marker for the presence of high-risk HPV infection with a sensitivity of 90-100% and specificity of 70% (10–13). Other methods used to determine HPV status in PSCC are polymerase chain reaction (PCR), in situ hybridization (ISH), and next-generation sequencing (NGS), which identify HPV DNA or RNA within tumor tissue(14).

In other HPV-associated cancers such as oropharyngeal SCC and vulvar SCC, high risk HPV DNA detection or p16 overexpression have been demonstrated to be associated with more favorable clinical outcomes (15,16). Although PSCC shares several characteristics with these malignancies, previous

studies have yielded conflicting results regarding the prognostic significance of HPV and p16 in PSCC (17–19). In 2018, the first two meta-analyses were published on the topic (20,21). Zhang et al. analyzed five studies and found that p16 positivity was linked to better cancer-specific survival (CSS)(20). Sand et al. reviewed 20 studies, showing that both p16 and HPV positivity were associated with improved CSS, but not overall survival (OS)(21). Both literature searches covered studies published between 1992 and 2017. An updated systematic review by Parza et al. (2023), with its meta-analysis published by Mustasam et al. (2025), included 34 studies (3,944 patients) from March 1992 to January 2023(22,23). They confirmed links between both p16/HPV status and improved CSS, and only found p16 positivity to be correlated with better OS(22,23).

Since early 2023, there has been an increase in observational studies with larger cohorts documenting the prognostic value of HPV DNA and p16 status in PSCC. However, previous meta-analyses do not include these recent higher-quality data and given that accurate prognostic markers could inform treatment decisions, stratification, and follow-up strategies for patients with PSCC, there is a pressing need for an updated synthesis of the evidence on the prognostic value of HPV status in PSCC. We therefore perform an updated systematic review and meta-analysis to evaluate the prognostic impact of HPV DNA and p16 status on cancer-specific survival (CSS) and overall survival (OS) in patients with PSCC. To enhance the reliability and clinical applicability of our findings, we applied strict inclusion criteria, including only studies with a cohort size of at least 50 patients and with a mean or medial follow-up of at least 24 months.

Methods

Protocol and registration

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (**Supplementary figure 1**)(24), Cochrane review principles(25) and AMSTAR2 criteria(26). The protocol for this review has been published (PROSPERO registration number: CRD42023420492).

Search strategy and study selection

The electronic databases MEDLINE, Embase, Cochrane CENTRAL (via Ovid) were searched for all relevant publications between January 1980 and February 2025. The literature search was carried out based on the search strategy provided in **Supplementary figure 2**. Following de-duplication, all abstracts and full text articles were screened by two independent reviewers according to the criteria identified in the eligibility form (**Supplementary figure 3**). Disagreement between two reviewers was resolved by discussion or interference of an independent third party.

Eligibility criteria

We included randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and conference abstracts. Publications reporting on HPV status and its association with survival outcome (OS and/or CSS) in men with PSCC were included. Case reports, narrative reviews, expert opinions, studies with less than 50 participants, and studies reporting a survival follow-up of less than 2 years were excluded. No exclusion was made based on T-stage, positive lymph nodes (N1, N2, N3), metastasis (M1), or treatment history. HPV detection tools such as p16 IHC, qualitative PCR testing, ISH, NGS, or any other unspecified techniques giving HPV status data were included.

Data extraction and quality assessment

Survival data, participant characteristics and study characteristics were independently extracted from the selected articles by one reviewer and checked for accuracy by a second reviewer. Any disagreement was resolved by discussion or by consulting a third review author. A standardized data extraction form was developed and piloted before its use. Data extraction was informed by the REporting recommendations for tumor MARKer prognostic studies (REMARK)(27). The following data were extracted from each study: study design, countries and institutions where the data were collected, recruitment period, follow-up period, HPV status definition and measurement, numbers of participants

included, participant demographic and clinical characteristics (e.g. disease stage, co-morbidities, treatment), number of patients with HPV+ and HPV- disease, loss and exclusions of participants, and all unadjusted (univariate) and adjusted (multivariable) associations between HPV status and outcome. The risk of bias (RoB) and quality of each included study was independently assessed by two review authors using the QUIPS tool (28), as recommended by the Cochrane Prognosis Methods Group(25). Important cofounding factors were defined as (neo-)adjuvant treatment, TNM stage, tumor grade, and age of the patients. Any disagreements were resolved by discussion or by consulting a third reviewer. A summary of the RoB assessment was generated in RevMan (v5.4).(29)

Statistical analysis and meta-analysis

Descriptive statistics were used to summarize all studies included in this systematic review.

For the meta-analysis, only studies with sufficient data to determine hazard ratios (HR) for OS or CSS were included. Both unadjusted (univariate) and adjusted (multivariable) HR were extracted. When both adjusted and unadjusted HR were available, adjusted values were preferentially included in the meta-analysis to minimize heterogeneity. If standard errors were absent, we filled in the missing values using reported P-values or 95% confidence intervals (CI). For consistency, HR were recalculated whenever necessary so that HR > 1 indicate a better prognosis in HPV-positive patients relative to HPV-negative patients. If survival data were presented only as survival rates, HR were derived based on the reported values whenever possible. For studies that did not report HR or survival rates directly but only provided Kaplan–Meier survival curves, with or without the number of patients at risk, we extracted survival data from published Kaplan–Meier plots and estimated HR and 95% confidence intervals using the method described by Tierney et al (30). Studies that did not provide sufficient data to calculate HR using any of the aforementioned approaches were excluded from the meta-analysis. Moreover, studies with overlapping study populations were carefully reviewed and in such cases where overlap was identified, we prioritized the selection of studies with the longest follow-up duration, to minimize duplication bias.

Finally, standardized regression coefficients for continuous outcomes were converted to log HR as appropriate for synthesis (31,32). We conducted the meta-analyses using a random effects model, HR were pooled using the inverse variance method, and forest plots were generated in RevMan (v5.4) to visualize the extracted effects of p16 and HPV status on the survival outcomes (29). Heterogeneity among studies was assessed using the I^2 statistic, with <20%, 25-50, 50-75 and >75% representing unimportant, moderate, substantial, and considerable heterogeneity, respectively(25). Publication bias was evaluated through funnel plots and Egger's test using metafor package (v4.6.0) in R (v4.3.2)(33). All other statistical analyses were performed using RevMan (v5.4) (29).

Results

Results of the literature search

The results of our literature search are summarized in the PRISMA flow diagram **(Figure 1).** Our initial electronic searches retrieved a total of 1238 references, of which 879 unique titles and abstracts were assessed after removing duplicates. Subsequently, 108 potentially eligible references were screened based on their full text. Ultimately, 31 studies were included in this systematic review. The primary reasons for exclusion were unreported or insufficient follow-up duration (n=45). An overview of the included studies and main characteristics are summarized in **Table 1.** All studies were retrospective in nature and were published between March 2001 and 2025. Twelve articles were multicentric studies and 26 out of 31 studies were conducted in a penile cancer referral center or academic hospital. The sample sizes of the included studies ranged from 57 to 611 participants per study (median 152 months, interquartile range (IQR) 116–264 months). Median follow-up ranged from 27 to 107.9 months (median 49.9 months, IQR 35-70 months).

Of the 31 studies included in the systematic review, 23 were eligible for meta-analysis. The remaining 8 studies were excluded from the meta-analysis due to overlapping study populations (17,19,34,35), or lack of sufficient survival data (36,37). Additionally, we excluded two studies from the meta-analysis because their study populations were too heterogeneous compared to the other included studies: one

study focused exclusively on patients who received radiotherapy (38), while the other only included patients with N2 and N3 disease stages (39). Eventually a total of 5291 men were included in our meta-analysis with median or mean age of participants ranging from 52 to 69 years and a median follow-up of 55 months. Of all patients, 1946 (36.6%) were reported to have HPV-associated disease, determined by any method.

HPV detection methods

The included studies substantially varied in terms of HPV detection methods **(Table 2).** Nineteen studies determined HPV status solely based on DNA measurements using either HPV PCR (n = 15), ISH (n=2), or a combination of these techniques (n=2). A total of 3246 (65.25%) men underwent HPV DNA measurement, of which 1108 (35.75%) were HPV-positive and 2138 (64.25%) were HPV-negative. In 10 studies, p16 IHC was used as a surrogate marker to determine HPV-dependent and HPV-independent PSCC. A total of 970 (42.77%) participants showed p16 positivity and 1298 (55.23%) showed p16 negative staining in these studies. However, the included studies varied substantially in their definition of p16 positivity (**Table 2**). Four included studies used both HPV DNA measurements and p16 IHC staining methods to determine final HPV status(38–40) and two articles determined HPV status based on histological subtypes alone(41,42). The latter classified tumors as HPV-related or non-HPV-related based on the WHO histological subtype classification of tumors(43). HPV-related subtypes included basaloid, warty, and warty-basaloid carcinomas, while non-HPV-related subtypes included usual, verrucous, papillary, pseudohyperplastic, pseudoglandular, sarcomatoid, and adenosquamous carcinomas(41–43). As this method does not directly assess HPV presence or activity, these studies were analyzed separately under the category “others.”

Risk of bias (RoB) and confounding assessment of included studies

Overall, the studies demonstrated a generally high RoB across several key domains. There was a particularly high RoB in the domain of study confounding, as more than 50% studies did not adequately

report important cofounding factors such as (neo-)adjuvant treatment, or tumor histopathological characteristics. Additionally, the domains of study attrition and prognostic factor measurement were assessed to have a moderate to high RoB in over 60% of the included studies. This was mainly due to poorly detailed descriptions of HPV or p16 measurements. A summary of the RoB assessment for all included studies is provided in **Figure 2.**

Cancer-specific survival (CSS)

CSS was reported in 21 out of the 31 studies. The reported mean or median follow-up period ranged from 27 to 107 months (median 57 months, IQR 37-77 months). For our meta-analysis, we included data from 16 studies, of which three reported on p16 status, 9 focused on HPV status, two reported both p16 and HPV status, one study determined HPV status based on histological subtype(41), and another based on a combination of methods(44). The overall pooled HR for CSS was 0.51 (95% CI [0.37-0.71], p<0.0001), suggesting a favorable CSS for patients with HPV-associated disease **(Figure 3).** The funnel plot showed a symmetrical distribution, indicating a low risk of publication bias (Egger's test, p=0.0596) **(Supplementary figure 4).**

p16 status and cancer-specific survival (CSS)

Five studies examining the relationship between p16 status and CSS were included in the meta-analysis. This analysis included 1,266 participants, of whom 536 (42.3%) were p16-positive. The pooled effect HR was 0.40 (95% CI [0.20-0.80], p=0,009), indicating a significantly better CSS for p16-positive patients (**Figure 3).** The HR ranged from 0.15 to 1.07, with only one study reporting a HR above 1 (45). Heterogeneity analysis showed considerable interstudy heterogeneity (I^2 = 77%, p=0.004).

HPV status and cancer-specific survival (CSS)

Fourteen studies investigated the association between HPV DNA detection and CSS in PSCC. After exclusion of three studies due to overlapping study populations (17,34,35), 11 studies remained for

inclusion in the meta-analysis. The meta-analysis encompassed a total of 1,708 participants, of whom 604 (35.3%) were HPV-positive and 1,104 (64.6%) HPV negative. Kaplan-Meier reconstruction method was applied in five studies (18,46–49). The pooled effect estimate revealed a HR of 0.54 (95% CI [0.35-0.83], p=0.005) , indicating a CSS benefit for HPV-positive patients (**Figure 3**). However, two studies reported HR above 1 and study heterogeneity was substantial (I^2 = 59%, p=0.007).

Overall survival (OS)

From our literature search, 21 of the 31 studies examined OS with median or mean follow-up durations ranging from 27 to 88.7 months (median 46.8 months, IQR 33-57). Of these, we included 15 in our meta-analysis, comprising 3 that assessed p16 status, 7 that evaluated HPV status, 3 analyzing both p16 and HPV status, one study determined HPV status based on histological subtype(42), and another based on a combination of methods(40). The pooled HR for OS was found to be 0.67 (95% CI [0.52-0.86], p=0.002) indicating a statistically significant association with HPV positivity and improved OS **(Figure 4).** However, the funnel plot showed an asymmetrical distribution and thus high risk at publication bias (Egger's test, p=0.0074) **(Supplementary figure 5)**.

p16 status and Overall Survival (OS)

Six studies in the meta-analysis assessed the impact of p16 status on OS, including 1189 participants of which 515 (43.3%) were p16-positive. The HR of one study was calculated based on KM reconstruction method(50). The pooled HR was 0.49 (95% CI [0.29-0.85], p=0.01), with HR ranging from 0.28 to 1.45 **(Figure 4)**. Similar to CSS, only one study reported a HR above 1 (45). However, considerable interstudy heterogeneity was observed (I^2 = 77%, p=0.0002).

HPV status and Overall Survival (OS)

Twelve studies reported on the impact of HPV DNA detection on OS, of which 10 were included in the meta-analysis. Out of 1903 participants, 1150 (60.4%) HPV-independent and 753 (39.6%) HPV-

associated. The pooled HR was 0.86 (95% CI [0.70-1.07], p=0.17), with HR ranging from 0.14 to 1.19, indicating no significant association between HPV positivity and OS **(Figure 4)**. Kaplan-Meier reconstruction method was applied in three studies (47,48,50).

Discussion

In this systematic review, we included 31 studies, of which 23 were eligible for inclusion in our meta-analysis. We showed that p16 positivity in patients with PSCC is significantly associated with improved CSS (HR 0.40, 95% CI [0.20, 0.80], p=0.009) and OS (HR 0.49, 95% CI [0.29, 0.85], p=0.01). In contrast, HPV DNA positivity only showed a statistically significant association with CSS (HR 0.54, 95% CI [0.35, 0.83], p=0.005), but not with OS (HR 0.86, 95% CI [0.70, 1.07], p=0.17). These findings align with previous reports(20–23) and build upon the analysis of Mustasam et al(23). While the systematic review by Parza et al. (2023) and the meta-analysis by Mustasam et al. (2025) included 34 studies, our review included 31. This difference is due to our more stringent inclusion criteria, which required a minimum cohort size of 50 patients and a follow-up duration of at least two years to minimize heterogeneity and enhance the reliability of survival estimates. Notably, despite these stricter criteria, our extended search still identified six additional eligible studies published after the previous reviews' cutoff dates.

Our systematic review confirms that HPV-associated PSCC appears to be linked with more favorable survival outcomes compared to HPV-independent PSCC —an observation consistent with other HPV-related cancers(51,52). This supports the importance of two distinct etiological pathways in PSCC: one that is HPV-driven, typically occurring in younger patients and associated with better prognosis, and another that is HPV-independent, often linked to chronic inflammatory conditions such as lichen sclerosis, balanitis, or phimosis(53,54). Accurately defining these two pathways is essential for reliable prognostication and for guiding treatment decisions tailored to the underlying tumor biology. Given

that p16 in our meta-analysis was significantly associated with both improved CSS and OS, while HPV DNA positivity was only correlated with CSS, our findings suggest that p16 expression may serve as a more reliable prognostic marker in PSCC compared to HPV DNA detection alone. A first possible explanation for this discordance in OS might be that p16 more accurately reflects transcriptionally active, oncogenic HPV involvement. The presence of viral DNA without integration or expression of viral oncoproteins (e.g., E6/E7), and thus p16, may have low or no impact on tumor progression and might explain why HPV DNA positivity fails to consistently correlate with OS outcomes(55,56). HPV DNA-based assays may detect contaminating or non-integrated viral fragments, which can lead to the false classification of PSCCs as HPV-associated. Additionally, several studies in our review included both high-risk and low-risk HPV types in their DNA-based analyses(46,57), which further reinforces that HPV detection using these methods does not necessarily imply a oncogenic role in tumor biology or progression. In contrast to HPV detection tools, p16 IHC reflects downstream functional effects of viral oncogenic activity, making it a more reliable marker of HPV integration(11,12,58). It is also noteworthy that p16 IHC is more cost-effective, widely available, and technically straightforward compared to molecular HPV assays. It is currently recommended by the WHO for the diagnosis of HPV-associated disease(53). However, heterogeneity in p16 IHC interpretation remains a challenge. Current reports recommend defining p16 positivity as a “block-positive” pattern only when ≥75% of tumor cells show strong nuclear and cytoplasmic staining(10,11). In our literature search, only 3 of the 10 studies assessing p16 status clearly adhered to this standard. Moreover, p16 IHC has limited specificity and may be false positive due to alternative mechanisms, such as inactivation of Rb by mutations or deletion, amplification of p16, and mutations of histone H3 lysine 36 methyltransferase genes(59,60). Studies in head and neck squamous cell carcinoma (HNSCC) have shown that discordant p16+/HPV– or p16-/HPV+ tumors exhibit a worse prognosis than p16+/HPV+ cancers, supporting a growing consensus that p16 should not be used in isolation to define HPV-driven tumors(61). Similar findings are emerging in vulvar cancer, where a recent study demonstrated that while p16 positivity was generally associated with improved survival, this benefit was significantly greater when high-risk HPV DNA was also present,

underscoring the added prognostic value of confirming active viral involvement(52). Combinatory diagnostic strategies using both p16 IHC and HPV DNA detection, as is currently used in treatment de-escalation trials for head-and neck cancers, therefore may provide a more precise classification of HPV-associated disease(62).

Several methodological limitations across the included studies need to be acknowledged when interpreting our findings. First of all, we observed significant variation in patient characteristics, tumor stages, and the use of (neo-)adjuvant therapies across studies, which adds complexity to the interpretation of results. To minimize these challenges, we applied stringent inclusion criteria. While this may have excluded smaller studies, it also strengthened the robustness of our meta-analysis and reduced the RoB in evaluating long-term outcomes like OS and CSS. Additionally, there was high variability in the methodology used to determine HPV status, including different p16 positivity definition and HPV genotypes used. Two studies included in our meta-analysis defined HPV status based on morphological classification alone, grouping tumors into HPV-related and unrelated subtypes based on WHO-defined histologic patterns(43). However, this is not a definitive method for confirming the presence of transcriptionally active HPV and can be potentially misleading. Therefore, these studies were analyzed separately under "others" in our synthesis to avoid skewing the pooled effect estimates.

To understand the underlying biology contributing to the more aggressive nature of HPV-independent PSCC, it is important to consider underlying molecular and immunological mechanisms. Chronic inflammation and somatic gene alterations likely contribute to the pathophysiology and more aggressive phenotype of HPV-negative PSCC, with approximately 75% of these cases being driven by loss-of-function mutations in TP53(63,64). Emerging evidence suggests that these TP53 mutations lead to poorer CSS and influence carcinogenesis and disease behavior through mechanisms such as epithelial-mesenchymal transition (EMT), angiogenesis, and the development of an immune-excluded tumor microenvironment(65). Moreover, tumor budding has been described as a significant negative

predictor in this PSCC TP53 mutated subgroup and may be understood as a histomorphological correlate of EMT(45). Other genomic profiling studies in PSCC have identified frequent alterations in *CDKN2A, PIK3CA, NOTCH1, TERT, FAT1, CASP8*, and *HRAS*, many of which occur predominantly in HPV-negative tumors(64,66). Furthermore, HPV-negative tumors often exhibit lower tumor mutational burden (TMB) compared to HPV-positive PSCC(64,67). Immunologically, HPV-negative PSCC is associated with a more immunosuppressed phenotype, characterized by higher expression of PD-L1(68). Nonetheless, further research is required to elucidate these mechanisms and determine how they can be exploited for clinical benefit.

In summary, our systematic review and meta-analysis provide strong evidence that p16 positivity, more so than HPV DNA status, is associated with improved CSS and OS in PSCC. Given its biological relevance and practical advantages, p16 IHC—when assessed using standardized, block-positive criteria—emerges as a potentially useful prognostic marker in this setting. However, its application as a stand-alone diagnostic marker is not without limitations. International efforts are now needed to standardize the definition of HPV-associated PSCC, ensuring that future clinical studies, trials, and routine diagnostic work can adopt a unified and biologically meaningful approach.

Data Availability Statement

Not applicable.

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Figure and table Legends

Figure 1: PRISMA flow diagram

Figure 2: Risk of Bias Assessment

Figure 3: Forest plot of CSS in men with HPV-associated PSCC compared with HPV-independent PSCC using different measurement methods.

Figure 4: Forest plot of OS in men with HPV-associated PSCC compared with HPV-independent PSCC using different measurement methods.

Table 1: Main characteristics of included studies Abbreviations: FA = Full Article, CA = Conference Abstract, NA = Not Applicable, CSS = Cancer Specific Survival, OS = Overall Survival

Table 2: HPV and p16 measurement methods. Abbreviations: HPV = Human Papilloma Virus, PCR = Polymerase Chain reaction, ISH = in situ hybridization, IHC = immunohistochemistry, CMC = Chinese multicenter, MCC = Mofitt Cancer Center

Author Contribution Statement

Conception and design: TVDB, MA. Data acquisition: KV, LE, CD, LL, YY, TVDB. Synthesis and interpretation of data: KV, LE, TVDB. Drafting of Manuscript: KV, LE, TVDB. Critical revision of manuscript: KV, LE, TVDB, MA. Supervision: TVDB and MA. Approval of the final manuscript: KV, LE, TVDB, MA.

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Ethical Approval

Not applicable.

Competing Interests

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