

# INPLASY PROTOCOL

To cite: Wang et al. Feasibility of immunohistochemical p16 staining in the diagnosis of human papillomavirus infection in patients with squamous cell carcinoma of the head and neck: A systematic review and meta-analysis. Inplasy protocol 202070068. doi: 10.37766/inplasy2020.7.0068

## Feasibility of immunohistochemical p16 staining in the diagnosis of human papillomavirus infection in patients with squamous cell carcinoma of the head and neck: A systematic review and meta-analysis

Wang, HH<sup>1</sup>; Zhang, YY<sup>2</sup>; Bai, W<sup>3</sup>; Wang, B<sup>4</sup>; Wei, JL<sup>5</sup>; Rui, J<sup>6</sup>; Xin, Y<sup>7</sup>; Dong, LH<sup>8</sup>; Jiang, X<sup>9</sup>.

Received: 16 July 2020

Published: 16 July 2020

**Corresponding author:**  
Huanhuan Wang

[wanghh2714@mails.jlu.edu.cn](mailto:wanghh2714@mails.jlu.edu.cn)

**Author Affiliation:**  
The First Hospital of Jilin University, China

**Support:** None.

**Review Stage at time of this submission:** Piloting of the study selection process.

**Conflicts of interest:**  
None.

**Review question / Objective:** This systematic review and meta-analysis aimed to investigate the feasibility of using IHC-p16 for diagnosing HPV infection in HNSCC and its value for de-escalating treatment. Further, we aimed to assess whether the results varied by tumor site and country.

**Condition being studied:** Treatment of head and neck squamous cell carcinoma(HNSCC), Diagnosis, individualized treatment, and radiosensitivity of human papillomavirus(HPV) associated HNSCC.

**Information sources:** PubMed, EMBASE, Web of Science, Cochrane Library and contact with authors.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 July 2020 and was last updated on 16 July 2020 (registration number INPLASY202070068).

### INTRODUCTION

**Review question / Objective:** This systematic review and meta-analysis aimed to investigate the feasibility of using IHC-p16 for diagnosing HPV infection in HNSCC

and its value for de-escalating treatment. Further, we aimed to assess whether the results varied by tumor site and country.

**Condition being studied:** Treatment of head and neck squamous cell carcinoma

---

(HNSCC), Diagnosis, individualized treatment, and radiosensitivity of human papillomavirus (HPV) associated HNSCC

## METHODS

**Search strategy:** We searched PubMed, EMBASE, Web of Science, and Cochrane Library for relevant articles published from the establishment of the database until October 2019, without language restrictions. The search was assisted by an experienced library staff member. We used a combination of MeSH words and free text words including “Papillomaviridae” and “Head and Neck Neoplasms.” The search strategy and the number of relevant articles identified in each database are shown in the supplementary documents. The references of the identified articles were also reviewed to further search for other relevant articles. All articles were searched according to international standards.

**Participant or population:** Inclusion: Patients with head and neck squamous cell carcinoma (confirmed by histopathology) Exclusion: Metastases from other sites to the head and neck.

**Intervention:** Immunohistochemical staining(IHC) was used to detect the overexpression of p16 in head and neck squamous cell carcinoma(HNSCC).

**Comparator:** HPVE6E7mRNA expression in head and neck squamous cell carcinoma(HNSCC) was detected by in situ hybridization(ISH) or polymerase chain reaction(PCR) to diagnose HPV infection.

**Study designs to be included:** We will include diagnostic studies, retrospective studies to assess the accuracy of immunohistochemical staining(IHC) for p16 in the diagnosis of huma.

**Eligibility criteria:** (i) the included patients had HNSCC; (ii) the samples tested were biopsy or puncture specimens; (iii) HPV E6/E7mRNA detection was used as the gold standard for the diagnosis of HPV infection; (iv) p16 expression was detected using IHC;

(v) the total sample size was greater than 10. All case reports, preclinical studies, case series, animal studies, and conference summaries will be excluded. In addition, papers will be also excluded if the specific location of HNSCC was not clearly defined. Further, the included studies must present the specific true positive (TP), false positive (FP), false negative (FN), and true negatives (TN) values or have adequate data so these can be calculated. If data were lacking, we will contact the author by email to ask for the data, and the study will be excluded if the author do not respond. Study selection will be divided into two parts. First, the authors (JLW and BW) will screen all the articles independently by browsing the titles and abstracts. Second, the same two authors independently evaluate the full text of the initially included articles. Any disagreements will be resolved by the third author (XJ).

**Information sources:** PubMed, EMBASE, Web of Science, Cochrane Library and contact with authors.

**Main outcome(s):** Sensitivity, specificity, positive likelihood ratio (LR), negative LR, and the diagnostic odds ratio (OR), the area under the curve (AUC) value.

**Additional outcome(s):** None.

**Quality assessment / Risk of bias analysis:** Two authors (JLW and BW) will independently assess the methodological quality of the included studies using the QUADAS-2 tool. Briefly, the QUADAS-2 tool comprises four domains, namely, patient selection, index test, reference standard, and flow and timing. In addition, the first three sections will be evaluated with respect to clinical applicability. Patient selection primarily evaluates whether the selection of patients have introduced bias, including whether the patient selection is random and whether there is inappropriate exclusion. The index test primarily evaluates whether the conduct or interpretation of the test has bias, including whether the process of the experiment is detailed. The reference standard evaluates biases caused by reference criteria and

---

their interpretations. The flow and timing evaluates whether all patients are using the same criteria. Evaluation of the these four parameters helps to assess the risk of bias.

**Strategy of data synthesis:** Given that the accuracy of p16 positivity in diagnosing HPV infection is related to the positive threshold, differences in thresholds between studies may have an impact on the sensitivity and specificity. Thus, we will further evaluate whether there is a threshold effect using Spearman correlation coefficient. If there is no threshold effect, the sensitivity, specificity, and other indicators were further combined. All data will be combined using Meta Disc and STATA 15.0 software. We will develop a forest map that graphically displays estimates of sensitivity and specificity and visualize heterogeneity between studies. Moreover, heterogeneity will be examined using  $I^2$  and Cochrane Q tests. An  $I^2$  of  $>50\%$  indicate heterogeneity, and the source of heterogeneity will be further explored. After obtaining the sensitivity and specificity values, we will further use the receiver operating characteristic curve (ROC) model to obtain the positive likelihood ratio (LR), negative LR, and the diagnostic odds ratio (OR) and their 95% confidence intervals (CI). The ROC curve will be also drawn to obtain the area under the curve (AUC) value to comprehensively evaluate the efficacy of p16 positivity in diagnosing HPV infection. In addition, a funnel plot will used to further evaluate the presence of publication bias.

**Subgroup analysis:** Because the head and neck are divided into many regions, and there are two methods for HPVE6/E7mRNA detection, we expected that the data included in the meta-analysis might be uneven. Therefore, we divided the study into several different subgroups based on factors such as tumor location and the detection methods for HPVE6/E7mRNA set as the gold standard.

**Sensibility analysis:** We will use STATA for sensitivity analysis.

**Country(ies) involved:** China.

**Keywords:** human papillomavirus, squamous cell cancers of the head and neck, immunohistochemical staining, p16, meta-analysis.

**Contributions of each author:**

Author 1 - Huanhuan Wang.

Author 2 - Yuyu Zhang.

Author 3 - Wei Bai.

Author 4 - Bin Wang.

Author 5 - Jinlong Wei.

Author 6 - Ji Rui.

Author 7 - Ying Xin.

Author 8 - Lihua Dong.

Author 9 - Xin Jiang.