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The landscape of circulating tumor HPV DNA and TTMV-HPVDNA for surveillance of HPV-oropharyngeal carcinoma: systematic review and meta-analysis

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Abstract

Background Human papilloma virus (HPV) related cancers of the oropharynx are rapidly increasing in incidence and may soon represent the majority of all head and neck cancers. Improved monitoring and surveillance methods are thus an urgent need in public health.

Main text The goal is to highlight the current potential and limitations of liquid biopsy through a meta analytic study on ctHPVDNA and TTMV-HPVDNA. It was performed a Literature search on articles published until December 2023 using three different databases: MEDLINE, Embase, and Cochrane Library. Studies that evaluated post-treatment ctHPVDNA and TTMV-HPVDNA in patients with HPV + OPSCC, studies reporting complete data on the diagnostic accuracy in recurrence, or in which the number of true positives, false positives, true negatives, and false negatives was extractable, and methods of detection of viral DNA clearly defined.

The meta-analysis was conducted following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines.

The aim of this meta-analysis was to evaluate the sensitivity, specificity, and accuracy of ctHPVDNA and TTMV by ddPCR to define its efficacy in clinical setting for the follow up of HPV-OPSCC.

Conclusion The 12 studies included in the meta-analysis provided a total of 1311 patients for the analysis (398 valuated with ctHPVDNA and 913 with TTMV-HPVDNA). Pooled sensitivity and specificity were 86% (95% CI: 78%-91%) and 96% (95% CI: 91%-99%), respectively; negative and positive likelihood ratios were 0.072 (95% CI: 0.057–0.093) and 24.7 (95% CI: 6.5–93.2), respectively; pooled DOR was 371.66 (95% CI: 179.1–918). The area under the curve (AUC) was 0.81 (95% CI, 0.67–0.91).

Liquid biopsy for the identification of cell free DNA might identify earlier recurrence in HPV + OPSCC patients. At the present time, liquid biopsy protocol needs to be standardized and liquid biopsy cannot yet be used in clinical setting. In the future, a multidimensional integrated approach which links multiple clinical, radiological, and laboratory data will contribute to obtain the best follow-up strategies for the follow-up of HPV-OPSCC.

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Keywords Oropharyngeal squamous cell carcinoma, Liquid biopsy, Circulating tumour HPVDNA, HPV, TTMV-HPVDNA, Follow up

Introduction

Incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising exponentially in high-income countries [1], despite the decreased exposure to classic risk factors associated with the development of head neck cancers, namely cigarette smoking and alcohol consumption. This epidemiological trend can be attributed to an epidemic spread of high-risk oncogenic Human Papillomavirus (HPV) infection, a well-known risk factor for the development of oropharyngeal squamous cells carcinoma [2]. Of the over 200 genotypes currently known, 13 are associated with the development of neoplastic pathology in humans. Among these, the most well-known and studied is the HPV-16, which is responsible for almost 90% of these cases [3]. The increase in incidence of HPV + OPSCC is so exponential that the number of men affected by HPV-OPSCC has surpassed the number of women affected by HPV-related cervical carcinoma, making OPSCC the most commonly HPV-related cancer in industrialized countries [4].

Despite the ongoing evolution of treatment modalities with the introduction of robotic surgery, the diagnostic workup has not evolved for several years [5].

Regarding follow-up, the current National Comprehensive Cancer Network guidelines indicate the execution of imaging at baseline after treatment and clinical assessment at regular intervals for a minimum of five years. Positron emission tomography (PET) at 3 months after completion of chemoradiation is considered standard of care [6]. However, over time, several critical issues have emerged regarding this surveillance modality. For instance, it has been highlighted that the use of PET scans in post-radio chemotherapy treatment is characterized by a high number of false positives [7–9]. PET-CTs have a poor positive predictive value of 30% on 12 week surveillance for HPV-OPSCC [10]. A recent meta-analysis highlighted that PET-CT results were equivocal for 22.5% (95% CI, 12.5–36.9) and equivocal/positive for 34.2% of patients (95% CI, 25.1–44.5) [11].

Even when combining this method with Magnetic Resonance Imaging (MRI), distinguishing between disease persistence and normal post-treatment metabolic response remains complicated [9, 12, 13]. Furthermore, the use of cyto/histological typing through fine needle aspiration in these cases is characterized by a failure rate of approximately 30% [14, 15].

The use of multiple visits leads to increased costs for the national healthcare system and the development of anxiety and depression for the patients [16].

On the other hand, an early and precise disease diagnosis coupled with a timely treatment is likely associated with better overall survival [17].

Due to this gray area in the diagnostic workup, the search for new biomarkers has risen over the years, and an increasing number of studies are investigating the utility of liquid biopsy at diagnosis and during follow up. In detail, circulating tumor HPVDNA (ctHPVDNA) and circulating tumor tissue–modified viral HPV DNA (TTMV-HPVDNA) are emerging as promising biomarkers to improve clinical decision- making in the care of OPSCC patients.

Although several academic groups have developed research- grade circulating tumor HPV DNA (ctHPVDNA) assays, the first commercial ctHPVDNA assay, based on detection of circulating tu- mor tissue–modified viral HPV DNA (TTMV-HPV DNA), became available in the USA in 2020 and allowed for widespread clinical practice to this technology [18].

Previous meta-analyses demonstrated that digital drop PCR (ddPCR) for ctHPVDNA has good accuracy, sensitivity and specificity for first diagnosis of HPV-related OPSCC [19].

However, a recent narrative review on TTMV-HPVDNA and ctHPVDNA development for early detection of cancer recurrence highlights existing knowledge gaps and suggests research that should be prioritized to understand the association between biomarker-based surveillance and patient outcomes [18].

In this setting we elaborate a systematic review and meta-analytic study on ctHPVDNA and TTMV-HPVDNA, to highlight the current potential and limitations of liquid biopsy.

Thus, the aim of this meta-analysis is to evaluate the sensitivity, specificity, and accuracy of ctHPV DNA and TTMV by ddPCR to define its efficacy in the clinical setting for the follow up of HPV-OPSCC.

Materials and methods

Systematic review and meta-analysis were conducted following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE).