HPV+ Non-Oropharyngeal Cancer

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HPV status is a well known prognostic factor for oropharyngeal cancer. However, its predictive role has not been proved yet and HPV positive cases are not treated differently outside of a clinical trial. In non-oropharyngeal cancer, the role of HPV status is not entirely clear and results from observational studies are conflicting.

Keywords: HPV, head and neck cancer

1. Introduction

It is widely known that HPV and p16 are prognostic biomarkers for HPV+ OSCC. However, several studies have pointed out the prevalence of HPV infection in non-oropharyngeal areas, such as the oral cavity, larynx, and oropharynx. More specifically, 3%–5% of oral cavity and laryngeal cancers are HPV+ [1]. The question that arises is whether p16 is a surrogate marker for a transcriptionally active HPV in non-OSCC HPV+ HNSCC. In addition, it is unknown whether p16 and HPV are prognostic factors in non-OSCC HPV+ HNSCC. In a study published in 2011, Harris et al. evaluated the incidence of HPV and p16 positivity in young patients with oral cavity cancer using p16 IHC and HPV ISH and PCR. In this cohort of patients, p16 was expressed in 11 out of 25 patients and p16 expression was significantly associated with relapse free survival (RFS) and OS benefit. However, HPV16 was detected by PCR only in two tumor samples and not detected by ISH in any sample examined [2]. In another retrospective study in a larger cohort of patients with oral cavity cancer (409 patients), HPV was determined using high-risk (HR)-HPV *E6*/*E7* oncogene expression by RT-PCR and p16 was assessed by IHC. It was shown that 3.7 % of patients were HPV16 positive and 2.2% were positive for other HR HPV subtypes. P16 IHC had good sensitivity (79.2%), excellent specificity (93%) and high negative predictive value (98%) but low positive predictive value (41.3%) for HPV detection [3].

2. Studies status

Studies suggest that there are differences regarding the role of p16 and HPV positivity in non-OSCC HNSCC. Chung et al assessed HPV status by ISH and p16 expression by IHC in patients with non-OSCC HNSCC (laryngeal, oral cavity and hypopharyngeal cancer) included in three RTOG studies (0129, 0234, 0522) [4]. It was shown that p16 was not a good surrogate marker for HPV positivity, since it was positive in 14.1%, 24.2% and 19% of cases in the RTOG 0129, 0234, and 0522 respectively compared to 6.5%, 14.6% and 6.9% of cases with HPV ISH positivity. In addition, p16 was found to be a prognostic biomarker for non-OSCC HNSCC; however, it is not so profoundly associated with improved outcome compared to HPV+ OSCC. Of note, p16 negative OSCC and non-OSCC cases have similar OS and PFS. HPV positivity was not shown to be prognostic in non-OSCC cases [61]. In another study that was focused on laryngeal cancer, 324 samples were assessed for p16 status by IHC and HPV status by RNA-ISH. The incidence of p16 positivity was 6.9% and only seven cases were found to be HPV+. Interestingly, neither p16 nor HPV were prognostic [5].

More recently, Fakhry et al. retrospectively tested HNSCC cases diagnosed between 1995 and 2012 for HPV status using DNA and RNA-ISH and p16 status by IHC. In non-OSCC patients, p16 and HPV status were not found to be prognostic [6]. Similarly, De Souza et al. showed no significant prognostic role of HPV/p16 status in 845 non-OSCC cancer patients from Brazil, US and Europe [7]. In contrast, Ko et al examined a large cohort of patients with non-OSCC HNSCC (19,993) from the National Cancer Database (NCD) and showed a significant survival benefit in HPV+ non-OSCC patients [8]. This survival benefit was confirmed only for hypopharyngeal and locally advanced laryngeal primaries in a retrospective analysis of patients with known HPV status included in NCD who were diagnosed between 2010 and 2013 [9].

Altogether, studies focusing on prognostic impact of HPV status in non-OSCC HNSCC have shown conflicting results. In addition, p16 has been shown to be a poor surrogate biomarker for HPV infection in these cases. Thus, routine HPV testing is not recommended for non-OSCC cases. Prospective studies are required to elucidate the potential role of HPV status in non-OSCC HNSCC.

HPV+ OSCC currently represents a global epidemic, a widely recognized increasingly prevalent entity. Similar to cervical cancer, the majority of HPV+ cases are attributed to high-risk HPV16 subtype. P16 positivity serves as a surrogate marker for HPV infection and is an independent prognostic factor for those patients. In addition to the differences in risk factors and clinical presentation, HPV+ OSCCs display a substantially improved survival. Thus, HPV status is now routinely used as a stratification factor in clinical trials and is a clinically relevant parameter for patient consultation. This has been depicted in the new edition of AJCC/TNM staging that includes a separate staging manual for HPV+ OSCC. However, randomized trials evaluating de-intensification strategies substituting cisplatin with cetuximab have failed to show non-inferiority in terms of outcome and current guidelines do not recommend a different treatment approach for HPV+ OSCC. HPV status has no confirmed prognostic role for non-OSCC HNSCC. Future studies are necessary to establish the role of de-escalation treatment approaches in HPV+ OSCC. Until then, the cornerstone of treatment is an interdisciplinary team approach with emphasis on quality of life during the treatment and survivorship periods.

References

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