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review

HPV RELATED HEAD AND NECK CARCINOMA: A SHORT LITERATURE REVIEW ON TREATMENTS

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SUMMARY
Human papillomavirus (HPV) is responsible for a growing subset of oropharyngeal squamous cell carcinomas (OPSCCs) in the United States and abroad. At the time of the primary diagnosis, HPV-positive tumor status is associated with improved response to chemo-radiation, progression-free survival, and overall survival. Patients with HPV-related cancer look very different than the prototypic patient with tobacco-related SCC of the oral cavity. They tend to be white males that are younger, of higher socioeconomic status, and more highly educated. Moreover, they are often non-smokers who do not abuse alcohol. HPV-related SCC has a strong predilection for the oropharynx, particularly the lingual and palatine tonsils. HPV-16 genotype is the most common genotype, accounting for up to 92% of HPV-positive oropharyngeal squamous cell carcinomas. The need for routine HPV testing of oropharyngeal carcinomas is urgent and compelling. First, HPV status is a powerful indicator of patient prognosis. HPV positivity correlates with a lower risk of tumor progression and death, reflecting in part an enhanced sensitivity to ionizing radiation with or without chemotherapy. In our understanding, HPV status, which is easily acquired with routine investigations, should be included in the standard operational procedures for the diagnosis and treatment of head and neck cancer patients.

Key words: oropharyngeal cancer, HPV, radiochemotherapy.

Introduction

Human papillomavirus (HPV) is responsible for a growing subset of oropharyngeal squamous cell carcinomas (OPSCCs) in the United States and abroad (1-3). At the time of the primary diagnosis, HPV-positive tumor status is associated with improved response to chemo-radiation, progression-free survival, and overall survival (OS) (4, 5). Despite improved prognosis, locoregional and distant metastatic recurrences still pose a significant disease burden. Within 3 years of diagnosis, approximately 24 to 27% of patients with HPV-positive OPSCC experience disease recurrence (5, 6). Although the unique clinical features of HPV-positive OPSCC have been well characterized, few studies have addressed the clinical implications of recurrent disease (7).

Earlier reports have suggested unusual clinical presentations for HPV-associated recurrences (8-11). Recent prospective data from Radiation

Therapy Oncology Group trials demonstrated that site distribution and time to disease recurrence does not differ by HPV tumor status (4).
Previous studies have revealed the correlation between histopathologic grading and prognostic parameters including lymph node involvement, metastases to neural tissues and other organs, and recurrences after treatment. For example, the poorer grading is associated with regional lymph node invasion, extracapsular spreading, and perineural invasion (7).
Cancers of the oropharynx are unique in that HPV associated OPSCCs represent a distinct clinical and prognostic entity compared to tobacco-associated and alcohol associated OPSCCs. Epidemiologically, these cancers often occur in younger patients (9) and have significantly better and locoregional control rates than non-HPV associated or smoking-related OPSCC (12).
The HPV-associated OPSCCs manifest different clinical and biological characteristics in comparison with the HPV-negative OPSCCs. In addition, patients with HPV-positive OPSCCs have a favorable prognosis in comparison with those with HPV-negative OPSCCs, and mutations associated with tumor suppressor genes like p53 are relatively infrequent in the former (13).
The increased incidence of HPV-associated head-and-neck cancers could be attributable to changes in sexual norms, such as increased oral sex practices and more oral sex partners However, HPV-positive OPSCCs are also documented in patients reporting very few oral sexual partners, with almost 8-40% of the patients reporting never having had oral sex. Thus, oral sex may not be the only significant attribute, and sexual behavior as well as other factors must be further evaluated (14).

HPV-Related Squamous Cell Carcinoma is a Distinct Variant of HNSCC

Patients with HPV-related cancer look very different than the prototypic patient with tobacco-related SCC of the oral cavity (3, 15, 16). They tend to be white males that are younger, of higher socioeconomic status, and more highly educated. Moreover, they are often non-smokers who do not abuse alcohol (14, 17). HPV-related SCC has a strong predilection for the oropharynx, particularly the lingual and palatine tonsils (18). HPV-16 genotype is the most common genotype, accounting for up to 92% of HPV-positive oropharyngeal squamous cell carcinomas. The unique spectrum of molecular alterations associated with HPV infection is of both biologic and diagnostic relevance. A key step in HPV-related carcinogenesis is the transcription of the viral oncoprotein E7. E7 is known to functionally inactivate the Retinoblastoma (Rb) gene product, causing a perturbation of other key components of the critical Rb pathway. As one example, functional inactivation of Rb by E7 is known to induce upregulation of the p16 tumor suppressor gene product (19) reaching levels that can be readily detected by routine immunohistochemistry. Indeed, p16 immunohistochemistry is now commonly used as a diagnostic assay to differentiate those oral SCCs that are HPV-related from those that are not (18).
The Hybrid Capture 2 assay is a commercially available microplate analysis approved by the US Food and Drug Administration for the detection of HPV DNA as part of cervical cancer screening (17, 20). It is a liquid-phase hybridization assay that uses an RNA probe mixture for the detection of up to 13 high-risk HPV types. Studies have shown that the assay is highly sensitive and specific when it comes to detecting high-risk HPV in cytologic brushes from the uterine cervix (20), but its use as a tool to evaluate the HPV status of HNSCCs is largely unexplored. The development and implementation of HPV detection strategies that are transferrable to clinical cytologic specimens is compelled by factors that restrict tissue access for HPV testing. The first is related to tumor size. HPV-related HNSCCs are often small and deeply concealed within the crypts of the lingual or palatine tonsils. A second is related to evolving treatment practices. HPV related HNSCCs tend to be sensitive to radiation and chemotherapy such that surgical removal is often unwarranted (21). A

third is related to current diagnostic practices. The routine use of FNAs for establishing a diagnosis of HNSCC in patients with lymph node metastases renders subsequent tissue acquisition unnecessary and excessive (22).

Consideration in therapy

The need for routine HPV testing of oropharyngeal carcinomas is urgent and compelling. First, HPV status is a powerful indicator of patient prognosis. HPV positivity correlates with a lower risk of tumour progression and death, reflecting in part an enhanced sensitivity to ionizing radiation with or without chemotherapy (23). Second, knowledge of HPV status is compulsory for meaningful comparison of treatment responses for patients enrolled in clinical trials. The direction of current clinical trials, in which patient selection for specific therapies is predicated on HPV tumor status, dramatically heightens the stakes for accurate HPV detection.

For patients with early-stage HPV-positive head and neck squamous cell carcinoma, a single-modality treatment by either surgery or radiation is sufficient, as documented by a favourable prognosis in these patients. Radiation therapy is more commonly used, but surgery is preferred in selected cases-for example, for tonsillar cancers that are now often HPV related. Minimally invasive techniques such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have been used in carefully selected early oropharyngeal cancers, with excellent oncologic and functional outcomes (20). For locally advanced cancers, surgery could be combined with adjuvant radiation therapy, especially in scenarios with the concomitant presence of additional risk factors, including positive surgical margins, bone erosion, lymph-vascular involvement, and extracapsular lymph node extension. However, care needs to be exercised to ensure that a combination approach as described above is not used for cancers localized to critical areas in the oral cavity, since the involvement of surgery could result in impairment of the normal functioning of that area (20). This is exemplified in a scenario where, in tumors localized to the larynx, surgical resection of the tumor could definitely result in speech impairment in the patient (24). In these conditions, only non-surgical approaches are favoured; thus, a concurrent chemo-radiotherapy with high-dose cisplatin is widely administered to patients with advanced laryngeal cancer, resulting in localized control of the tumor with preservation of the larynx. Therapies encompassing concurrent chemo-radiation have been shown to result in significant decreases in rates of local-regional recurrence and death, though the occurrence of distant metastases was not reduced (25).

Discussion

HPV is responsible for an oncologic epidemic (26): over 60% of oral squamous cell carcinoma (OSCC) was estimated to be secondary to HPV in the 2010s *versus* 16% in the 1980s. 2 OSCC associated with HPV positivity has a distinct, favorable, prognosis following primary chemoradiotherapy; HPV positivity is the single strongest prognostic factor for OSCC (27, 28). Similarly, smoking status is known to be an independent risk factor for the development of OSCC; HPV positivity in the setting of at least 10 pack year smoking history behaves prognostically as an intermediate risk group.

That HPV infection enhances the overall survival is indisputable. The diagnosis of HPV positivity implies a significant better outcome with a half risk of death compared to negative HPV status (4).

One reason why HPV could be involved in carcinogenesis is that high risk HPVs can develop their transforming potential through two viral oncoproteins, E6 and E7. These oncogenes are able to functionally inactivate the tumour suppressor genes p53 and pRB (29-31). On the other side, mutations of p53 were significantly lower in HPV-positive SCCs than in HPV negative tumours (10) which could be an explanation why HPV-positive carcinomas show an improved re-

sponse to therapy and overall survival. Perrone et al. observed that patients with HPV-positive squamous cell carcinomas show significantly less p53 mutations (32), which leads to the suggestion that the decreased overall survival in HPV negative patients is due to the more frequent p53 mutations. Friesland et al. investigated 34 patients for HPV and p53 status and could not correlate HPV and p53 status to response to radiation, but observed a tendency toward a better overall survival for HPV-positive patients, which was significant for advanced stage tumors (23). No difference in survival was detected for p53-positive or negative tumors. That HPV-positive carcinomas show a better response to radiotherapy might not be attributed to the increased radio sensitivity but to a less genetic instability.

In summary we could observe a considerable better response to treatment including concomitant radiochemotherapy or radioimmunotherapy or even radiation alone in HPV-positive patients compared to the HPV-negative group in an Eastern Austrian patient collective. HPV status, which is obligatory to determine in cervical cancer, is also, as it seems, of utmost importance in patients with head and neck malignancies as it is a very strong predictor of therapeutic outcome after radiochemotherapy. In clinical routine this could mean that the decision for a HPV-negative patient to undergo surgery is made even in an advanced state, or vice versa, in the case of positivity is more likely to go for radiochemotherapy. In our understanding, HPV status, which is easily acquired with routine investigations, should be included in the standard operational procedures for the diagnosis and treatment of head and neck cancer patients (21).

References

1. Chaturvedi AK, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26(4):612-9.
2. Chaturvedi AK, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.
3. D'Souza G, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356(19):1944-56.
4. Fakhry C, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol. 2014;32(30):3365-73.
5. Ang KK, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24-35.
6. Ang KK, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol. 2014;32(27):2940-50.
7. Pfister DG, Fury MG. New chapter in our understanding of human papillomavirus-related head and neck cancer. J Clin Oncol. 2014;32(30):3349-52.
8. Huang SH, et al. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. Int J Radiat Oncol Biol Phys. 2012;82(1):276-83.
9. Huang SH, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. Oral Oncol. 2013;49 (1):79-85.
10. Ruzevick J, Olivi A, Westra WH. Metastatic squamous cell carcinoma to the brain: an unrecognized pattern of distant spread in patients with HPV-related head and neck cancer. J Neurooncol. 2013;112(3):449-54.
11. Muller S, et al. HPV positive squamous cell carcinoma of the oropharynx. Are we observing an unusual pattern of metastases? Head Neck Pathol. 2012;6(3):336-44.
12. Forastiere A, et al. NCCN practice guidelines for head and neck cancer. National Comprehensive Cancer Network. Oncology (Williston Park). 1998;12(7A):39-147.
13. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer. 2011;11(1):9-22.
14. Gillison ML, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709-20.
15. Gillison ML, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407-20.
16. Smith EM, et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer. 2004;108(5):766-72.
17. Begum S, et al. Detection of human papillomavirus in cervical lymph nodes: a highly effective strategy for localizing site of tumor origin. Clin Cancer Res. 2003;9 (17):6469-75.
18. El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: a guide for interpretative relevance and consis-

tency. Head Neck. 2012;34(4):459-61.
19. Strati K, Lambert PF. Role of Rb-dependent and Rb-independent functions of papillomavirus E7 oncogene in head and neck cancer. Cancer Res. 2007;67(24):11585-93.
20. Begum S, et al. Detection of human papillomavirus-16 in fine-needle aspirates to determine tumor origin in patients with metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res. 2007;13(4):1186-91.
21. Agrawal Y, et al. Oral human papillomavirus infection before and after treatment for human papillomavirus 16-positive and human papillomavirus 16-negative head and neck squamous cell carcinoma. Clin Cancer Res. 2008;14(21):7143-50.
22. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clin Cancer Res. 2009;15(22):6758-62.
23. Lill C, et al. Survival of patients with HPV-positive oropharyngeal cancer after radiochemotherapy is significantly enhanced. Wien Klin Wochenschr. 2011; 123(7-8):215-21.
24. El-Mofty SK, Zhang MQ, Davila RM. Histologic identification of human papillomavirus (HPV)-related squamous cell carcinoma in cervical lymph nodes: a reliable predictor of the site of an occult head and neck primary carcinoma. Head Neck Pathol. 2008;2(3):163-8.
25. Bishop JA, et al. HPV analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. Am J Surg Pathol. 2012;36(1):142-8.
26. Ding XW, Wu JH, Jiang CP. ABCG2: a potential marker of stem cells and novel target in stem cell and cancer therapy. Life Sci. 2010;86(17-18):631-7.
27. Kong D, et al. Cancer Stem Cells and Epithelial-to-Mesenchymal Transition (EMT)-Phenotypic Cells: Are They Cousins or Twins? Cancers (Basel). 2011;3(1): 716-29.
28. Facompre N, et al. Stem-like cells and therapy resistance in squamous cell carcinomas. Adv Pharmacol. 2012;65:235-65.
29. Fakhry C, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-9.
30. Friesland S, et al. Human papilloma virus (HPV) and p53 immunostaining in advanced tonsillar carcinoma—relation to radiotherapy response and survival. Anticancer Res. 2001;21(1B):529-34.
31. Baldassarri R, et al. Detection and genotype of high-risk human papillomavirus in fine-needle aspirates of patients with metastatic squamous cell carcinoma is helpful in determining tumor origin. Am J Clin Pathol. 2015;143(5):694-700.
32. Perrone F, et al. Molecular and cytogenetic subgroups of oropharyngeal squamous cell carcinoma. Clin Cancer Res. 2006;12(22):6643-51.

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