HPV-related HNC – new challenge and hope for head and neck cancer subjects

Krzysztof Szyfter¹, Kiwerska Katarzyna¹, Małgorzata Wierzbicka¹, ²

¹ Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland
² Department of Otolaryngology, Head and Neck Surgery, Poznań University of Medical Sciences, Poland

ABSTRACT
Recent years there are observed substantial changes in epidemiology of head and neck cancer. An incidence of laryngeal cancer is declining as a consequence of decreased tobacco smoking. Contrary, oropharyngeal cancer associated with HPV infection transmitted on sexual way is becoming much more frequent. The latter one is characterized with a better prognosis that most likely does not require intensive therapy. De-escalation of therapy in case of HPV-associated tumor is a matter of current studies.

Keywords: HPV-related cancer, head and neck, epidemiology, treatment.

A casual involvement of Human Papilloma Virus (HPV) infection in gynecological cancer is being known for a long time. Owing to the experimental and intellectual contribution of Harald zur Hausen (awarded by the Nobel prize at 2008) it has become clear that HPV preferentially penetrates mucosa that can be followed by tumor formation in genital, anal and head and neck regions of both sexes [1]. The latter remains in the frame of our research and clinical interest.

Head and neck cancer mostly affecting squamous cells (abbreviation: HNSCC) is the 6th leading cause of world cancer mortality. Tobacco smoking and abusing of strong alcoholic beverages have been the well recognized causing factors. The main group of tobacco smoke carcinogens include polycyclic aromatic hydrocarbons, aromatic amines, N-nitrosamines and reactive oxygen species. An intensive anti-smoking campaign have produced a decline of tobacco smoking at least in the developed countries that was followed by changes in epidemiologic data concerning HNSCC [2]. A detailed analysis has shown a decrease of laryngeal cancer and increase of oropharyngeal cancer incidence that altogether indicated for a stagnation of an incidence of HNSCC [3]. The noticed trends were explained with by a growing number of HPV-associated HNSCC [3–5]. HPV infection affects oropharynx much more frequently than larynx. Within oropharynx tonsils [6] and the base of tongue were found to be the primary targets for HPV infection [7]. However, the data concerning a partition of HPV-associated HNSCC cancer are not very convergent for two reasons. First, a percentage of HPV(+) HNSCC is constantly growing. As an example the meta-analysis done by Termine et al. [8] established a prevalence of HPV infection in oropharyngeal cancer for 38.1% as compared to 24.1% in not site-specific HNC. Next, the established techniques for HPV determination are operating on protein, RNA and DNA level exploring a battery of techniques including immunohistochemistry, Southern bloting, PCR, and in situ hybridization [9]. The most commonly applied technique is derived from an observation concerning over-expression of p16 protein highly correlating with HPV integration. Though, p16 staining is serving...
as surrogate but highly reliable marker of HPV infection [10, 11]. It is clear that the techniques vary with their sensitivity, accuracy, complexity and costs [9, 10]. To summarize, a prevalence of HPV-associated oropharyngeal cancer could be estimated for roughly almost 50%, when a casual impact of HPV in laryngeal cancer is estimated for 5% only [12].

Contrary to inhaled tobacco smoke carcinogens HPV is sexually transmitted [13]. Further, it was found that sexual history is notable for by multiple sexual partners and focus on oral sex. For this and other reasons it affects mostly young adults [14, 15]. Altogether, at presentation it appears a new face of head and neck patient that is much younger than typical patients at their 6th–7th decade of life, lacking commonly recognized risk factors as drinking and tobacco smoking, having a reasonably style of life and enjoying rather high economic status [15]. It is to remind that in the typical HNC patients a social margin is having a good share.

The mechanism of HPV-associated carcinoenic transformation was established to be different than that following activity of tobacco smoke carcinogens. Human papilloma viruses form a group of over 150 members that could be divided according to their oncogenic potential for high- and low-risk HPVs. HPV16 and HPV18 represent high risk types and are found most frequently in human tumors. A fully recognized functional structure of HPV16 circular DNA encodes the long control region (LC) and genes coding early proteins (E1–E7) and two late proteins (L1 and L2) (Figure 1). HPVs infect basal epithelial cells characterized with a high proliferation capacity. Infected cells provide two options: viral latency that is a type of abortive infection or integration of viral DNA sequence into human genome. Integration is necessary to maintain expression of viral proteins [16–18]. At this point a cell could be driven onto oncogenic transformation (Figure 2). Integrated viral genome does not affect directly host genetic information that is the case for chemical carcinogenesis. Tobacco smoke carcinogens frequently mutate TP53 gene bearing a function of tumor suppressor gene. The protein coded by mutated TP53 gene is losing its function on control the cell cycle and does not provide time sufficient to remove DNA lesions. Contrary, HPV integration leaves TP53 gene undamaged, producing fully functional TP53 protein. However, E6 viral protein inactivates TP53 protein via complex formation when E7 is responsible for inactivation of Rb. On this way the whole TP53/Rb anticancer pathway is blocked [19, 20]. Further, is was shown that the number a viral copy number and viral integration sites are having an impact on progression of cancer [20, 21]. Another consequence of HPV integration is an appearance of genomic instability manifested by centrosome dysregulation, division errors, chromosome rearrangement and replication stress that altogether promotes oncogenesis [16, 18, 22].

Later on, an attention was paid on HPV-positive HNSCC subjects who were also current or former tobacco smokers. Mirghani et al. [23] using next-generation sequencing examined mutation profile in 39 genes known to be most frequently mutated in HNSCC. It was established that smoking does not contribute to an increased level of mutations in HPV-positive HNC subjects. The finding is in agreement with the publication of Farsi et al. [24] who claim a lack of synergy between HPV infection and tobacco smoking that are independent etiological agents in HNSCC. Nevertheless, the research group of Thomas Carey [25] who were following up the group of already treated HPV-positive HNSCC subjects have found that current tobacco smokers as compared to never-tobacco users are at higher risk of disease recurrence.

Concerning characteristics of HPV-positive HNSCC subjects are lacking commonly recog-
nized risk factors as drinking and tobacco smoking, having a reasonable style of life and enjoying rather high economic status and are younger than typical patient [15]. Young age as well as sexual activity was confirmed in other studies as e.g. [26]. Moreover, high risk HPV was detected significantly more often than in aged patients [27].

A favorable prognosis for HPV-positive HNSCC compared to HPV-negative was recognized early. The contributing factors are smaller size tumors at presentation, good health conditions that offers a longer disease-free period and longer survival [28]. Such findings published in numerous papers have been confirmed in a large meta-analysis [29]. Altogether a less severe progression and a better prognosis in case of and HPV-positive HNSCC subject have implicated a question of therapy de-intensification. Nowadays this is one of the topic questions in oncological laryngology. Although there is no agreement about sensitivity to radio- and chemotherapy [compare: 29 v. 30] in HPV-positive HNSCC subjects a therapy avoiding acute toxicity is being suggested [30–32]. Nevertheless, so far as official recommendations do not differentiate between HPV-positive and -negative HNSCC, there is no safe way both for patients treatment as well for clinicians civil responsibility.

So, nowadays laryngologists are recognizing two types of HNSCC dependently on its origin. The first one is derived from an exposure onto chemical carcinogens most commonly present in tobacco smoke when the second results from HPV infection. Progression of the HPV-associated is connected with a better curability and longer survival but on optimal strategy of therapy requires still more studies. The other consequence is that highly heterogenous group of HNSCC is becoming even more differentiated and oropharyngeal and laryngeal cancées should be definitively recognized as separate entities.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References


