Human Papillomavirus (HPV): The New Head and Neck Cancer Epidemic

The incidence of head and neck cancer (HNC) has been gradually increasing over the last 3 decades. Although certain subsets of HNC (such as larynx cancer) have decreased in incidence in parallel with the reduction in smoking, rates of oral cavity tumors (including tongue and tonsil) have risen among young (<45 years old) men and women. In addition to the classic risk factors of tobacco and alcohol use (that used to be responsible for the majority of HNC) recent data have linked infection with a virus to cases of HNC especially from the oral cavity and related sites. The virus strains responsible belong to the human papillomavirus family (HPV). HPV is the main cause for cervix cancers in women, and the HPV subtypes associated with HNC are rather similar with those causing cervical cancer. Subtype HPV16 accounts for the majority of HPV-positive cases (> 65% of oral tumors, >80% of oropharynx cancers, and 70% of laryngeal cases), with HPV18 having a far second place (around 5-8% of HPV-positive cases). Epidemiological data seem to suggest that sexual transmission is important but other transmission routes are under investigation.

It has been shown that HPV strains (particularly HPV16) are able to transform and immortalize epithelial cells (make them cancerous) in laboratory experiments. These effects are caused by the E6 and E7 viral capsid proteins, which truly function as if they were oncogenes (genes promoting cancer). Once the virus enters the cells and starts multiplying, the E6 and E7 capsid proteins (essentially are the bricks that make the outer membrane or cover of the virus) inactivate two key genes, P53 and RB that in normal circumstances are tumor suppressor genes. The interpretation we have for this is that the HPV virus induces permanent multiplication of infected cells (to perpetuate itself) by “taking the brakes off” infected cells, that is, by inactivating proteins such as P53 or RB whose normal function is to control and limit growth. This inactivation leads to protein P16 over-expression, and this is important because detection of P16 has been utilized as a surrogate for HPV infection, in part because it is a simpler marker to detect in a clinical setting. Another aspect further supporting that HPV is an early, causative event of HNC is that genetic analysis typically find HPV genetic material integrated in basically all cells comprising a tumor, which indicates it was present in the original cell that gave rise to it. Whereas there is hope that vaccination of young girls to prevent cervical cancer will decrease HNC as a secondary event, this has yet to be proven. It is unknown at this point whether there is any influence of the immune system on already established cancers.

Accumulating evidence suggests that HPV status is an important prognostic factor, and that patients with HPV positive head and neck cancers have a favorable outcome, compared with those HNC initiated by alcohol or tobacco that are HPV negative. In a recent prospective multi-centre clinical study patients with HPV positive tumors had better responses after neoadjuvant chemotherapy (82% vs. 55%), and after chemotherapy plus radiation therapy (84% vs. 57%) compared to patients with HPV negative tumors. Subjects with HPV positive cancers had a 33% better overall survival of 33%, and lower risk of progression compared to patients with HPV negative tumors.
The explanation for this better outcome may in part be that unlike tobacco and alcohol-related HNC (where mutations in p53 and RB are present and these pathways are inactivated permanently), in HPV-related HNC these control/override mechanisms are only functionally suppressed. When chemotherapy and radiation therapy hit the cancer cells and induce DNA damage, these pathways are able to become re-activated, and “put the brakes” on the cancer cell again, leading to its arrest or programmed death (apoptosis). Another reason why patients with HPV-related HNC have a better outcome is that they are usually younger and therefore can tolerate therapy better overall, be it surgical therapy with improved healing, chemotherapy with improved blood count recovery, or radiation therapy where healthier patients are at a significantly lower risk of developing severe complications such as dehydration. This leads to less interruptions in therapy and a higher percentage of patients receiving all planned treatments, and possibly contributes to a better overall outcome. A third factor is that the prevalence of heavy smoking or alcohol use history is also lower, and thus these patients have less associated co-morbidities, such as liver, cardiac or lung disease, that have historically limited the intensity of therapy.

On the other hand, because patients with HPV-related cancer are younger and healthier, they have a longer life expectancy, and this has several implications. The first is that long-term risk of relapse is still a significant concern. This is because even if the risk of relapsing is (and this is a simplified version for clarity) reduced by a third or half, considering patients live 3 to 5 times longer, the overall number of relapses could be the same or higher. We currently do not have sufficient information as to the long-term (10 or 20-year) natural history of this relatively new class of HNC. The second aspect is that the long-term side effects of therapy will likely become more relevant as a deciding factor in planning the therapy. Advances in supportive medication for chemotherapy and (more importantly) improvements in sparing normal tissues when delivering radiation therapy will very possibly ameliorate those long-term side effects. We are pending the results of 1) long-term follow-up studies and 2) clinical trials addressing whether therapy should be significantly different depending on HPV status.

Overall these data fully support considering HPV-related HNC as a completely distinct epidemiological, biological and clinical entity, with features that are specific and rather different from HPV-unrelated HNC. Much more research and data will be necessary to fully understand how much therapy is appropriate for each individual patient, modulating the intensity to find the right balance to achieve maximal cure with minimal side effects and impact on quality of life.

Finally, the better prognosis and treatment responses to chemotherapy and radiotherapy by HPV+ tumors may mean that HPV status detection is required to better plan and individualize patient treatment regimes. This is especially important for HNC from the oral cavity and oropharyngeal regions, where HPV testing will very likely be soon considered part of any routine assessment.

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