The role of human papillomavirus in head and neck cancer

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Over the last 20 years, there has been increasing awareness of a subset of squamous cell carcinomas of the head and neck (HNSCC), i.e. HPV-positive HNSCC. These cancers seem to differ somewhat from HPV-negative HNSCC. Patients with HPV-positive HNSCC tend to be younger and have a lower intake of tobacco and alcohol. Distinct molecular profiles separate them from HPV-negative cancers and show similarities with HPV-positive cervical SCC. There is evidence that HPV-positive HNSCC is a sexually transmitted disease. Patients with HPV-positive HNSCC are often diagnosed at a late stage with large cystic lymph nodes in the neck. HPV-positive HNSCC show an affinity for the oropharynx, especially the tonsils and the base of the tongue, and tend to show low differentiation histopathologically. There is a better prognosis regardless of the treatment regimen for HPV-positive HNSCC compared with HPV-negative HNSCC, and this seems to be related to the immune system. Whether the new vaccines for HPV will protect not only against cervical cancer but also against HPV-positive HNSCC remains unknown.

Key words: Human papillomavirus; head and neck cancer; tonsil; immune system; prognosis.

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Approximately 1100 persons in Denmark are diagnosed with squamous cell carcinomas of the head and neck (HNSCC) each year. More than 21 000 patients within the European Union die from cancer of the oral cavity and pharynx each year (1). Alcohol and tobacco are disposing factors for developing this type of cancer, but HPV also is now known to be associated with head and neck cancer, especially SCC of the oropharynx (tonsils and base of the tongue). There are indications that the prevalence of HPV-induced head and neck cancers is increasing, while the prevalence of tobacco- and alcohol-induced cancers is declining (2).

HPV-positive HNSCC appears to be distinct from HPV-negative HNSCC with regard to a number of different characteristics, and in the future we may have to look at these two types of cancers separately, both from a scientific, diagnostic, epidemiological and clinical point of view but also with regard to treatment.

This paper provides a review of recent data linking HPV to HNSCC and the distinct molecular and clinical features of HPV-positive HNSCC.

The involvement of human papillomavirus (HPV) in head and neck carcinogenesis was first suggested by Syrjanen in 1983 (3–5). Prior to this, from 1974 to 1977, zur Hausen suggested that cervical cancer may arise from the same virus as is found in condylomata acuminata, i.e. HPV (6–8). Today it is well established that the infection with specific types of HPV can cause cervical cancer. More than 95% of cervical cancer biopsies contain high-risk HPV genomes (9).

Vaccination against HPV allows us to state that essential precursor lesions of this cancer
type are effectively prevented (10, 11). High-risk HPV infection has also been associated with anogenital carcinomas including cervical, anal, vulvar and penile cancers, and more recently breast cancer (12).

Since Syrjanen’s first proposal regarding the involvement of HPV in head and neck cancer, several other studies have demonstrated HPV in oral cavity, pharyngeal and laryngeal SCC. The incidence varies considerably depending on the population studied, location of the tumours and the methods used for identification.

The HPV types (most often HPV 16 and occasionally HPV18) identified in HPV-positive tonsillar SCC are similar to those found in cervical cancers.

METHODS – SEARCH STRATEGY

A systematic review of the literature was conducted using the NIH PubMed search engine and the following Mesh words: papillomavirus, and head and neck neoplasms. Furthermore, a search was made using the words HPV in ‘All Fields’ and/or head and neck cancers in ‘All Fields’. Only studies published in English have been considered, especially those within the last 10 years.

MOLECULAR FACTORS

HPV-positive HNSCC seem to have a different molecular profile compared with that of HPV-negative HNSCC. In addition, HPV-positive HNSCC share some similarities with cervical carcinomas.

The HPV genome is comprised of three major regions: the long control region, the early (E1-8) genes and the late (L1-2) genes. High-risk oncogenic subtypes HPV-16, 18, 31, 33 and 35 have been shown to be capable of transforming oral epithelial cells through the viral oncoproteins E6 and E7 (13). The function of E6 is discussed in Chow, Broker and Steinberg (14) and Pim and Banks (15). E6 binds to a cellular ubiquitin/protein ligase, E6–AP, and simultaneously to the tumour suppressor protein p53, resulting in ubiquitination of p53 and its subsequent proteolytic degradation.

The function of E7 is also discussed in Chow, Broker and Steinberg (14) and Pim and Banks (15). E7 binds and destabilizes the tumour suppressor retinoblastoma protein (pRb), preventing it from binding to the E2F transcription factor and thereby promoting cell cycle progression. This functional inactivation of pRb results in a reciprocal overexpression of p16 tumour suppressor protein p16INK4A. The HPV-positive tonsillar SCC share a disruption of the pRb pathway as a common biological marker. By immunohistochemistry (IHC), most HPV-positive HNSCC show p16 overexpression. In non-HPV-related HNSCC, continuous tobacco and alcohol exposure can lead to mutational loss of the TP16 and TP53 genes. These early neoplastic events are seen in up to 80% of HNSCC and cause uncontrolled cellular growth (16). The expression of p53 and bcl-2 is not associated with HPV-positive oral cavity SCC (17) and mutations in TP53 are rarely seen in HPV-positive tumours compared with HPV-negative tumours (18, 19). There seems to be an inverse relationship between epidermal growth factor receptor expression and HPV status (20, 21).

Genetic signatures of HPV-positive oropharyngeal SCC have been shown to be different from those of HPV-negative oropharyngeal SCC, and, in addition, distinct chromosomal alterations were of prognostic significance, reflecting a possible difference in tumour development and progression (22). Parallel to this, gene expression profiles show a different pattern in HPV-positive oropharyngeal cancers compared with HPV-negative oropharyngeal cancers (23).

Pyeon et al. carried out genome-wide expression profiling comparing HPV-positive and HPV-negative HNSCC with cervical cancers (24). This revealed that HPV-positive HNSCC and cervical cancers differed in their patterns of gene expression but shared many changes when compared with HPV-negative HNSCC. Notably, HPV-positive HNSCC and cervical cancers were upregulated in their expression of a distinct and larger subset of cell cycle genes compared with HPV-negative oropharyngeal cancers. Moreover, HPV-positive cancers overexpressed testis-specific genes that are normally expressed only in meiotic cells. Many, although not all, of the hallmark differences between HPV-positive HNSCC and HPV-negative HNSCC were a direct consequence of HPV and, in particular,
the viral E6 and E7 oncogenes. This included a novel association of HPV oncogenes with testis-specific gene expression (24).

To summarize, at the molecular level, HPV-positive HNSCC differ from HPV-negative HNSCC and similarities exist between HPV-positive HNSCC and HPV-positive cervical SCC.

THE INFLUENCE OF TUMOUR LOCATION AND METHODS USED FOR HPV PREVALENCE ANALYSIS

A serious problem in HPV research is that there is no consensus as to how to identify HNSCC caused by HPV. This may undermine the true importance of HPV for HNSCC patients. There are many assay variables that differ between studies, making it difficult to compare various studies and to generalize from the results.

The frequencies of HPV-positive tumours in HNSCC show considerable variation in published studies. Some studies report frequencies of 0% (25, 26) in oral and laryngeal carcinomas, whereas others report up to 93% in oropharyngeal carcinomas (2). In a meta-analysis by Termine et al. (27), the pooled prevalence of HPV DNA in the overall samples was 34.5%, in oral cavity SCC (OSCC) it was 38.1%, and in non-tumour site-specific HNSCC it was 24.1%. Regarding the detection methods, PCR-based studies report a higher prevalence rate than for in situ hybridization (ISH)-based rates (34.8 vs 32.9%) especially in the OSCC subgroup (OSCC PCR-based: 39.9%) (27).

In a meta-analysis, Hobbs et al. found that the association between HPV16 and cancer was the strongest for the pharyngeal tonsils (OR: 15.1), intermediate for the oropharynx (OR: 4.3), and weakest for the oral cavity (OR: 2.0) and the larynx (OR: 2.0) (28).

Besides the influence of tumour site and technical aspects on outcome of the analyses, different results may be obtained when using fresh frozen or formalin-fixed paraffin-embedded material. There may also be a problem associated with the type of assay used and the criterion for positivity (29). In Table 1, the prevalence of HPV in malignant head and neck lesions from the most important reports is listed. In 2009, more than 90 studies of HPV in HNSCC were published, and only selected studies from this period with comprehensive materials or remarkable HPV prevalence are included.

Many different assays for HPV detection are available, each with its own analytical sensitivity. There are the PCR-based assay systems, often linked to a specific genotyping system. Amplicor35 and SPF1036, as well as various type-specific PCR methods, are very sensitive systems, whereas GP5+/GP6+-PCR37 and PGMY38 are somewhat less sensitive in detecting HPV (29). In addition, there are methods based on DNA hybridization with specifically labelled RNA probes ISH that can be applied to detect HPV on histological sections (30). In a recently published study by Shi et al., the prognostic value of HPV16 E6 mRNA was compared with that found using ISH and p16 immunostaining in human oropharyngeal SCC (31). HPV16 E6 mRNA was positive in 73 (66%) of 111 samples; ISH was positive in 62 of 106 samples (58%), with 86% concordance. p16 was overexpressed in 72 samples (65%), and strongly associated with HPV16 status by either method. Classification of HPV positivity by HPV16 E6 mRNA, HPV16 ISH or p16 IHC was all associated with better disease-free survival. However, the latter two assays were technically easier to perform (31). Winder et al. compared the MY09/11 and GP5+/GP6+ primer sets with a GP5+/GP6+ nested PCR, showing that the older and commonly used MY09/11 and GP5+/GP6+ primer sets may not be sufficient for primary HPV detection on non-cervical clinical samples, and that negative results with primary PGMY PCR screening should be considered for GP5+/GP6+ nested PCR (32). Another approach for detecting clinically relevant HPV infection is by a combination of p16 immunohistochemistry and GP5+/6+ PCR. This can be used for high-throughput analysis of paraffin-embedded material and has been used in several studies.

HPV in saliva and oral exfoliated cells has been detected in some recent studies, but the sensitivity and specificity for HPV-related HNSCC are too low and the role of HPV detection in saliva and oral exfoliated cells seems uncertain (33, 34).

In general, it is recommended that at least two standardized and recognized methods should be used to confirm the diagnosis of clinically relevant HPV-positive HNSCC.
Recent data have shown an increase in the incidence of HPV-related cancers in the head and neck region from 1970 to 2007, especially in the tonsils. At the same time, tobacco- and alcohol-related cancers in the same region have decreased (35). In a very recent study in Sweden, a remarkable increase in the rate of HPV-positive tonsillar cancers was found. In the 1970s, 23% of tonsillar cancers were HPV positive vs 93% in 2006/2007 (2).

No correlation between HPV-positive HNSCC and tobacco or alcohol consumption has been demonstrated. In contrast, a weak correlation with the use of marijuana has been demonstrated (36).

Several studies indicate that HPV infection of the oral cavity and pharynx is a sexually transmitted disease. A strong association between sexual behaviour and risk of oropharyngeal cancer (37) as well as HPV16-positive HNSCC (36) has been demonstrated. It has also been reported that oral sexual activity and open-mouthed kissing are associated with the development of oral HPV infection (38).

There is an increased risk of secondary pharyngeal cancer in patients treated with or without radiotherapy for cervical cancer. This may reflect a transmission of HPV by sexual

### Table 1. Prevalence of HPV in malignant head and neck lesions

| Study                      | Year | Type and location of lesion | Method      | No. positive cases | % HPV type |
|----------------------------|------|----------------------------|-------------|--------------------|------------|
| Syrjanen et al. (60)       | 1987 | LSCC                       | ISH         | 15/116             | 13 11, 16, 6, 30 |
| Syrjanen et al. (61)       | 1988 | OSCC                       | ISH         | 6/51               | 12 16, 18  |
| Chang et al. (62)          | 1990 | OSCC                       | ISH/PCR     | 11/40              | 28 16, 18, 6 |
| Zeuss et al. (26)          | 1991 | OSCC                       | ISH         | 0/15               | 0          |
| Holladay et al. (63)       | 1993 | OSCC                       | PCR         | 7/37               | 19 16, 18  |
| Ostwald et al. (64)        | 1994 | OSCC                       | PCR/SB      | 16/26              | 62 16, 18, 6, 11 |
| Balaram et al. (65)        | 1995 | OSCC                       | PCR         | 67/91              | 74 16, 18, 6, 11 |
| Cruz et al. (66)           | 1996 | OSCC                       | PCR         | 19/35              | 55 16      |
| Wilczynski et al. (67)     | 1998 | TSCC                       | PCR         | 14/21              | 64 16, 33, 59 |
| Van Houten et al. (68)     | 2001 | HNSCC                      | PCR/E6R-PCR | 20/84              | 24 16      |
| Kojima et al. (69)         | 2002 | OSCC                       | PCR         | 35/53              | 66 38      |
| Sugiyama et al. (70)       | 2003 | OSCC                       | PCR         | 30/86              | 35 16      |
| Smith et al. (71)          | 2004 | OSCC/OPSCC                 | RT-PCR      | 38/193             | 20 16, 18, 33 |
| Koppikar et al. (72)       | 2005 | OSCC                       | PCR         | 6/102              | 6 16, 18   |
| Slebos et al. (73)         | 2006 | HNSCC                      | RT-PCR      | 8/36               | 22 16      |
| Luo et al. (74)            | 2007 | OSCC                       | PCR         | 13/51              | 25 16, 18, 33, 52 |
| Zhang et al. (43)          | 2008 | HNSCC                      | ISH         | 10/30              | 33 –       |
| Chuang et al. (42)         | 2008 | HNSCC                      | RT-PCR      | 20/59              | 34 16      |
| Simonato et al. (53)       | 2008 | OSCC                       | nPCR        | 5/29               | 17 –       |
| Luginbuhl et al. (75)      | 2009 | TSCC                       | ISH         | 17/48              | 35 –       |
| Avissar et al. (76)        | 2009 | HNSCC                      | PCR         | 19/109             | 17 16      |
| Lohavanichbutr et al. (23) | 2009 | OSCC/OPSCC                 | PCR         | 41/119             | 35 16      |
| Gallo et al. (77)          | 2009 | LSCC                       | PCR         | 0/40               | 0 –        |
| Khovidhunkit et al. (78)   | 2008 | OSCC                       | PCR         | 1/65               | 2 –        |
| Gudleviciene et al. (79)   | 2009 | HNSCC                      | PCR         | 13/48              | 27 16      |
| Attner et al. (80)         | 2009 | BTSCC                      | PCR         | 71/95              | 75 16, 33  |
| Näsman et al. (2)          | 2009 | TSCC                       | PCR         | 43/46              | 93 16, 33, 35, 59 |
| Shi et al. (31)            | 2009 | OPSCC                      | PCR/ISH/IHC | 73/111             | 66 16      |
| Straetmans et al. (49)     | 2009 | TSCC                       | ISH         | 33/81              | 41 16      |
| Weinberger et al. (81)     | 2009 | OPSCC                      | PCR/IHC     | 47/77              | 61 16      |
| Lassen et al. (51)         | 2010 | HNSCC                      | IHC         | 84/131             | 25 –       |
| Bennett et al. (82)        | 2010 | TSCC                       | PCR         | 9/16               | 56 16      |
| Hoffmann et al. (83)       | 2010 | TSCC                       | RT-PCR/IHC  | 21/39              | 53 16      |

HPV, human papillomavirus; OSCC, oral squamous cell carcinoma; TSCC, tonsillar squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; LSCC, laryngeal squamous cell carcinoma; BTSCC, base of tongue squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; RT-PCR, real-time polymerase chain reaction; PCR, polymerase chain reaction; ISH, in situ hybridization; IHC, immunohistochemistry.
behaviour and/or a genetic or immunological susceptibility to the oncogenic effects of HPV (39).

Hemminki et al. showed that in addition to an increased risk of tonsillar cancer among women with cervical lesions, a higher rate of tonsillar and tongue cancers was found among husbands of women with invasive cervical cancer and in situ cancer (40).

To summarize, there is evidence of an increasing incidence in HPV-positive HNSCC. Indications of HPV-positive HNSCC as an infectious sexually transmitted disease exist, although transmission of HPV in other ways as, for example, from mother to child either in utero or during delivery cannot be ruled out.

**CLINICAL FACTORS**

Patients tend to be younger and with no prior history of tobacco and/or high alcohol consumption. HPV-associated tumours more often present at a higher stage and often with large metastatic cystic lymph nodes (41, 42). Many patients present with a tumour of the neck, with the origin of the tumour (Tsite) first being diagnosed when a diagnostic tonsillectomy is performed in the process of unravelling the unknown primary tumour. Zhang et al. suggested that the detection of HPV-related SCC by cytology and by ISH of fine needle aspirate of cervical metastasis could be an important tool for identifying the site of origin of an unknown primary tumour with cervical lymph nodes to the neck (41). They found that non-keratinizing SCC in metastatic cervical lymph nodes predicted positive HPV-ISH and was strongly suggestive of an oropharyngeal primary tumour. These tumours are often basaloid and poorly differentiated (41, 44).

**PROGNOSTIC FACTORS**

Many studies have now confirmed that HPV-positive tumours in the head and neck region have a better prognosis compared with those that are HPV negative (45, 46). In a recent paper by Lassen et al., overall 5-year survival rate was 62% in the p16-positive patients compared with 26% in the p16-negative patients treated with radiotherapy (45).

The better prognosis seems independent of the treatment given. There is a better prognosis not only for patients treated with radiotherapy or concomitant chemo/radiation therapy (45), but also for patients treated with surgery alone (35, 47, 48). Fischer et al. found that in patients with tumours located in the oropharynx and treated with surgery, the 5-year survival rates for p16-negative and p16-positive patients were 26.8% and 57.1% respectively (48).

The prognosis for HPV-positive tonsillar cancer seems to be more independent of stage and especially nodal metastases compared with that for HPV-negative tonsillar cancers, where nodal metastases at the time of diagnosis are the most important prognostic variable (49). The positive prognosis is more pronounced in HPV-positive patients who are p16 positive than in patients who are p16 negative (21, 50). In another paper by Lassen et al., the effect of hypoxic modifications with nimorazol was examined in p16-positive and p16-negative patients. Hypoxic modification improved outcome in patients with HPV/p16-negative tumours but was of no significant benefit in patients with HPV/p16-positive tumours, suggesting that hypoxic radioresistance may not be clinically relevant in these tumours (51).

There is a marked difference in survival rate between smokers and non-smokers with HPV 16-associated tonsillar carcinomas (52).

A few authors were incapable of confirming the better prognosis of HPV-positive oral cavity cancer patients (53) and of patients with laryngeal carcinomas (54) vs similar HPV-negative cancer patients. However, in the study by Simonato et al. the HPV-positive patients had higher tumour stages compared with HPV-negative patients, and the number of included patients was small.

Most studies confirm that HPV is the most important independent prognostic factor in HNSCC.

**HPV AND THE IMMUNE SYSTEM**

HPV-positive cell lines have been shown to be more radioresistant than HPV-negative cell lines (55), suggesting that the better prognosis of patients with HPV-positive HNSCC is not due to intrinsic sensitivity to radiation and cisplatin. Spanos et al. performed a trial where they looked at the effect of radiotherapy on
HPV-positive and HPV-negative tumours in immunocompetent and immunoincompetent mice as well as the responses of radiation and chemotherapy in human cancer cell lines (56). For human and murine transformed cell lines, HPV-positive cells were more resistant to radiation and cisplatin compared with HPV-negative cells. In vivo, HPV-positive tumours were more sensitive to radiotherapy compared with their HPV-negative counterparts. Cisplatin in vivo cleared HPV-positive tumours but not HPV-negative tumours. In addition, neither radiotherapy nor cisplatin therapy cured immunoincompetent mice. Adoptive transfer of wild-type immune cells into immunoincompetent mice restored HPV-positive tumour clearance with cisplatin therapy. This certainly indicates that radiation and cisplatin induce an immune response to this antigenic cancer and better prognosis seems not to be due to increased radiosensitivity and chemosensitivity in HPV-infected epithelial cells.

The hypothesis that the immune system response may play a positive prognostic role in HPV-positive HNSCC is further supported by a study by Williams et al. (57). In this study, they generated HPV-positive and HPV-negative tonsil cell lines by transducing primary mice tonsil epithelial cells. These cells are capable of forming squamous cell cancers in immunocompetent mice. Wild-type mice were injected with the two cell lines. In the HPV-positive tumour-burdened group, about one-third of the animals cleared their tumours compared with none of the animals in the HPV-negative group. Among the mice that received HPV-positive tumour cells and cleared their initial tumours, a subset was found to be immune to future HPV-positive tumour cell challenge. When comparing survival rates in immunocompetent mice that did not clear their tumours, those injected with HPV-positive cells had a significantly longer survival than those injected with HPV-negative cells. There was no difference in growth pattern or survival between the HPV-positive and -negative group when the cells were injected into mice lacking B- and T-cell immunity. In an adoptive transfer experiment, whole splenocytes from mice that had cleared their tumours were transferred into immunoincompetent mice. These were then injected with HPV-positive tumour cells; all developed tumours, and clearing of the tumours was subsequently seen in 100% of recipients (57).

In a recently published article by Vu et al., it was suggested that there is increasing evidence of radiotherapy modulating immune response, and that the underlying mechanism behind the better prognosis of HPV-positive tumours may be enhanced by immune response following radiotherapy (58). This does not explain why HPV-positive patients treated with surgery alone also have a better prognosis. Whether surgery likewise is capable of triggering the immune system remains unanswered.

In conclusion, there seem to be strong indications that the immune system plays a significant role in explaining the positive prognostic impact of HPV positivity on HNSCC.

VACCINE

At present, two vaccines for prevention of HPV-related diseases have been developed and are available for primary vaccination in the EU. Cervarix® (produced by GlaxoSmith Kline, Brentford, UK) is a vaccine against HPV-16 and HPV-18. Gardasil® (produced by Sanofi Pasteur MSD Lyon, France) is a quadrivalent vaccine protecting against the oncogenic HPV-16 and HPV-18, but also HPV-6 and HPV-11, which are capable of inducing genital condylomas. The vaccines are now part of the public vaccination programme in several countries and are offered to girls from the age of 12 years or prior to sexual debut.

The efficacy of the vaccines in preventing HPV-related HNSCC is at present unknown. The value and cost benefit of vaccinating boys is under discussion in many countries.

The vaccines have been shown to be very effective against cervical intraepithelial neoplasia (CIN) and infiltrative cervical carcinomas. In a population of HPV-naive women approximating the target population for universal mass vaccination programmes, the efficacy of Cervarix® in preventing cervical CIN2+ lesions was 70.2%, and 87% against CIN3+. Cervarix® has been observed to induce a high-level antibody response and efficacy against both HPV-16 and HPV-18 that persists for over 7.3 years (10). In addition, Gardasil® has been examined in a phase 2 trial with an
average follow-up time of 36 months. Vaccine efficacy against CIN1 or worse related to HPV 6/11/16/18 in the general HPV-naive European population was 97.9%. Vaccine efficacy against HPV 6/11/16/18-related external genital lesions (vulvar or vaginal intraepithelial neoplasia, condyloma, vulvar or vaginal cancer, EGL) was 97.6%. Efficacy in the European population against CIN2/3 or adenocarcinoma in situ related to any HPV type was 56.6%, and the efficacy of the vaccine in preventing EGL related to any HPV type was 86.6% (11).

Smith et al. recently studied HPV-16 DNA tumour-positive HNC cases for HPV-16 E6 and E7 antibodies (33). Seropositivity was more often associated with the late stage (76%), poor grade (65%), positive nodes (82%) and localization in the oropharynx (82%). Median disease-specific and recurrence-free survival were longer in E6- and E7-seropositive compared with E6/E7-negative cases (2.2 years vs 1.4 years, both outcomes), although the results were not statistically significant. When examined jointly with p16 expression, E6 and/or E7-positive/p16-positive cases showed better disease-specific survival (2.1 years vs 1.1 years, p = 0.06) and recurrence-free survival (2.3 years vs 1.1 years, p = 0.03) compared with E6−/ E7−/ p16-negative cases (59). These findings support the hypothesis that the immune system may have a role in the better prognosis in HPV-positive HNSCC and vaccination may have a protective role in the development of HPV-related HNSCC.

FUTURE PERSPECTIVES

HPV-positive HNSCC appears to be different from HPV-negative HNSCC both in its molecular and clinical features. The research field focusing on HPV in HNSCC is expanding rapidly and we hope that a consensus regarding preferred methods for defining ‘true HPV positive’ will be reached. In future, it may be possible to select more advanced and individual treatment strategies based on the molecular and aetiological differences in HNSCC, especially with regard to HPV. Further molecular research into HPV-positive cancers will expand our understanding of head and neck cancer biology and may provide the basis for developing new treatment strategies. We anticipate that the role of vaccines and new specifically targeted drugs for HPV will eventually be revealed.

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THE ROLE OF HUMAN PAPILLOMAVIRUS IN HEAD AND NECK CANCER

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