HPV-related head and neck cancer

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General discussion and valorization
Chapter 9

9.1. IMPLICATIONS OF HPV-RELATED TUMOR BIOLOGY ON TUMOR STAGING AND PROGNOSIS

In the past decade it has become clear that a biological association is present between oncogenic HPV and a subgroup of OPSCCs. HPV-induced OPSCCs show distinct molecular and clinical features that are different from tobacco-and-alcohol-induced tumors and these differences seem to underlie prognostic differences between both tumor subgroups. In chapter 2 we showed that HPV-positive tumors, which are associated with less smoking and alcohol consumption, have a different tumor biology. They have smaller primary tumor sizes, although regional lymph node involvement is comparable to HPV-negative tumors. In our study, this resulted in a different choice of treatment, but independent of treatment modality, HPV-positive tumors had a better prognosis. The prognostic value of nodal involvement is reduced by the presence of HPV. It was not until 2007 that the World Health Organization officially recognized HPV as causative agent in the development of head and neck cancer. Our study described in Chapter 2 was the first to address that lymph node involvement and extent of nodal disease do not have a reliable predictive value when the seventh edition UICC staging system for OPSCCs is used. We therefore advised an HPV-dependent staging system for the diagnostic work-up in oropharyngeal tumor staging. Similar results to our findings were found by the groups of Klozar et al. and Fritsch et al. When reviewing literature reporting on the prognostic value of N-status in tonsillar squamous cell carcinomas (TSCCs), 10 studies were published prior to 1990, which all reported that N-status was of prognostic importance (although only 2 studies provided results based on statistical analysis). In contrast, from 1990 onwards, only 4 out of 12 studies showed N-status to be of prognostic relevance. This indicated that the prognostic shift of nodal status in TSCCs in literature runs parallel with the increase in HPV-prevalence in HNSCCs. In 2013, Dahlstrom et al. described in a US population of 3891 patients with OPSCCs collected between 1955 and 2004, a similar shift in prognostic reliability of TNM-status over time: compared to the previous study period, patients after 1995 were more often of younger age, had more tongue base or tonsillar tumors, were more often never smokers or former smokers and died only half as often. The TNM-classification predicted the survival of patients treated prior to 1995 accurately, but lost its predictive value for patients treated between 1995 and 2004. They also noted an unusually favorable outcome for stage III and IV disease in the most recent decade. In 2015, data of the Surveillance, Epidemiology, and End Results (SEER) database for OPSCC – also without knowledge of HPV status - described similar changes in prognostic significance. Similar to our results in chapter 2, the SEER-study noted a reduction of hazard ratio for survival for all N2 subcategories in the 7th edition UICC staging system compared with N0 disease.

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In this period, it was recognized that in OPSCCs HPV-positivity devalued the prognostic value of N-status described in the 7th edition UICC staging system. Therefore, a new staging system for HPV-positive OPSCCs was the next step. First, Ang et al. presented a risk-model to predict survival for stage III and IV OPSCCs treated with concomitant chemoradiotherapy, in which smoking status was combined with N stages “N0-2a” and “N2b-3”. In the HPV-positive group, smoking status (more or less than 10 pack years) discriminated between mild and moderate risk. Within the HPV-positive smoking group, difference in outcome was based on nodal status “N0-2a” and “N2b-3”, respectively, resulting in mild and moderate risk-associated groups. Spector et al. subsequently, subdivided N-status on the basis of diameter and number of nodes in 3 risk groups: a single node <6cm ipsilaterally or contralaterally as “HPV+ N1”, a single node ≥ 6cm or ≥ 2 nodes ipsilaterally/contralaterally or ≥ 3 nodes bilaterally as “HPV+ N2”. “HPV+ N3” was defined as neck node status with matted nodes. In 2015, Huang et al. studied a large group of 810 patients with OPSCCs and noted prognostic discrimination by using the 7th edition UICC staging system in HPV-positive tumors. Compared to the HPV-negative tumors showing outcomes worsening from stage I to IV, their HPV-positive group showed no significantly different survival rates from stage I to IV. Two additional classifications were proposed using the existing T and N categories of the 7th edition UICC staging system for the HPV+ cohort. The first model, which was based on recursive partitioning (RPA), showed a better predictive value for prognosis (stage I: T1–3, N0–N2b; stage II: T1–3, N2c; stage III: T4 or N3, stage IV: M1 as stage IV). Interestingly, 56% of patients classified as stage III or IV according to 7th edition UICC staging system, changed to stage I when using the new model. The second model proposed by Huang et al. was based on adjusted hazard ratios (AHR): 4 prognostic groups in HPV-associated OPSCCs without hematogenous metastases were discriminated, based on N status (N0-2c vs. N3), T status (T1-3 vs. T4), smoking behavior (fewer vs. more than 20 pack-years history) and age (younger vs. older than 70 years). Dahlstrom et al. (2016) were not able to validate Huang’s results; consequently, they proposed an own HPV-associated system, in which N status was staged corresponding to nasopharyngeal carcinomas. Finally, the classification system suggested by O’Sullivan et al. (ICON-S; 2016) was used for the clinical TNM-classification in the 8th edition of the UICC staging system for HPV-positive carcinomas. In this classification, N-status is based on the sidedness and maximum diameter of the nodes rather than on the number of nodes. It enhances the UICC staging system into more valid groups compared with the 7th edition to facilitate patient counseling, cancer surveillance, and translational research, and furthermore to optimize clinical trials design and outcome reporting. For this multi-institutional analysis, also the data on HPV-positive OPSCCs of our study group were included. Besides the clinical staging system, a pathological staging system has been introduced to establish prognosis and guide adjuvant therapy decision in surgically-managed HPV-positive OPSCCs. In contrast to clinical staging, the number of nodes (with a cut-off point of 4) determines N status (ranging from N0 to N2 without differentiation between N2a, N2b and N2c) for pathological staging.
This newly introduced 8th edition UICC staging system for HPV-positive OPSCCs was validated by others.\textsuperscript{38-42} We also compared this 8th edition with the previous 7th edition UICC staging system for HPV-positive OPSCCs in this thesis. In our study only TSCCs were included, a very strict definition of HPV-positivity was used, and the added prognostic value of additional non-anatomical parameters was tested, as described in chapter 7 and further on discussed in this chapter in 7.6.

9.2. ADEQUATE DETECTION OF BIOLOGICALLY RELEVANT HPV-POSITIVITY IN OPSCCS

In chapter 2 we showed that the impact of HPV on tumor biology, prognosis, and choice of treatment is large. Therefore, detection of biologically relevant HPV-positivity is of increasing importance. Literature has addressed the issue of more consensus on the exact definition of HPV-associated OPSCCs.\textsuperscript{44} HPV infection alone is not sufficient to classify an OPSCC as HPV-related, because the presence of HPV-DNA may only reflect a transient infection. In chapter 3, the reliability of p16INK4A immunohistochemistry (p16Ink4a-IHC) as surrogate marker for HPV was tested. We scored the p16Ink4a-IHC staining patterns according to the “block-type” immunopositivity approach, defined as p16Ink4a-IHC only being block positive if continuous (>70%) strong nuclear with or without cytoplasmic staining is present (in all head and neck lesions) and staining is observed in the basal cell layer with extension upwards (in benign and premalignant lesions).\textsuperscript{45} Our results indicate that a strong nuclear and cytoplasmic p16Ink4a-IHC pattern can accurately predict the presence of HR-HPV16 in OPSCC and tonsillar dysplasias.\textsuperscript{46} In low-risk-HPV6/11-positive benign and premalignant tonsillar and laryngeal lesions, however, the predictive value of p16Ink4a-IHC was lower and therefore caution is recommended when using this surrogate marker for HPV-infection. More recent studies have shown that in tumors outside the oropharynx, p16Ink4a-IHC has also less predictive value for HPV-presence.\textsuperscript{46-48} Despite the good correlation between P16Ink4a and the presence of HR-HPV16 in OPSCC, the decision to use p16Ink4a-IHC as sole diagnosticum to identify a HPV-positive OPSCC in the 8th edition UICC staging system may result in false-HPV-positive tumors. This was also recently emphasized by Bussu et al.\textsuperscript{49} Moreover, differences in geographical patterns of HPV-prevalence implicate, that the positive predictive value of p16Ink4a-IHC as solitary diagnostic tool will drop if the a priori probability of having a HPV-positive OPSCC is lowered by 30 to 40%, as is the case in Europe compared to the US.\textsuperscript{50} Throughout this thesis, therefore, p16Ink4a-IHC was combined with HPV-DNA PCR and/or Fluorescence In Situ Hybridization (FISH). We found that 14 out of 124 p16Ink4a-positive patients were not HPV-positive (11.2%). Taberna et al. recently investigated the treatment outcome of HPV-positive OPSCCs depending on the definition of HPV-positivity.\textsuperscript{51} They confirmed that definitions of HPV-positivity have
impact on TNM-classification and patients' prognosis and adequate testing with at least PCR for detecting HPV DNA next to p16Ink4a-IHC is emphasized. Nevertheless, p16Ink4a-IHC is a widely available, low-cost test in the general pathology laboratory in contrast to more expensive HPV DNA PCR and HPV-in situ hybridization analyses, which require a specialized laboratory and expertise. Therefore, it has been adopted as surrogate marker for HPV in the since 2018 used 8th edition UICC staging system for OPSCCs. Prigge et al. suggested in their meta-analysis the most desirable technique to identify HPV-positive OPSCCs: the detection of HPV E6 and/or E7 oncogene transcripts of all HR-HPV types (a), in the form of all splice transcript variants (b), from fresh-frozen tumor tissue (c), and performed on isolated tumor cells (d), e.g. by means of tumor microdissection. This “ideal” detection strategy is considerably laborious and, consequently, not realizable in the routine diagnostic setting. Therefore, the combined p16Ink4a-IHC and HPV-DNA PCR assay significantly enhances specificity while maintaining high sensitivity. This diagnostic test combination thus represents an attractive testing strategy for the reliable diagnosis of HPV-positive OPSCCs in the clinical setting and may constitute an inclusion criterion for future therapeutic trials.

9.3. IS THERE ADDITIONAL VALUE FOR HPV-TESTING IN CUP-SYNDROME?

Because HPV-positive OPSCCs often spread to the lymph nodes already at low T-stages, a clear role for HPV-detection in the diagnostic work-up of cervical metastases of unknown primary tumors (CUP), to identify primary tumors in the oropharynx, has been advocated. However, studies on the prevalence of HPV in lymph node metastases of which the primary tumor could not be detected after a comprehensive diagnostic workup, so-called “true” CUPs, are scarce and contradictory. In these studies, HPV prevalence rates range from 0% to 100% and were tested in very small sample numbers (range 1-25). In chapter 4, we collected 29 true-CUP patients, of which the primary tumor was not present within 6 months of follow-up after treatment. Treatment consisted of a neck dissection and/or (chemo)radiotherapy. In this patient group 5/29 neck metastases were p16Ink4a-positive but in none of the specimen HPV DNA was detected by FISH and PCR (0%). No association between p16Ink4a-positivity and survival was found. All specimens were therefore regarded HPV-negative. This indicates that the additional value of HPV-testing, next to a thoroughly performed diagnostic work-up, including panendoscopy, blind biopsies of tongue base and nasopharynx, bilateral tonsillectomy, and additional imaging, including PET-CT scanning, is limited.
9.4. SHOULD PATIENTS WITH CUP SYNDROME WITH OR WITHOUT HPV ALWAYS BE TREATED EXTENSIVELY, OR IS DE-ESCALATION AN OPTION?

More than a decade ago in the Netherlands, patients with CUP were treated extensively with postoperative radiotherapy of the bilateral neck and radiotherapy of the pharyngeal axis, in some cases combined with concurrent chemotherapy. The question arose whether de-escalation of therapeutic regimes in patients with CUP with or without HPV is possible. To enlarge our CUP patient group (see 7.3), we united the patient collectives of two European University medical centers (Cologne, Germany and Maastricht, the Netherlands; n = 51) and compared their data (chapter 5). Only true CUP patients (no primary tumor found within 6 month of follow-up) whose neck metastases were primarily treated surgically were included. The prevalence of HPV in this Maastricht-Cologne cohort of true CUP-patients was 7.8% (4/51 HPV-positive true CUPs). No statistically significant difference of HPV-positivity between Maastricht and Cologne was found. Because of the low percentage of HPV-positivity, the influence of HPV positivity on outcome after therapy could not be assessed. Comparable to chapter 4, the added value of HPV testing in neck metastases of CUPs was found to be limited in chapter 5, especially when compared with OPSCCs in which the prevalence of HPV is much higher.

In the same study data about the therapeutic strategy for cervical metastasis of CUPs were retrospectively compared. All patients underwent a neck dissection, but the postsurgical management differed between patients and institutions. This enabled us to compare ipsilateral and bilateral radiotherapy, with or without radiation of the pharyngeal axis and with or without addition of chemotherapy. No significant differences in disease specific and overall survival between all subgroups was found, indicating that de-escalation might be a safe option in CUP-patients. Advanced nodal disease was, however, associated with a worse outcome, independent of treatment modality. The same was the case for the occurrence of regional recurrences after therapy: in almost half of the patients with regional recurrences during follow-up, distant metastases occurred (n = 6/13). Recently, also Sprave et al. found a high incidence of metachronous distant metastases in patients with regional recurrences. In that study, the combined radiochemotherapy of the pharyngeal axis and bilateral cervical lymph nodes led to good results in case of specific risk factors (extra nodal spread and residual tumors), which were not included in our study.

The presented data of the Maastricht-Cologne study contribute evidence to the ongoing discussion, in which the need for uniform international guidelines to treat patients with cervical CUP syndromes is claimed. Our data indicate that the omission of radiotherapy of the pharyngeal axis and the contralateral neck after neck dissection,
as well as the omission of concomitant chemotherapy, might be safe under certain conditions. However, the variety of therapeutic strategies in both institutes in this complex population of patients with cervical CUP syndrome, prohibited any statistical evaluation or definitive conclusion in our study. Therefore, further research in a more homogeneous patient population was needed, addressed in chapter 6.

**9.5. FURTHER EVIDENCE FOR SAFE DESCALATION OF THERAPY FOR CUP PATIENT: NEED FOR TRIALS?**

In order to homogenize treatment modalities of the neck and to exclude regional influences on the prevalence of HPV-positive CUPs, we merged our Maastricht database with a patient population collected at the Radboud University Medical center, Nijmegen, the Netherlands (n=80) (chapter 6). The protocols for diagnostics and treatment of CUP patients were similar in Nijmegen and Maastricht, and de-escalation of therapy in CUP patients was performed simultaneously in both institutes, starting in 2002. Again, in only 4 out of 72 neck dissection specimen presence of HPV DNA in tumor cells was found (6%) confirming previous results. Therefore, also in this merged patient cohort HPV testing did not add value to the described diagnostic workup and did not influence therapeutic decision-making, for example, additional postsurgical radiotherapy of the oropharynx. This might be unexpected taking into consideration that small (T1-2 stage) HPV-positive OPSCC frequently are spreading to the lymph nodes and thus in principle could account for a substantial number of CUP. Probably, most HPV-positive primary tumors of the oropharynx are detected by tonsillectomy or “blind biopsies” of the oropharyngeal region, resulting in low percentages of HPV-positive true CUPs. Altogether, our studies in chapters 4-6 revealed that HPV-status was of insignificant importance to be used as in stratifying patients with CUP. Because of the low prevalence of HPV-positive CUPs, HPV-diagnostics improved neither the diagnostic and therapeutic work-up nor the outcome. As a result, the current treatment of patients with HPV-related CUP does not differ from the standard of care treatment. Nevertheless, de-intensification of therapy remains an interesting option to be examined in the (small) group of HPV-positive CUP-patients. Furthermore, in chapter 6, we confirmed our previous observation that omitting irradiation of the pharyngeal axis in patients with cervical true CUP syndrome does not result in the emergence of a primary tumor in the pharyngeal axis during five years of follow-up. This can avoid acute and late toxicity of comprehensive radiotherapy of the pharyngeal mucosa with significant improvement of long-term quality of life for these patients. Also, the absence of post-surgical radiotherapy of the contralateral neck in CUP did not lead to a decrease of regional control rates nor of survival rates.
In order to compare the outcome of ipsilateral radiotherapy solely with a comprehensive radiotherapeutic regime in CUP-patients, Nieder et al. recommended a randomized controlled trial already in 2001. Only one randomized controlled trial was started since 2002, but was never completed (EORTC-24001-22005) as a consequence of limited patient enrollment. Still, a prospective multicenter approach to analyze the true impact of radiotherapy target volume in CUP-patients is needed. However, the low prevalence of patients with CUP and the heterogeneous treatment strategies in different countries and regions are important limiting factors to design a large international study providing sufficient evidence for an international guideline.

For that reason, the American Society of Clinical Oncology convened an Expert Panel of medical oncology, surgery, radiation oncology, radiology, pathology, and advocacy experts to conduct a literature search including 100 relevant studies published from 2008 through 2019 including our presented results in this thesis. Available evidence and informal consensus was used to develop evidence-based guideline recommendations about appropriate pre-operative evaluation, appropriate surgical diagnostic and therapeutic procedures, treatment considerations for surgical management, radiotherapy and chemotherapy in patients with CUP. Regarding radiotherapy of the occult primary tumor site, it was stated that solely radiotherapy of the ipsilateral oropharynx (i.e. ipsilateral tonsillar bed, ipsilateral soft palate and the mucosa of the entire tongue base) is recommended in patients with CUP treated with primary radiotherapy for one or more unilaterally located lymph nodes, not greater than 6 cm (AJCC 8th N1 HPV+ve and AJCC 8th N1-N2b HPV-ve), and in case of available PET-CT scan and performed contralateral tonsillectomy. Patients with CUP presenting with bilateral located lymph nodes not greater than 6cm (AJCC 8th N2 HPV+ve and AJCC 8th N2c HPV-ve), require bilateral treatment of the oropharyngeal mucosa. Patients with CUP presenting with nodes in the lower cervical stations (III and IV) should be considered for treatment of the larynx and hypopharynx, given the marginally higher risk of spread to stations III and IV from these organs.

The following argumentation was offered regarding radiotherapy of the unilateral versus bilateral neck: as bilateral neck irradiation for CUP has been considered standard of care historically, this approach is accompanied with considerable toxicity, including increasing dose to salivary glands, larynx, pharyngeal constrictors, mandible, hypopharynx, and esophagus. Following high-resolution imaging, ipsilateral only radiotherapy has been demonstrated to results in very acceptable rates of contralateral failure and reduced doses to the above-named structures. Ipsilateral neck irradiation is recommended in patients with CUP with a unilateral single node without extranodal extension and preferably in lymph node level II. In all other patients with CUP (multiple nodes, nodes, node(s) greater than 6 cm, level III or IV nodes, and/or clinical or radiologic ENE), bilateral neck treatment is recommended as in these patients higher rates of contralateral involvement are noted and prognosis is worse.

These above cited recommendations are in line with our presented results. However, the outcomes of interest in the above cited ASCO guidelines were survival, local and
regional disease control, and quality of life. In our presented results in chapters 5 and 6, the occurrence of distant metastases was the most important limiting factor of survival. Again, this affected the more advanced staged necks, i.e. more than one lymph node or lymph node size more than 6cm (AJCC 7th N2b or higher). This underscores the importance of including distant disease control as primary endpoint in the evaluation of therapeutic strategies in CUP patients, as recently also was emphasized by Sprave et al.

9.6. THE PROGNOSTIC VALUE OF LYMPH NODE METASTASES IN HPV-POSITIVE TSCCS AND HOW IT INFLUENCED THE 7TH AND THE 8TH EDITION OF THE UICC CLASSIFICATION SYSTEM.

Chapter 7 describes that the predictive value of the 7th edition UICC tumor staging system for OPSCCs, and N-status in particular, has shifted over time as a consequence of the epidemic of HPV-associated HNSCCs. Since our study in 2009 (chapter 2), which was the first to report the direct correlation of HPV-status and the diminished prognostic value of N-status, different larger studies followed confirming our data. This finally resulted in the new 8th edition UICC tumor staging system, in which a separate classification system for HPV-positive tumors has been introduced. In chapter 7 we first summarized the changes of the 8th compared to the 7th edition of the UICC staging system: nodal stages underwent a transformation, clinical neck stages N1 until N2b were re-classified as cN1 including all ipsilateral neck metastases no greater than 6 centimeters, bilateral neck nodes were classified as cN2, and nodes greater than 6 cm as cN3. Along with the clinical staging, a pathological staging system was introduced based on the number of positive nodes identified by histopathological examination after neck surgery. These changes in tumor staging were then evaluated by testing the prognostic value of the different 7th- as well as 8th UICC tumor stages in HPV-positive OSCCs. The examination also included the separate T-, N-, and M-stages. An unselected population of 368 patients with SCCs of the tonsil, which is the site associated with the highest prevalence of HPV, was included in the study. Next to T-, N-, and M-stages the influence of patient-associated clinical variables including tumor differentiation grade, age, smoking behavior, alcohol consumption and treatment were taken into account. In total, 110 tumors were tested HPV-positive with p16Ink4a-IHC, HPV16-DNA PCR and/or FISH. Advanced stage HPV-positive tumors staged with the 7th edition UICC tumor staging system had a favorable prognosis. These tumors, however, had despite more advanced N-status (resulting in a higher overall stage) smaller primary tumors. When applying the 8th edition staging system we noted that 54% of all tumors were...
classified as stage I compared to 5% of patients in the 7th edition. At the same time in the 7th edition 56% of the TSCCs were classified as stage IVa compared to only 3% of patients that were classified as stage IV in the 8th edition. We found that the 8th edition UICC tumor staging system, therefore, did better separate the different staged tumors in survival analysis. Our results were in line with other studies confirming that the introduction of the 8th HPV-associated tumor staging system is a step forward in staging HPV-associated OPSCCs. However, when testing T-, c/pN- and M-status separately we found only cN3- and M1-status to be “anatomical” variables that significantly influence prognosis negatively. As a consequence of a favorable prognosis in HPV-positive T4-tumors, T-status in general was not associated with survival in our study. There was also no difference in survival dependent on pN-status. However, pN-status could be classified in only 38 HPV-positive TSCCs, because in those patients a neck dissection was performed.

Cramer et al. recently validated the 8th edition UICC staging system in a population of more than 15,000 patients (USA) and demonstrated an improved prediction of prognosis for HPV-positive OPSCC patients compared to the previous 7th edition UICC staging system. Also for T-, cN- and pN-status, the prognostic value could be validated in the HPV-positive population. In contrast to the validation study by Cramer et al., our study focused exclusively on SCCs of the tonsil, which is the subsite with the highest percentage of HPV-positive tumors. HPV-positivity was tested using HPV16-DNA PCR and/or FISH in addition to p16-IHC, which was the only test used in the study by Cramer et al. On the other hand, our study contained a much smaller patient population, although 110 unselected HPC-positive TSCCs were included. Despite these differences, the overall outcome of both studies were not similar. In our study population, the 8th edition of the UICC tumor staging system was also associated with a better prognostic value for tumor stage. However, in our study no significant prognostic value of N-stages cN0 to cN2 and pN0 to pN2 was found. Only cN3-status and M1-status were significantly associated with unfavorable prognosis. The cut-off point for a favorable prognostic value in our study of TSCCs was N3, however, only very few bilaterally involved (and thus cN2) neck stages were diagnosed. The study of MacKenzie et al. confirmed this observation and reported that only lymph nodes larger than 6cm (cN3) were associated with a worse survival.

A clinically negative (cN0) neck status was not associated with a better prognosis compared to N1 in our HPV-positive TSCC patient population, and showed even a worse prognosis than the N1 neck. In the validation study by Cramer et al., also no significant differences in survival were found between cN stages cN0 versus cN1 and cN2. Moreover, although the validation of the prognostic value of the clinical N-status (8th edition) was successfully performed, cN1-status was associated with a significantly better survival than N0 and also the bilateral involved neck (cN2-status) was not associated with a significantly worse survival than the clinically negative neck after adjustment for age, sex and race. Only cN3-status was significantly associated with a worse survival.
In previous research, it was noticed that patients with HPV-positive carcinomas more often had a lymph node as presenting symptom when compared to their HPV-negative counter parts. In HPV-positive carcinomas such a finding thus may guide the subsequent discovery of the primary tumor, and furthermore it led to the hypothesis that oncogenic HPV infection may play a substantial role in CUP-syndrome. As a consequence, patients presenting with these “alarming” nodes are expected to have a better prognosis upon treatment, which we did find in our study. Fritsch et al. and Ang et al. also described that patients with an HPV-positive single neck node between 3 and 6cm (N2a, 7th edition) had a better outcome than patients without lymph node metastases. Fritsch et al. compared outcome based on N-status between HPV-dominant (tonsillar fossa and base of tongue) and non-HPV-dominant oropharyngeal subsites in more than 15,000 OPSCCs. In the HPV-dominant population, cN2a (7th ed.) was associated with a better survival than cN0/1 and in the total population no differences in outcome were noted as long as lymph node metastases were unilateral (cN2c). In our study only patients with TSCCs were included. In this strongly HPV dominant subgroup similar results were found and a clinically negative neck (cN0) in HPV-positive TSCCs was not associated with a better survival than necks with lymph nodes smaller than 6 centimeter in diameter (i.e. cN1- and cN2-status). Possibly, unknown factors next to HPV-driven carcinogenesis play a role in the outcome of the clinical negative neck in HPV-positive OPSCCs, taken also into account the fact that the presentation of OPSCCs without involved neck nodes is atypical for HPV-associated tumoral behavior.

A point of discussion in the literature is that the influence of N-status on prognosis in HPV-positive tumors is often analyzed for all oropharyngeal subsites, without even discriminating between HPV-dominant or non-dominant subsites. In chapters 2 and 7, patients with TSCCs, the most HPV-dominant oropharyngeal subsite, were selected. Sood et al. described that a bilaterally involved neck status predominantly is seen in base of tongue tumors, indicating that lymph node dissemination patterns even differ within the HPV-dominant oropharyngeal sites. This may explain the low number of bilaterally involved necks in TSCCs and the lack of significance of the cN2-stage classifying for bilateral neck involvement in the 8th edition which we found in our study. The location of the tumor in the different subsites of the oropharynx therefore likely plays a prominent role in the development of advanced (N-) tumor stages in HPV-positive OPSCCs.

All in all, the cN status classification assessed for HPV-positive OPSCCs according to the 8th edition UICC tumor staging system still turns out to be a suboptimal predictor of survival. In our study only cN3 and M1 were associated with a worse survival. Therefore, other, “non-anatomical” variables have been investigated to improve risk assessment of HPV-positive tumors.
9.7. ADDITIONAL NON-ANATOMICAL FACTORS IMPROVING PROGNOSIS IN HPV-RELATED OROPHARYNGEAL TUMOR STAGING.

The goal of implementing the 8th UICC staging system for HPV-positive OPSCCs was to more accurately represent the superior survival outcomes seen in these tumors and thereby to improve the prognostic value of the system and possibilities to guide treatment decisions.77

As mentioned earlier, our results described in chapter 7 were in line with other studies confirming that the introduction of the 8th HPV-associated tumor staging system is a step forward in staging HPV-associated OPSCCs. However, in our study the survival of HPV-positive TSCCs was not predominantly dependent on TNM-status even when using the 8th edition. The most significant prognostic factors in HPV-positive TSCCs were smoking, age, N3-status, and the presence of distant metastases. Our study indicated that the prognostic value of the 8th edition UICC staging system can be improved by including smoking history and age with a cut-off point of 65 years as additional prognostic factors. Therefore, we have proposed a risk model for HPV-positive TSCCs based on smoking history, age, nodal size of >6 cm and presence of distant metastases resulting in 4 groups. The first group consisting of non- or former smokers (patients who quitted smoking more than 10 years prior to the diagnosis of TSCC independent of the number of previously smoked pack years) was associated with a 5-yr OS of 95.1% even in advanced tumor stages. In groups 2 and 3, all patients smoked daily. Group 2 included smokers aged 65 or younger with an associated overall survival rate of 75.6%. In group 3 patients older than 65 who smoked had a 5-yr OS of 46.2%. Group 4 consisted of patients with N3- and M1-status (5-yr OS: 0%). Interestingly, two patients survived with a N3-staged neck, they were both non-smokers. Within the different groups, T- and/or N-status did not further differentiate between survival rate.

The issue of re-staging HPV-associated OPSCCs using N status alone or in combination with other clinical parameters has been addressed from various perspectives in the literature. Results of our research group on a prognostic model for OPSCCs was previously presented by Rios et al.78 These results were validated by Rietbergen et al. in a larger cohort, showing the large impact of performance status on outcome in the whole patient group.79 However, within the HPV-positive subgroup no further differentiation in risk profiles was provided.

In the recursive partitioning analysis of the radiation therapy oncology group by Ang et al. (2010), non-anatomic parameters such as age and tobacco smoking were included for the first time and an important prognostic value was found for tobacco smoking.75 A predictive model for the prognosis of stage III and IV OPSCCs treated with concomitant chemoradiotherapy was presented, in which smoking status was combined with N stages “N0-2a” and “N2b-3”. In the HPV-positive groups, smoking status discriminated between mild and moderate risk. These results were validated by others.80 81
et al. (2015) discriminated 4 prognostic groups in HPV-associated OPSCCs without hematogenous metastases based on N status (N0-2c vs. N3), T status (T1-3 vs. T4), smoking behavior (fewer vs. more than 20 pack-years history) and age (younger vs. older than 70 years), with associated 5-year overall survival rates of respectively 89%, 64%, 57% and 40%. Regarding smoking, Marur et al. noticed that treatment failures in a de-escalating regime of combining cetuximab with radiotherapy were seen in smokers (>10 packyears). However, Haigentz et al. emphasized that including smoking in a predictive model goes along with great limitations as a consequence of the lack of validated, prospective data and the subjectivity of the data collection on tobacco use. Further study by Rietbergen et al. showed no differences in outcome regarding smokers versus non-smokers. In that study, smoking status was defined based on the number of pack years and no separate classification was performed for former-smoker status, which might have influenced the results for the smoking group. Moreover, Broughman et al. postulated to leave the 10 packyear rule, proposed by Ang et al. as stratifier in HPV-positive OPSCCs, because of the favorable prognosis of former-smoking status independent of the number of pack years in their recent study. These findings correspond with our results which show favorable outcomes in former-smokers with HPV-positive OPSCCs as presented in chapter 7. This stresses the importance of adequate history taking regarding smoking status in the work-up in a patient population with HPV-positive OPSCCs. In conclusion, in our study the outcome of HPV-positive TSCCs was not predominantly dependent on TNM status even when using the 8th edition. The most significant prognostic factors in HPV-positive TSCCs were smoking, age, and also N3-status and the presence of distant metastases. In our predictive model, a prognostic role for age with a cut-off point of 65 years was observed. Non- or former smokers had a very favorable prognosis of more than 95% 5-year OS even in more advanced tumor stages and in former smokers who quitted smoking longer than 10 years ago the number of pack years had no influence on prognosis. We think that this model could provide a simple additional tool for predicting the prognosis of HPV-positive TSCCs in the clinical setting.

9.8. HPV-POSITIVE HNSCC BIOLOGY AND DIRECTIONS FOR THERAPY.

The previous chapters of this thesis pointed out that detection of biologically active HPV in HNSCCs has prognostic relevance and, therefore, a separate classification of HPV-induced tumors has been introduced. Further optimization of treatment protocols for this distinct group of HNSCCs is the next step. Data on treatment response of OPSCCs indicate that large low-risk subgroups of patients with HPV-positive tumors show up to 30% better survival rates than patients with HPV-negative tumors, independent of the type of treatment, as a consequence of their different tumor biology (Chapters 2 and
Due to these advances in insights in the clinical and molecular behavior of HPV-positive OPSCCs, the National Comprehensive Cancer Network (NCCN) Guidelines have made a distinction between treatment pathways for P16INK4a-positive and -negative OPSCCs. However, the incorporated treatment strategies for both groups in the current guidelines remain almost identical and are mainly based on surgery, radiotherapy and chemotherapy.

To improve the efficacy of treatment while preventing increased side effects in patients with HPV-positive OPSCCs, the question arose whether treatment de-intensification and/or new HPV-targeted therapeutic options are possible. This question was addressed in chapter 8, in a large review on (future) therapeutic options for HPV-positive tumors. Literature describes two main strategies for specific treatment of HPV-positive tumors. The first strategy focuses on the unique clinical behavior of HPV-associated HNSCCs and selects the patients based on risk-profiles to modulate and possibly de-intensify treatment. Do HPV-positive tumors need treatment protocols as intensive as their HPV-negative counterparts? Does the high chemo- and radiosensitivity of HPV-positive HNSCCs offer possibilities for de-escalation of therapy leading to reduced therapy-induced toxicities? In chapter 8, future directions for de-intensified treatment of HPV-positive HNSCCs were discussed. Until now, mainly improved techniques associated with less treatment-related morbidity like IMRT/IMPT or TORS have been implemented in clinical practice. Since the publication of our review, several de-escalation therapy trials for HPV-positive OSCCs have been performed, which can be summarized in three categories. In the first category, there are four large phase II studies, in which induction chemotherapy followed by reduced-dose RT led to less toxicities in p16INK4a-positive and/or HPV-positive patients treated with the reduction dose RT: different low-risk profiles (‘less than 20 pack years’: Quarterback-trial, ‘< T4, < N2c, and ≤ 10 pack-year smoking history’: ECOG E1308-study) and ‘T1-T3, N0-N2b, and <10 pack-years’: Optima II -trial) were associated with favorable outcomes in the reduction dose RT groups. These data support phase 3 clinical trials of radiation dose reduction after induction chemotherapy to be tested as a treatment strategy in HPV-positive OPSCCs and to quantify survival gain compared to standard of care.

A second category is dose reduction of concurrent chemoradiotherapy. Chera et al. reported results of two performed phase II trials, in which patients with T0-T3, N0-N2c, M0, p16INK4a-positive disease and a minimal smoking history were treated with 60 GY (16% less than standard dose) of intensity-modulated radiotherapy with concurrent weekly intravenous cisplatin (30 mg/m2; 40% less than standard dose). A good preservation of quality of life and an excellent 3-year tumor control and survival was found. These first promising results have been reported in the second half of the last decade, and a phase III trial have to be awaited for.

In a third category, outcome was evaluated when concurrent cetuximab-based chemotherapy instead of cisplatin-based chemotherapy was administered. Phase III-trials by Gillison et al. and Mehanna et al. both noticed a higher locoregional control in the cetuximab-arm, however, overall survival was superior in the cisplatin-arm.
et al. recently updated the results of this large phase III trial and concluded that the standard regimen of concurrent chemoradiation therapy being cisplatin-radiotherapy should not be replaced in HPV-positive OPSCCs. On the basis of the above-mentioned conflicting results, there are no phase III trials to provide sufficient evidence that systemic therapy or radiotherapy may be de-intensified in HPV-positive HNSCC. Dose reduction of RT after a clinically good response to induction chemotherapy seems promising, particularly in well-defined low-risk subgroups of HPV-positive OPSCCs.

A second strategy of altering the therapeutic approach for HPV-positive HNSCC is to target HPV-specific molecular characteristics and search for new therapeutic options, in other words to provide HPV-positive tumors with another treatment protocol than their HPV-negative counterparts? In chapter 8, we, therefore, focused next on present therapeutic HPV-targeting strategies.

Different prophylactic and therapeutic alternatives for the current treatments of HPV-positive OPSCCs were discussed: 1) immunomodulating therapies including prophylactic and therapeutic vaccines. 2) antiviral therapies including interfering RNA and cidofovir; and 3) molecular therapy based on cellular targets including, protease inhibitors ritonavir and lopinavir, artificial zinc fingers, NFκB and anti-EGFR therapy. Currently, these above mentioned targeted therapies for HPV-positive HNSCC seem promising, but still have not proven their efficacy in HPV-positive OPSCCs, i.e. data on vaccine efficacy in OPSCCs is lacking, or data is currently too preliminary. Interfering RNA has also not been tested in vivo in human HNSCCs up to now, and cidofovir was recently tested in human HPV-positive HNSCC cell lines where it induced S- and G2/M phase arrest, resulting in mitotic catastrophe but not in apoptosis. Protease inhibitors ritonavir and lopinavir have proven their efficacy in the treatment of HPV and although their therapeutic effect seems promising in cervical high-grade squamous intraepithelial lesions, clinical trials in HPV-positive OPSCCs are needed. Regarding EGFR-targeted therapy, finally, the inferiority of cetuximab to cisplatinum in concurrent radiotherapeutic regimes in overall survival in the general HPV-positive populations was described above. A second EGFR-targeted therapeutic agent, panitumumab, did also not show better outcome in HPV-positive OPSCCs in the SPECTRUM and PARTNER trials. The lack of overexpression of EGFR in a large group of HPV-positive OPSCCs may contribute to the failure of improving outcome based on EGFR-targeted therapies. Notwithstanding, narrowcasting EGFR-targeted therapy to the right selection of HNSCC patients still seems a serious option to explore.

A recent perspective regarding alternative therapies for HPV-positive HNSCC since the publication of our review is immunotherapy. Kim et al. recently classified OPSCCs immunologically into immune-rich (IR), mesenchymal (MS) and xenobiotic (XB) subtypes based on RNA-sequencing data. All IR type tumors were HPV-positive, most XB types were HPV negative, and MS types showed both HPV-positive and -negative tumors. The IR type was associated with a favorable response signature during anti-PD-1/PD-L1
therapy, which seems a promising target in this HPV-positive OPSCC subgroup. The programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pathway (referred to as the PD pathway) induces immunosuppression in the tumor microenvironment: tumor cells and other cells in tumor microenvironment can express high levels of PD-L1, which results in suppressed immunity upon interaction with PD-1. PD-L1–expressing cells use multiple mechanisms to suppress tumor immunity, e.g. PD-L1 on tumor cells can act as a receptor, and the signal delivered from PD-1 on T cells can protect tumor cells from cytotoxic lysis. Normal human tissues seldom express PD-L1 protein on their cell surface, with the exception of tonsillar tissue a.o. Based on durable objective response rates and a favorable safety profile (according to the results of the CheckMate 141 and KEYNOTE-048 trials), PD-L1-checkpoint inhibitors Nivolumab and Pembrolizumab (i.e. antibodies targeting the PD-1 receptor of lymphocytes) have been approved by the US Food and drug administration (FDA) for the treatment in HNSCCs. So far, however, no phase 3 trials were conducted regarding outcome after immunotherapy in HPV-positive OPSCCs. 

The implementation of immune checkpoint inhibitors revealed a new research field in cancer therapeutics which is evolving quickly. Besides anti-PD-1 and anti-PD-L1 therapy, other therapeutics which interfere with immune checkpoint are currently subject of ongoing studies in HNSCCs. Table 1 gives an overview of the ongoing studies related to anti-PD-1, anti-PD-L1, anti-CTLA4, anti-NKG2A and anti-PI3K therapeutics in HNSCCs.

Overall, the development of new antiviral and immunomodulatory treatments may be instrumental in the future therapy management of HPV-positive HNSCCs to improve survival rates and decrease disease- and treatment-related morbidity. There is rapidly increasing evidence for molecular and immunologic subgroups within the HPV-positive OPSCCs and also within HNSCCs in general, including the HPV-positive tumors. These subgroups most likely will show a different tumoral behavior and response to therapy. For example, Zhang et al. described different subgroups of HPV-positive HNSCCs that can be identified molecularly, i.e. HPV-KRT (upregulation of keratinization and oxidation-reduction process) and HPV-IMU (upregulation of mesenchymal and immune-response genes). They emphasizes that further research is needed for a better understanding of these HPV-positive subgroups. The HPV-KRT group for example proved to be associated with the occurrence of PIK3CA mutations in the tumor. Recently, Beaty et al. performed two phase II trials in which the clinical significance of PIK3CA mutations in 77 HPV-associated OPSCC patients was studied. In these studies de-intensified CRT (60 Gy intensity-modulated radiotherapy with concurrent weekly cisplatin) was given. PIK3CA mutation was the only variable which was significantly associated with a worse disease-free survival (multivariate analysis: HR 5.71). Furthermore, recent research by Locati et al. reclassified these two molecularly defined subgroups (HPV-KRT en HPV-IMU) into three clusters. Cluster 1 is an immune-related subgroup characterized by high IFNγ signaling, associated with a good prognosis and probably the subgroup with a good response to immunotherapy. The HPV-KRT subgroup was further reclassified into two subgroups: Cluster 2 is an epithelial-mesenchymal transition-related subgroup (EMT),
characterized by fibroblast infiltration, increase in hypoxia and EMT-upregulation, and
Cluster 3 is a proliferation-related subgroup, characterized by upregulation of E2F
(G1 checkpoint transcription factor) and G2M checkpoint genes. HPV-positive tumors
in Cluster 3 are associated with an intermediate risk profile and tumors in Cluster 2
with a high rate of integration of HPV DNA into the host genome and an unfavorable
prognosis. HPV-positive tumors in this latter Cluster 2 subgroup are potential candidates
for treatment intensification according to Locati et al. Further research must help to gain insight and develop tools for identification of risk-
profiles based on clinical (smoking, age, cN3-status a.o.) and molecular characteristics
(PIK3CA-mutation a.o.), which will play a key role in the stratification of patients for
therapeutic decision making.

9.9. CONCLUSION: CHOOSING THE RIGHT THERAPY FOR THE RIGHT PATIENTS

HPV-positive OPSCCs have a different tumor biology and clinical behavior compared
with their HPV-negative counterparts. The reported favorable prognosis despite
frequent spread of HPV-associated tumors to the cervical lymph nodes have strongly
influenced the discussion of adequate tumor staging in HPV-positive OPSCCs. This
led to the implementation of a separate staging system for HPV-positive OPSCCs in
the 8th UICC tumor staging edition. The associated favorable prognosis make HPV-
related tumors more eligible for de-escalation of therapy to reduce treatment-related
toxicities. However, HPV-positive tumors also prove to be a heterogeneous group of
tumors and additional parameters are needed in stratifying risk groups, e.g. non-and
former smoking status and age. Moreover, the rapidly increasing evidence of molecular
and immunologic subgroups within the HPV-positive OPSCCs and within HNSCCs in
general indicate that also other factors are influencing tumoral behavior and response
to therapy. Therefore, when developing new HPV-targeted therapeutic strategies, these
different molecular and biological characteristics must be taken into account.
The expected role of HPV infection in cervical lymph nodes of unknown primary origin
was refuted in this thesis. Nevertheless, de-escalation of therapy in CUP still remains a
serious option, independent of HPV, because it proved to be safe in a comprehensive,
treated patient population described in this thesis.
Future trials on next generation treatment strategies for HPV-associated cancers
should focus on reducing adjuvant radiotherapy and chemotherapy, whether or not in
combination with therapeutic options specifically targeting HPV, HPV-related molecular
biomarkers, and HPV-related subgroups defined by immunological and biological
characteristics. This will enable the selection of superior treatment strategies for high-
risk tumors and possible de-escalation therapies for low-risk groups to reduce toxic
side-effects and minimalize compromised functional outcome.
REFERENCES

46. Castellsagué X, Mena M, Alemany L. Epidemiology of HPV-Positive Tumors in Europe and in the World. Recent Results Cancer Res. 2017;206:27–35


111. https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications
### Table 1. Ongoing clinical trials involving immunomodulation in HNSCC

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug types</th>
<th>Trial number</th>
<th>name</th>
<th>phase</th>
<th>status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cempilimab + ISA101B</td>
<td>anti PD-1 agent + therapeutic vaccine</td>
<td>NCT03669718</td>
<td>II</td>
<td>recruiting</td>
<td>Blinded, placebo-controlled, randomized, phase 2 study</td>
<td></td>
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<tr>
<td>cempilimab + ISA101B</td>
<td>anti PD-1 agent + therapeutic vaccine</td>
<td>NCT04398524</td>
<td>II</td>
<td>not yet recruiting</td>
<td>Phase II study in Recurrent/Metastatic HPV16 Positive OPSCC with disease progression after prior anti-PD-1 therapy</td>
<td></td>
</tr>
<tr>
<td>avelimab + TG4001</td>
<td>anti PD-L1 agent + therapeutic vaccine</td>
<td>NCT03260023</td>
<td>Ib/II</td>
<td>recruiting</td>
<td>Phase Ib/II Trial in HPV-16 positive Recurrent or Metastatic Malignancies (incl. OPSCC)</td>
<td></td>
</tr>
<tr>
<td>durvalumab + MEDI0457</td>
<td>anti PD-L1 agent + therapeutic vaccine</td>
<td>NCT04001413</td>
<td>II</td>
<td>recruiting</td>
<td>Phase 2 trials in HPV-positive HNSCC.</td>
<td></td>
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<tr>
<td>pembrolizumab + PDS0101</td>
<td>anti PD-L1 agent + therapeutic vaccine</td>
<td>NCT04260126</td>
<td>Versatile-002</td>
<td>II</td>
<td>not yet recruiting</td>
<td>Phase 2, open-label, multicenter study in the first line treatment of HPV16 and PD-L1 positive recurrent or metastatic HNSCC: comparing results with KEYNOTE-048 study.</td>
</tr>
<tr>
<td>pembrolizumab + CUE-101</td>
<td>anti PD-L1 agent + a E7-pHLA-IL2-Fc Fusion Protein</td>
<td>NCT03978689</td>
<td>KEYNOTE KN-A78</td>
<td>I</td>
<td>recruiting</td>
<td>Phase1 study of CUE 101 in second line or CUE 101 with pembrolizumab in first line HPV+ R/M HNSCC. CUE-101 is a novel fusion protein stimulating tumor specific T cells to eradicate HPV-driven malignancies.</td>
</tr>
</tbody>
</table>
Table 1. Continued.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug types</th>
<th>Trial number</th>
<th>name</th>
<th>phase</th>
<th>status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pembrolizumab + GSK3359609</td>
<td>anti PD-L1 + anti-ICOS agent</td>
<td>NCT04128696</td>
<td>INDUCE-3</td>
<td>II</td>
<td>recruiting</td>
<td>Randomized, double-blind, adaptive Phase II/III study comparing GSK3359609 inducible T cell co-stimulatory receptor (ICOS) agonist and pembrolizumab to pembrolizumab plus placebo in participants with programmed death receptor 1-ligand 1 (PD-L1) combined positive score (CPS) &gt;=1 R/M HNSCC.</td>
</tr>
<tr>
<td>nivolumab + ipilimumab + RT</td>
<td>anti PD-1 agent + anti-CTLA4 agent + RT</td>
<td>NCT03799445</td>
<td>II</td>
<td>recruiting</td>
<td>Phase 2 Study in LAHPV-positive OPSCCs.</td>
<td></td>
</tr>
<tr>
<td>nivolumab + ipilimumab</td>
<td>anti PD-1 agent + anti-CTLA4 agent</td>
<td>NCT03003637</td>
<td>IMCISION</td>
<td>Ib/Ii</td>
<td>recruiting</td>
<td>Phase Ib/II trial in advanced stage HNSCC</td>
</tr>
<tr>
<td>durvalumab + tremelimumab + SBRT</td>
<td>anti PD-L1 agent + anti CTLA4 agent + SBRT</td>
<td>NCT03618134</td>
<td>Ib/Ii</td>
<td>recruiting</td>
<td>Phase Ib/II trial in HPV-positive OPSCCs.</td>
<td></td>
</tr>
<tr>
<td>monalizumab + cetuximab</td>
<td>anti NKG2a agent + anti EGFR agent</td>
<td>NCT02643550</td>
<td>Interlink-1</td>
<td>Ib/Ii</td>
<td>recruiting</td>
<td>Phase 1b/2 trial in HPV+ and HPV- Recurrent or Metastatic HNSCC.</td>
</tr>
</tbody>
</table>
Table 1. Continued.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Drug types</th>
<th>Trial number</th>
<th>name</th>
<th>phase</th>
<th>status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>monalizumab + durvalumab (among other cohorts)</td>
<td>anti NKG2a agent + anti PD-L1 agent</td>
<td>NCT03088059</td>
<td>UPSTREAM</td>
<td>II</td>
<td>recruiting</td>
<td>Biomarker-driven trial in recurrent or metastatic HNSCC progressing after first-line platinum-based chemotherapy. Based on potential biomarkers and molecular alterations identified in the biopsy from the central platform, patients will be allocated in different biomarker-positive and immunotherapy cohorts.</td>
</tr>
<tr>
<td>buparlisib (BKM120) + cisplatin + XRT</td>
<td>PI3K inhibitor + chemotherapy + radiotherapy</td>
<td>NCT02113878</td>
<td></td>
<td>Ib/II</td>
<td>active, not recruiting</td>
<td>Phase Ib study is combining standard chemoradiotherapy with weekly cisplatin and BKM120 in LAHNSCC.</td>
</tr>
<tr>
<td>alpelisib (BYL719)</td>
<td>PI3K inhibitor</td>
<td>NCT03601507</td>
<td></td>
<td>II</td>
<td>currently suspended (IRB consent forms)</td>
<td>Phase II trial studies of alpelisib in HPV-associated stage I-IVA HNSCC that can be removed by surgery.</td>
</tr>
</tbody>
</table>

(Status was checked on www.clinicaltrials.gov, August 2020)