The Role of HPV Status in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

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Abstract: Although the prognostic role of human papillomavirus (HPV) in locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) is well established, its prognostic and/or predictive role in recurrent/metastatic settings remains to be defined. Despite epidemic growth of HPV-positive oropharyngeal carcinoma, a low recurrence rate in HPV-positive patients results in a small number of patients entering clinical trials for recurrent and/or metastatic SCCHN. The consequent lack of statistical power and also significant data contamination by misclassification of HPV-positive patients leads to premature study conclusions. Even emerging data from the analysis of 2 randomized trials, SPECTRUM and EXTREME, do not provide enough evidence for any HPV-based therapeutic strategy. Many upcoming studies for locally advanced disease, including the ones with de-escalated strategies, will have an increasing number of patients with HPV. Optimal HPV testing strategies for reliable patient selection and HPV-driven therapeutic approaches will be essential. Here, we comprehensively review the existing data regarding HPV status and prognostic or predictive outcomes in recurrent/metastatic settings and discuss current promising studies and future directions that may help in the design of upcoming trials.

Introduction

The expected incidence of squamous cell carcinoma of the head and neck (SCCHN) in the United States in 2014 is approximately 55,070, and the predicted number of deaths from this disease is 12,000. In 2011, there were an estimated 281,591 persons living with oral cavity and pharyngeal cancer in the United States.[1] Although tobacco is the most common risk factor for SCCHN, human papillomavirus (HPV) plays a significant role in the development of squamous cell carcinomas of the oropharynx.[2] The incidence of tobacco-related SCCHN is decreasing; however, the overall rate of newly diagnosed SCCHN has been stable from 2002 to 2011. This stability is attributable to the epidemic growth in the incidence of HPV-positive oropharyngeal cancers (OPCs).[1,3] Of great clinical significance, HPV status is now

Table 1. Overall Survival, Locoregional Failure, and Distant Failure Rates Based on HPV Status

Study	PFS		Local/Regional Failure		Distant Failure	
	HPV+	HPV–	HPV+	HPV–	HPV+	HPV–
RTOG 0129[4]	73.7% (3-year)	43.4% (3-year)	13.6% (3-year)	35.1% (3-year)	8.7%, NS (3-year)	14.6%, NS (3-year)
RTOG 0522 + RTOG 0129[20]	Not reported	Not reported	20%[a]	32.9%[a]	41%[a]	38.2%[a]
TROG 02.02[45]	87% (2-year)[b]	72% (2-year)[b]	~7% (2-year)	~13% (2-year)	~4% (2-year)	~4% (2-year)
TAX 324[5]	73% (5-year)	29% (5-year)	13% (5-year)	42% (5-year)	5%, NS (5-year)	11%, NS (5-year)
Deeken et al[22]	Not reported	Not reported	25%, NS	48%, NS	58%	24%, NS

HPV, human papillomavirus; NS, statistically nonsignificant; OS, overall survival; PFS, progression-free survival; RTOG, Radiation Therapy Oncology Group; TAX, docetaxel; TROG, Trans Tasman Radiation Oncology Group.

[a] Represents a percentage fraction within a group of patients whose disease progressed and were available for HPV testing.

[b] Failure-free survival, measured to the date of first treatment failure or death. Failure was defined as "persistent disease in the primary site (other than a stable radiologic abnormality without clinical evidence of disease), progression of disease in the neck in patients not undergoing neck dissection, residual disease left behind following neck dissection, locoregional relapse following complete response, or distant metastasis."[45]

well established as the most important prognostic factor for progression-free and overall survival of OPC patients at initial presentation. The prognostic value of HPV in OPC in recurrent and/or metastatic (R/M) SCCHN has not been well established and specific treatments or nuances of therapy have not been described for multiple reasons, including the relative paucity of recurrences, the recent identification of HPV as causal, and the technical difficulty of identifying HPV in tissues.[4-8]

Recurrent locoregional or metastatic SCCHN represents a biologically very heterogeneous disease, and traditionally patients with R/M disease have very poor prognoses.[9] Therapeutic strategies often depend on the patient's performance status and comorbidities, the anatomic site of recurrence, the speed of macroscopic growth at the site of recurrence, and the history and nature of previous therapies. Because of the very limited data available about treatment of HPV-positive patients with R/M SCCHN, there is a significant need to review the outcomes of trials for data on therapeutic strategies, efficacy, and overall prognosis for HPV-positive R/M SCCHN patients.

In this paper, we present current data on the role of HPV status in R/M SCCHN. We discuss the patterns and rates of failure in HPV-positive patients treated with curative intent, existing therapeutic options for R/M, and the prognosis for such patients.

Rate and Patterns of Failure in Patients With Previously Untreated, Locally Advanced, HPV-Positive SCCHN After Definitive Therapy

It is now firmly established from clinical studies that the prognosis for patients with locally advanced HPV-positive OPC at initial presentation is significantly better than that for patients with HPV-negative cancer. The 5-year survival rate has averaged approximately 80% for HPV-positive OPC, compared with 35% for HPV-negative OPC.[5] Prior smoking, extensive matted nodal disease, contralateral nodal disease, and T4 tumors appear to be the only major prognostic factors for recurrence.[10,11]

A low recurrence rate for HPV-positive patients (Table 1) limits the number of HPV-positive patients available for and enrolling in clinical trials after disease progression. However, there are increasing numbers of HPV-positive SCCHN patients and late recurrences are also appearing. Further, there are now a number of so-called de-escalated trials beginning.[4,12-14] These factors may lead to an increased prevalence of R/M HPV-positive patients in the future. These patients will require therapeutic strategies that address their potentially favorable prognosis based on their HPV status.[12] As the natural history of the disease and changes in therapy unfold, we will face some challenges in establishing therapeutic strategies because the R/M HPV-positive population may be very heterogeneous owing to unusual patterns of treatment failure, the effect of prior smoking, differences in the impact of prior therapy (eg, recurrences within the radiation field, salvage therapy, and metastasectomies), and unexpected patterns of distant metastases.[10,12,15]

A 10-year retrospective analysis (2000 to 2010) of 457 HPV-positive SCCHN patients at Princess Margaret Hospital in Toronto[12] identified the lungs as the most common metastatic site, but included other sites such as the skin, intraabdominal lymph nodes, brain, skeletal muscle, kidney, pericardial lymph nodes, and pancreatic tail. The analysis included 167 HPV-negative patients; in this group, distant metastases were found in the lungs,

liver, and bone. Although the rates of distant metastases in HPV-positive and HPV-negative patients remained unchanged, interestingly, significant improvement in locoregional control in HPV-positive patients created a new paradigm. Distant metastasis in HPV-positive patients is emerging as the leading cause of treatment failure. This contrasts with the pattern of locoregional failure that predominated prior to the epidemic growth of HPV-positive OPC, and remains the principal pattern in the HPV-negative population. Remarkably, 39 of 54 HPV-positive patients with distant metastases in the Princess Margaret study had no locoregional treatment failure. It also appears that in HPV-positive patients, distant metastases may occur well beyond 2 years, with some observed even after 5 years. In the HPV-negative counterparts, however, distant metastases usually occurred within the first 2 years.[12] Although proven benefit from more prolonged follow-up is lacking, because of late recurrences and because of the anatomic distribution of those recurrences, surveillance beyond 5 years with whole-body imaging tests such as positron emission tomography scans should be strongly considered. Caution should be advised in the number of posttreatment surveillance scans owing to the risk for secondary malignancies, especially in HPV-positive patients, who often are young.[16-19]

In a combined early analysis of RTOG 0129 and 0522 (Radiation Therapy Oncology Group studies), 181 patients had disease progression and had tumor samples available for p16 status assessment (95 patients in RTOG 0129 and 86 patients in RTOG 0522).[20] Although HPV testing was available for RTOG 0129 subjects, HPV tumor status was based on a surrogate marker, p16 expression, and it was scored as positive if strong and diffuse nuclear and cytoplasmic staining was present in at least 70% of the tumor cells. In these early results, with median follow-up of 4 years, the anatomic distribution of distant metastases was similar in HPV-positive and HPV-negative patients, and the lungs were found to be the most common metastatic site in both patient groups, followed by bone, liver, and other sites (Table 2). Median time to disease progression was 2.6 vs 0.8 years for HPV-positive vs HPV-negative patients, respectively. Cumulative measures of cigarette smoking at enrollment were available for 154 (85%) of 181 patients; the median number of pack-years was 38.5 in p16-negative patients vs 16.5 in p16-positive patients.[20]

In the original ECOG (Eastern Cooperative Oncology Group) study, which was trial 2399, a total of 96 patients with stage III or IV SCCHN of the oropharynx or larynx were treated with induction chemotherapy and chemoradiotherapy.[21] After a median follow-up of 39.1 months, there was a difference in the pattern of treatment failure between HPV-positive and HPV-negative

Table 2. Patterns of Failure in Combined Analysis of RTOG 0522 and RTOG 0129[20]

Type of Progression	HPV Negative (n=76)	HPV Positive (n=105)
Local	32.9%	20%
Regional	18.4%	30.5%
Local and regional	5.3%	3.8%
Local and distant	3.9%	2.9%
Regional and distant	1.3%	1.9%
Distant	38.2%	41.0%
DM anatomic distribution (n=81)	**HPV Negative (n=33)**	**HPV Positive (n=48)**
Lung	69.7%	72.9%
Bone	15.2%	14.6%
Liver	15.2%	8.3%
Other	12.1%	16.7%

DM, distant metastases; HPV, human papillomavirus; RTOG, Radiation Therapy Oncology Group.

OPC patients. With 38 HPV-positive OPC and 24 HPV-negative OPC patients, 2 local/regional and 3 distant recurrences were seen in the HPV-positive group vs 8 local/regional and 1 distant recurrence in the HPV-negative group. A statistically nonsignificant difference in the incidence of secondary primary tumors was seen; they occurred in 4 out of 38 patients (11%) in the HPV-positive OPC group and 3 out of 58 patients (5%) in the HPV-negative OPC and laryngeal cancer group (P=.43). The majority of these secondary primary tumors were not established as smoking-related.[21]

In a small retrospective analysis by Deeken and colleagues[22] of 37 patients (12 HPV+, 25 HPV–) treated for R/M SCCHN from 2008 to 2013 at the Lombardi Comprehensive Cancer Center in Washington, DC, there was a similar distribution of distant metastases and time to disease progression based on HPV status. The most common sites for metastatic disease were the lungs and the liver. Within the first 6 months of completion of primary treatment, 11 of 25 HPV-negative patients (44%) developed recurrence but none of the 25 HPV-positive patients did. With a mean follow-up of 21 months, the time to progression was statistically significantly shorter in HPV-negative patients: 11.5 months vs 19.2 months in HPV-positive patients (P=.0078). All tumors were tested with immunohistochemistry (IHC) analysis for p16 status and, if positive, HPV status was confirmed with polymerase chain reaction testing with specific primers to detect the presence of the E6 and E7 oncogenes for either HPV 16 or HPV 18 along with positive and negative controls for each.[22]

Table 3. Impact of HPV Status on Outcome in R/M SCCHN

Study Name and Endpoint	HPV Negative	HPV Positive (OPC Only)
E1395 + E3301[25]	n=52	n=11
Response rate	19%	55%
Median survival, mo	6.7	12.9
Median PFS, mo	3.2	5.9
EXTREME study[6]	n=92	n=18
RR in chemotherapy-only arm	25%	0 (n=0)
RR in chemotherapy plus cetuximab arm	31%	75%
OS in chemotherapy-only arm, mo	7.3	7.2
OS in chemotherapy plus cetuximab arm, mo	10.9	19.4
PFS in chemotherapy-only arm, mo	2.9	4.3
PFS in chemotherapy plus cetuximab arm, mo	5.9	5.8
SPECTRUM study[27]	n=344	n=99 (47 were OPC only)
OS in chemotherapy-only arm, mo	8.6	12.6[a]
OS in chemotherapy plus panitumumab arm, mo	11.7	11[a]
PFS in chemotherapy-only arm, mo	5.1	5.5[a]
PFS in chemotherapy plus panitumumab arm, mo	6.0	5.6[a]

E, Eastern Cooperative Oncology Group; EXTREME, Cetuximab (Erbitux) in Combination With Cisplatin or Carboplatin and 5-Fluorouracil in the First-Line Treatment of Subjects With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck; HPV, human papillomavirus; OPC, oropharyngeal cancer; OS, overall survival; PFS, progression-free survival; R/M, recurrent and/or metastatic; RR, response rate; SCCHN, squamous cell carcinoma of the head and neck; SPECTRUM, Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer.

[a] Outcome reported for all p16-positive patients: 47 OPX and 52 non-OPX SCCHN patients.

In summary, the small number of available studies highlights the differences in patterns of treatment failure and time to disease progression based on HPV status. These differences may lead to changes in surveillance recommendations, future clinical trial designs, and future follow-up recommendations. Thus, patients with HPV-positive tumors may need longer follow-up and surveillance strategies that address unusual metastatic sites, such as positron emission tomography scanning. In addition, there is the need to identify biomarkers for the risk of progression in order to stratify patients for more- or less-intensive surveillance strategies.

HPV as a Prognostic and Predictive Marker in R/M SCCHN

Several clinical and pathologic prognostic factors have been used in the R/M SCCHN setting, including: tumor cell differentiation, primary tumor location, prior radiation, weight loss or performance status, and pretreatment neutrophil-to-lymphocyte ratio.[23,24] Tumor HPV status's prognostic role in previously untreated and locally advanced R/M SCCHN is well established, but the prognostic utility of HPV in R/M SCCHN has not yet been defined.[4]

A combined retrospective analysis of 2 major Eastern Cooperative Oncology Group clinical trials for R/M disease, E1395 and E3301, looked at 65 patients analyzed for HPV status. The analysis found that HPV positivity was reported as a favorable prognostic factor in R/M SCCHN.[23,25] Despite this small study sample, 11 OPC patients were assessed as HPV-positive by in situ hybridization, 12 were positive for p16 by IHC cutoff of 80%, and 52 were both p16- and HPV-negative. Statistically significant improvements in response rate and survival were seen in the p16/HPV-positive population (Table 3). In those 2 studies, different chemotherapy doublets were tested: cisplatin/5-fluorouracil (PF) vs cisplatin/paclitaxel in E1395 and docetaxel/irinotecan in E3301. These limited findings support a prognostic role for HPV in R/M SCCHN but do not provide a predictive role for specific chemotherapy; nor was survival readily quantifiable, and data about responsiveness and progression-free survival (PFS) with second- and third-line therapies are not available.

Similar results were reported in both the EXTREME (Cetuximab [Erbitux] in Combination With Cisplatin or Carboplatin and 5-Fluorouracil in the First-Line Treatment of Subjects With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck) and SPECTRUM (Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer) studies, where the epidermal growth factor receptor (EGFR) inhibitor was added to PF chemotherapy. In the EXTREME study, 442 patients, all treatment-naive, were randomly assigned to receive PF every 3 weeks with or without cetuximab. The primary endpoint was overall survival, defined as the time from randomization to death, and the secondary endpoint was PFS.[9] IHC testing for p16 expression was considered positive if greater than 70% of tumor cells showed moderate or strong and diffuse nuclear staining; confirmatory testing for HPV DNA with the FDA-approved Cervista HPV 16/18 test was used. Of 416 patients who were available for p16 and HPV testing, only 41 (10%) were p16-positive, and within the p16-positive group only 19 of 41 were HPV-positive.[6] Since the role of p16 alone in non-OPC is questionable, which restricts the analysis to the HPV-positive OPC-only patients, results of the

study should be interpreted with caution.[7,26] Cetuximab addition provided a numerically significant difference between p16-positive and p16-negative patients in response rate and overall survival but not in PFS (Table 3). At the time of the EXTREME study, there were no second-line chemotherapeutic options for R/M SCCHN available, and cetuximab was not used after progression. In addition, there are no further data on follow-up treatments. Thus, there is no therapeutic information that would help explain why there is a difference in overall survival but not in PFS.

In the SPECTRUM trial, 657 previously untreated patients were randomly assigned to receive PF and panitumumab or PF alone.[27] Surprisingly, in a prospectively defined retrospective analysis, it was reported that within the p16-positive group, median survival in the experimental arm was shorter than in the control arm, 11.0 vs 12.6 months, respectively, but the *P* value was only .998. Also, this exploratory analysis showed favorable preliminary results within the experimental arm with regard to both PFS and overall survival for the HPV-negative patients compared with patients who were HPV-positive, suggesting no clinical benefit from panitumumab in HPV-positive patients with R/M SCCHN (Table 3). However, there are significant questions about the technical validity of the laboratory assessments of HPV status in this study. For example, a very low cutoff of 10% for p16 was used to define HPV positivity.[4,28] The currently recommended cutoff point for defining a positive p16 IHC assay result is that strong and diffuse nuclear and cytoplasmic staining should be seen in at least 75% of tumor cells.[29] Recent studies[28] also suggest that staining should be seen in at least 70% of cells; even in a recent report on the EXTREME study,[6] a 70% cutoff for p16 was used. There is a lack of standardization and consistency among trials in testing methods, such as the validity of p16 IHC, HPV polymerase chain reaction, HPV in situ hybridization, and nonkeratinizing morphology assessment. This highlights a tremendous need for a consensus among pathologists and clinicians on standard criteria and tests for ascertaining HPV status of a SCCHN. In the SPECTRUM study,[27] 443 of 657 patients (67%) were available for HPV analysis and 99 were p16-positive. The majority of p16-positive patients had cancer in non-oropharyngeal sites, and inappropriate HPV classification of non-OPC patients as HPV-positive and use of a lower cutoff for p16 positivity than the widely accepted standard led to a higher-than-expected number of R/M SCCHN HPV-positive patients in this study. Perhaps, out of 99 patients (99/657; 15%) who were reported as HPV-positive, only those OPC patients who were p16-positive (47/99; 47%) were truly HPV-positive patients—although there was a significant chance of false positives within this group as well.

Within these limitations, Spreafico and colleagues did a combined analysis of E1395, E3301, and the EXTREME study as well as the SPECTRUM study.[30] The analysis suggests that with chemotherapy alone, HPV- or p16-positive patients have better overall survival, with the studies showing a 30% to 40% reduction in the risk of death over time. In the same analysis, the combined EXTREME and SPECTRUM studies show no predictive value of p16 overexpression for response with the addition of an EGFR inhibitor to PF.

These data have significant limitations, such as unknown smoking status and inaccurate HPV classification based on the detection method.[7,31] Furthermore, other variables may have contaminated the data, such as the low rate of recurrence among HPV-positive cancers and the lack of data on subsequent therapies. According to the data reported in the SPECTRUM study, current knowledge does not allow us to state whether EGFR inhibitors provide more or less effective treatment for patients with HPV-positive R/M SCCHN, but the study results highlight the need for patient stratification based on HPV status in future trials. Most importantly, a validated and robust HPV testing algorithm and classification method is absolutely necessary for future studies.

Non–Chemotherapy-Based Treatment Modalities for HPV-Positive R/M SCCHN

The recent combined analysis of 2 major clinical trials for locally advanced SCCHN, RTOG 0522 and 0129, reported salvage surgery and HPV status as strong and independent predictors of overall survival.[20] Interestingly, salvage surgery was performed at the same rate for HPV-positive and HPV-negative patients (27.6% and 26.3%, respectively; *P*=.05) and provided a significant difference in survival, estimated at a 52% reduction in the risk of death after disease progression regardless of HPV status. Unfortunately, in this study patients were not treated in a uniform fashion and there are no data on the use of subsequent palliative chemotherapy or on the rate of metastasectomies, modalities that may have an impact on patients' survival. Overall, the currently available data from this study do not allow estimation of the true influence of salvage surgery on the observed survival difference owing to potential data contamination.

A retrospective analysis by the Metastatic Lung Tumor Study Group of Japan, of 97 patients with R/M SCCHN from primary sites other than the oral cavity, showed that the 5-year overall survival rate was 32 percent. Postoperative therapy after pulmonary metastasectomy included chemotherapy in 17 patients, chemoradiotherapy in 6 patients, and radiation in 5 patients, but no significant difference between the no adjuvant therapy group and the adjuvant therapy group was observed.[32] Unfortunately,

there are no HPV data available, but similar findings are seen in other studies.[33-35]

Deeken and colleagues reported the effects of multimodality treatment based on HPV status in patients with R/M SCCHN.[22] A total of 37 patients were heterogeneously treated with salvage neck surgery, metastasectomy, hypofractionated reirradiation, chemoembolization, and/or chemotherapy. Between 12 HPV-positive and 25 HPV-negative patients, there was no significant difference in smoking history (67% vs 76%, respectively) or total number of pack-years. The median survival in the HPV-negative group was 10.6 months, similar to that seen in the EXTREME study, suggesting that there is no benefit from multimodality or more aggressive treatment approaches in this population. However, in the HPV-positive group, median survival was not reached with a mean follow-up of 21 months. Interestingly, HPV-positive patients underwent liver or lung metastasectomy more frequently than HPV-negative patients (67% vs 12%; P=.001, respectively). In addition, a statistically nonsignificant trend toward better overall survival was seen with a higher number of total interventions (and a higher average number of lines of chemotherapy), and the improvement was greater in HPV-positive patients than in HPV-negative patients. This very small retrospective study suggests that multimodality and aggressive therapy may provide better survival for HPV-positive R/M SCCHN patients and that such therapy warrants further prospective evaluation, and emphasizes the need for stratification by HPV status in prospective clinical trials.

Role of immunotherapy in HPV-positive R/M SCCHN. Various preclinical studies have shown a promising role for immunotherapy in the treatment of HPV-positive SCCHN.[36-38] More preventive approaches with L1 protein–based vaccines developed for cervical cancer, such as Gardasil and Cervarix, hold significant promise for controlling the increasing incidence of HPV-related cancers—including SCCHN—decades from now. However, these approaches have no benefit for patients who are currently infected or already have been diagnosed with HPV-related SCCHN. The foreign nature of HPV in HPV-induced cancers makes it an attractive target for immunotherapy. Immunomodulators, such as the toll-like receptor agonists and cytokines, have shown the ability to enhance the antibody-dependent cell-mediated cytotoxicity of cetuximab and to potentiate the effect of chemotherapy by modulating the tumor microenvironment, with increased T-cell responses to antigenic debris generated by chemotherapy-based tumoricidal activity.[39,40]

Other attractive treatment options are therapeutic vaccines. A variety of vectors have been used to deliver vaccines: live viral vectors, peptides and proteins, and bacterial vectors.[38,41,42] Trojan-type constructs with melanoma antigen E-A3 HPV 16 vaccines have been tested with acceptable toxicity but showed no clinical responses as defined by Response Evaluation Criteria in Solid Tumors criteria.[42] TG4001, a modified vaccine virus vaccine, is being tested in clinical trials.[41] At our institution (Icahn School of Medicine at Mount Sinai), a therapeutic recombinant *Listeria monocytogenes* vaccine is being studied in HPV-positive OPC patients (NCT02002182).

Cytotoxic T-lymphocyte–associated protein 4 checkpoint inhibitors that may activate T-cell activation, such as ipilimumab (Yervoy, Bristol-Myers Squibb), also hold some promise and are being studied in HPV-positive SCCHN (NCT01935921). Other antibodies and fusion proteins that are capable of stimulation of immune cells are emerging as potent therapeutic options for the treatment of cancer. Recent reports demonstrated that pairing programmed cell death protein 1 (PD-1), expressed on T cells and pro-B cells, and programmed death ligand 1 (PD-L1), expressed on HPV-positive tumors, allows cancers to evade the host immune system.[36,37] Preclinical data have showed that PD-1/PD-L1 blockage leads to T-cell–based immune responses, making this pathway an attractive therapeutic target currently being tested in multiple clinical trials with R/M SCCHN (NCT02105636).

Conclusions and Future Directions

Although enrollment of HPV-positive patients in clinical trials for R/M SCCHN has been minimal, the increasing epidemic of HPV-positive cancer will increase the volume of patients with R/M disease, support stratification and valid data, and lead to more directed therapies. There is also a pressing need to recognize the biologic differences between HPV-positive and HPV-negative SCCHN and to develop therapeutic strategies that will address specific efficacy and the risk of toxicity in HPV-positive and HPV-negative patients. Currently available data are retrospective, limited by small patient numbers, and hampered by nonstandardized HPV assessments. We stress the importance of the creation of diagnostic standards for HPV testing to avoid significant data contamination and tumor misclassification, which obscure the data and lead to inaccurate conclusions. Patient stratification based on HPV status in R/M SCCHN should become standard in future clinical trials. More importantly, perhaps non–chemotherapy-based therapeutic options, such as surgery and stereotactic radiation, which have previously been reserved for treating locally advanced disease, should be considered in oligometastatic R/M SCCHN either as a reasonable alternative to chemotherapy or as part of combined-modality therapy with adjuvant systemic treatment for limited-stage cancers, and with more aggressive

systemic therapy for more extensive recurrences using combinations such as docetaxel, cisplatin, and fluorouracil. Even though, as reported in the Princess Margaret Hospital study, metastases in HPV-positive patients commonly involve multiple (>2) organs concurrently, unlike in HPV-negative patients (33% vs 0%, respectively, in that study), only 20% of HPV-positive distant metastases demonstrated an explosive character, with numerous metastatic lesions occupying almost an entire organ.[12] The optimal selection of patients who are candidates for resection or local therapy is evolving but, as seen in colorectal cancer, the presence of both liver and lung metastases or a history of previously resected hepatic metastases does not necessarily represent a contraindication to pulmonary metastasectomy, as long as a complete resection of all sites of disease can be accomplished.[43,44] The current paradigm of palliative chemotherapy as the only therapeutic option for oligometastatic disease has been challenged in other malignancies such as colon cancer, and probably should be re-evaluated in HPV-positive R/M SCCHN. Future directions also should explore cancer vaccination and immunotherapy for this virally driven cancer. The development of HPV-targeting immunotherapies and vaccines is a logical strategy based on the elevated incidence of HPV-positive lesions, as well as on promising preclinical and clinical results. Lastly, there is a significant need for biomarker-driven therapies in R/M SCCHN that would help us provide prognoses to patients and assign them to appropriate therapy.

Disclosures

The authors have reported no relevant financial disclosures.

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