Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment

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Abstract

Squamous cell carcinoma arises from multiple anatomic subsites in the head and neck region. The risk factors for development of cancers of the oral cavity, oropharynx, hypopharynx, and larynx include tobacco exposure and alcohol dependence, and infection with oncogenic viruses is associated with cancers developing in the nasopharynx, palatine, and lingual tonsils of the oropharynx. The incidence of human papillomavirus–associated oropharyngeal cancer is increasing in developed countries, and by 2020, the annual incidence could surpass that of cervical cancer. The treatment for early-stage squamous cell cancers of the head and neck is generally single modality, either surgery or radiotherapy. The treatment for locally advanced head and neck cancers is multimodal, with either surgery followed by adjuvant radiation or chemoradiation as indicated by pathologic features or definitive chemoradiation. For recurrent disease that is not amenable to a salvage local or regional approach and for metastatic disease, chemotherapy with or without a biological agent is indicated. To date, molecular testing has not influenced treatment selection in head and neck cancer. This review will focus on the changing epidemiology, advances in diagnosis, and treatment options for squamous cell cancers of the head and neck, along with data on risk stratification specific to oropharyngeal cancer, and will highlight the direction of current trials.
Worldwide, over 500,000 new cases of head and neck squamous cell carcinoma (HNSCC) are reported annually, with 40,000 new cases and 7890 deaths reported in the United States annually. Head and neck squamous cell carcinoma can arise from subsites within the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx. It is well known that sustained exposure to tobacco, tobacco-like products, and alcohol increases the risk of development of HNSCC. Over the past decade, there has been a shift in the primary site distribution, with a steady increase of oropharyngeal squamous cell carcinoma (OPSCC) and a decline in cancers of the larynx and hypopharynx. This change has been observed in parallel with a decrease in cigarette smoking and the identification of exposure to high-risk oncogenic human papillomavirus (HPV) as a risk factor for development of OPSCC.

The incidence of HPV-positive OPSCC in the United States increased by 225% between 1988 and 2004, and HPV-negative OPSCC declined by 50%. The changing landscape with increasing incidence of OPSCC and decline of laryngeal cancer between 1980 and 2011 is illustrated in the Figure. In North America, 56% of OPSCCs are HPV positive, followed by 52% in Japan, 45% in Australia, 39% in northern and western Europe, and 13% in the rest of the world. Patients with HPV-positive OPSCC are typically middle-aged, nonsmoking white men of higher socioeconomic status and with a history of exposure to multiple sexual partners. These patients may have some previous exposure to smoking, but most are not current smokers. Furthermore, the prognosis for patients with HPV-positive OPSCC is substantially better than that for patients with HPV-negative tobacco-related cancers treated similarly. This departure from the classic patient in their 7th decade of life with a history of tobacco and alcohol abuse has dramatically changed research directions within the head and neck cancer academic community.

The clinical presentation varies with the site of origin. At initial presentation, over 40% of patients have regional nodal involvement and disease classified as stage IVA or B, and 10% present with distant metastases considered stage IVC. The prognosis differs significantly on the basis of tumor site, tumor tissue HPV status, and overall stage. This review will focus on recent advances in diagnosis, distinct molecular and clinical phenotypes of HNSCC, treatment advances in early, locally advanced, and metastatic HNSCC, risk stratification for OPSCC, the challenges and pitfalls of current trials, and the direction of the next generation of trials.

CLINICAL ISSUES IN HNSCC

With the recognition of high-risk HPV infection (primarily type 16) as a risk factor for development of HNSCC and its prognostic importance, there is increasing interest in approaching HNSCC as 2 distinct types, HPV-positive and HPV-negative disease. This distinction is driving advances in our understanding of the biology, mutational landscape, predictors of response to treatment, and survival outcomes for these 2 distinct types of HNSCC.

De-escalation of the current standard chemoradiation approach in the HPV-positive population in order to avoid potential overtreatment and consequent late effects and the addition of targeted agents to the current standard approaches in HPV-negative patients to improve this group’s poor overall survival are the underlying themes and direction of the current generation of clinical trials.

DIAGNOSTIC ADVANCES IN HNSCC

HPV Testing

There is a distinct biology and molecular phenotype among HPV-positive OPSCCs when compared with HPV-negative HNSCCs (Table 1). It is critical to understand the HPV types and their role in carcinogenesis. Human papillomavirus is a small-DNA virus with predilection to cutaneous or mucosal squamous epithelium located in the cervix, anogenital region, and a subset of HNSCCs arising from the oropharynx. The oncogenic types HPV-16, HPV-18, HPV-31, and HPV-33 are sexually transmitted and considered as high-risk factors for malignant transformation of infected cells. In most individuals, the infection clears. However, in those infected individuals who do not mount an adequate immune response to clear the virus, viral DNA is integrated into the
host genome, HPV oncoproteins E6 and E7 alter the function of tumor protein p53 and retinoblastoma pocket protein Rb, resulting in malignant transformation, a key step in HPV carcinogenesis. The oncoprotein E7 binding to Rb pocket protein results in overexpression of p16 INK4A encoded by CDKN2A in the HPV-infected tissue. Immunohistochemical (IHC) analysis of the tumor tissue for p16 INK4A is now used in the head and neck community as the initial test of choice and a surrogate marker to identify high-risk HPV infection in tumor tissue. In conjunction with p16 IHC, methods to directly identify HPV DNA and RNA are available. The 2 methods used to detect HPV DNA are polymerase chain reaction (PCR) and in situ hybridization (ISH). Polymerase chain reaction is a highly sensitive and cost-effective method that uses a primer to detect a broad spectrum of HPV types. However, PCR has low specificity for distinguishing between episomal and integrated HPV DNA, only the latter occurring with clinically relevant infection. This disadvantage is overcome with ISH of tumor tissue, which can detect HPV DNA with high sensitivity and distinguish integrated HPV DNA by punctate signals and episomal HPV DNA by diffuse signals.

All of these methods can be performed on routine formalin-fixed paraffin-embedded biopsy samples. Currently, screening tumor tissue with p16 IHC first followed by HPV-specific testing with ISH or PCR is recommended.

Molecular Phenotypes of HNSCC and Whole-Genome Sequencing

In contrast to HPV-associated OPSCC, HNSCC caused by exposure to smoking and alcohol is more likely to be associated with mutations in tumor suppressor genes and specifically TP53, making these cancers less sensitive to chemoradiation. The HPV-positive cancers have gene expression and DNA methylation profiles that are unique (Table 2).

Whole-genome sequencing has identified, apart from TP53 mutation, additional mutations specifically, the tumor survival (PIK3CA-AKT1-MTOR-PTEN, EGFR and MET pathways), tumor proliferation (p16, RB, MET, CCND1, CDKN2A/CDKN2B), and tumor differentiation (NOTCH1) pathways.

The Cancer Genome Atlas Network reported the results of whole-genome sequencing on tumor tissue from 279 patients with HNSCC. The comprehensive profile of the somatic genetic alterations specific to HPV-positive and HPV-negative tumors is summarized in Table 2. These data confirm the nearly universal loss of function of TP53 mutations, the CDKN2A gene inactivation in high frequency in HPV-negative HNSCC. Among the HPV-positive HNSCCs,
recurrent deletions and mutations with tumor necrosis factor receptor–associated factor 3 (TRAF3), PIK3CA, and amplification of cell cycle gene E2F1 were noted.21 TRAF3 is important for innate and acquired antiviral response, and linking this gene to HPV-associated cancers is critical to understanding the biology of these tumors.21 Targeted therapies directed against one or more of these deranged pathways are already under investigation, and the data from the Cancer Genome Atlas Network will provide new insights on potential therapeutic targets in HNSCC.

### Role of Positron Emission Tomography in Staging and Response Assessment

Direct nasopharyngolaryngoscopy, computed tomography (CT), and magnetic resonance imaging are routinely used to determine the initial extent of disease involvement and stage. [18F]-Fludeoxyglucose–positron emission tomography (PET) has increased sensitivity in detecting small primary tumors and nodal disease not palpable on clinical examination or detected on direct visualization.22 This modality has led to improvement in staging accuracy and planning appropriate treatment with surgery for management of tumors of the neck and for radiation field planning for chemoradiation in locally advanced disease.22 In patients with distant disease detected on initial staging or follow-up PET-CT, systemic chemotherapy becomes frontline therapy.22,23 There is now ample evidence for the utility of PET-CT in the posttreatment assessment of patients with locally advanced disease managed with chemoradiation. The negative predictive value for assessment of response when [18F]-fludeoxyglucose–PET is performed 12 weeks following completion of treatment is 98.7% for the primary tumor and 99% for the neck.24,25 Negative findings on PET are prognostic for long-term local and regional control and can be reliably used for management of nonsurgically treated patients after chemoradiation.

### TREATMENT ADVANCES IN HNSCC

Surgery, radiation, and chemotherapy in various combinations are utilized in the management of HNSCC, depending on TNM stage and primary site.3,26 Limited or early-stage disease (stage I and II) is the presenting stage in approximately 40% of patients and is usually treated with surgery or radiation alone.3,26 For most patients with locally advanced disease (stage III and IVA/B), resectable or unresectable, treatment entails platinum-based chemoradiation, with or without induction chemotherapy (IC) as a sequential therapy.3,26 Metastatic disease is treated with combination chemotherapy for patients with good performance status and single-agent chemotherapy or best supportive care for patients with poor performance status.3,26 The treatment of local or regional recurrence depends on the site of recurrence, tumor burden, and prior therapy and may range from salvage surgery to radiation or reirradiation with chemotherapy or chemotherapy alone if the disease is not
amenable to salvage with either surgery or radiation.3,26 All of these treatments are associated with toxicity leading to some degree of late organ dysfunction that may be substantial whether a surgical or nonsurgical approach is taken.

Surgery
Primary curative surgery for HNSCC is reserved for resectable tumors in which clear margins can be achieved and function is preserved. Classic open surgery or minimally invasive procedures such as transoral robotic surgery (TORS) or laser surgery are employed depending on the anatomy and tumor characteristics.27 The former may result in cosmetic deformity and functional impairment and is less favored by younger, otherwise healthy, and socially interactive patients with HPV-positive HNSCC. Currently, TORS is offered as an alternative to chemoradiation as a function-preserving strategy with or without neck dissection. In experienced hands, TORS appears to be effective and oncologically safe for selected HNSCCs.27,28 Clinical trials of TORS or transoral laser surgery are in progress.

Radiation Therapy
For treatment of locally advanced disease, radiation therapy (RT) is employed as an adjunct to surgery or concurrent with chemotherapy.3,26 The dose of radiation for HNSCC varies from 60 Gy to 70 Gy, depending on timing of treatment and adjuvant vs definitive initial treatment.26 In the definitive setting, the Radiation Therapy Oncology Group (RTOG) 0129 phase 3 trial compared standard and accelerated boost radiation regimens with concurrent cisplatin and found no difference in local or regional control, overall survival, and late effects.25 The risk of long-term toxicity from radiation increases with delivery of doses exceeding 55 Gy to the salivary glands, pharyngeal constrictor muscles, and thyroid gland, leading to xerostomia, dysphagia, percutaneous endoscopic gastrostomy tube dependence, chronic aspiration, and hypothyroidism.30 Recent advances with intensity-modulated radiotherapy (IMRT) allow conformal fields and the application of dose constraints to the volume of the salivary gland treated. Salivary gland sparing is a major benefit of IMRT for improved quality of life through reduction of xerostomia. However, field contouring with dose constraints to the pharyngeal constrictor muscles is difficult to achieve in the treatment of oropharyngeal cancers, and the risk of aspiration, dysphagia, and percutaneous endoscopic gastrostomy tube dependence are still present.31 Strategies for dose deintensification in patients with low risk of recurrence are in progress and with IMRT delivery systems may be able to reduce these late effects.

Chemoradiation
Chemotherapy as part of initial curative multimodality management has been used in the setting of IC, concomitant with RT, and as adjuvant treatment.3,26 A comprehensive meta-analysis of clinical trials conducted between 1965 and 2000 by tumor site in HNSCC found an absolute benefit only for concomitant administration of cisplatin with radiation.32,33 High-dose cisplatin remains the standard radiosensitizer in the treatment of HNSCC. The MACH (meta-analysis of chemotherapy in head and neck cancer) meta-analysis revealed that the absolute benefit with chemoradiation was 7% at 2 years and 8% at 5 years, with a hazard ratio (HR) of 0.81 (95% CI, 0.76-0.88; P<.0001).32 Alternative drugs for radiosensitization—the EGFR monoclonal antibodies cetuximab34-36 and panitumumab37—have been investigated. The first study by Bonner et al,34 a proof-of-concept, phase 3 randomized trial in locally advanced HNSCC comparing radiation alone with radiation and concomitant weekly cetuximab, revealed improved overall survival (29.3 months vs 49 months; P=.03) and duration of locoregional recurrence-free survival (14 months vs 24.4 months; P=.005) with the combination treatment. The 5-year long-term follow-up revealed that the benefit was primarily for OPSCC, patients younger than 65 years, and those who received concomitant boost radiation rather than once-daily radiation.35 In contrast, the addition of cetuximab to cisplatin with radiotherapy revealed no improvement over cisplatin with radiotherapy alone in a phase 3 trial (RTOG 0522).36 The acute toxicity was worse with cetuximab, cisplatin, and radiotherapy. Similar toxicity findings were reported with the addition of panitumumab to cisplatin with radiotherapy.
and worse overall survival outcome compared with cisplatin and radiotherapy.37

**Chemoradiation in Laryngeal Cancer.** The phase 3 trial RTOG 91-11 compared 3 organ preservation strategies—radiation alone, induction cisplatin and 5-fluorouracil chemotherapy followed by radiation, and concomitant cisplatin and radiation—in patients with stage III and stage IV locally advanced laryngeal cancer, excluding T1 and bulky T4 primary tumors. The long-term follow-up report revealed a significant improvement in rates of larynx preservation and local control at 5 and 10 years with concomitant cisplatin and radiation compared with induction therapy or radiation alone and no significant difference in overall survival among the 3 treatment groups.38 Thus, concomitant cisplatin and radiotherapy is considered the standard of care and preferred approach in North America. Quality of life, speech, and swallowing assessments did not reveal differences between treatments. However, there were more deaths from unrelated causes, typical of a population with tobacco- and alcohol-related comorbid conditions, in the concomitant treatment group, suggesting the possibility of contributory, unrecognized late effects.39 To date, there are no reports for laryngeal cancer treated in the modern era of 3-dimensional conformal and IMRT delivery to help us better understand the long-term survival results of RTOG 91-11.40

**Chemoradiation in Oropharyngeal Cancer.** For locally advanced OPSCC, chemoradiation compared with radiation alone has documented significant improvement in overall survival, locoregional control, and disease-free survival.41,42 Chemoradiation is considered the standard of care for locally advanced OPSCC.3,26

**Risk Stratification of OPSCC**

A retrospective analysis of 266 patients with OPSCC in the phase 3 RTOG 0129 trial was performed to obtain a risk model using recursive partitioning analysis (RPA). Variables in the model were HPV status, smoking history, T and N stage, and survival outcome. The result was the identification of low-, intermediate-, and high-risk groups with 3-year overall survival rates of 93%, 70.8%, and 46.2%, respectively.43 The low-risk, favorable prognosis group was characterized by HPV-positive tumor, less than 10-pack-year history of smoking, and no or early nodal spread (N0-2a).

Another retrospective study reported by O’Sullivan et al44 analyzed 505 patients with OPSCC treated at the Princess Margaret Hospital in Toronto, Ontario, Canada. Patients were stratified into groups at high and low risk for development of distant metastases on the basis of HPV status and T and N stage. The HPV-positive group, with T1-3N0-2c disease had the lowest risk of development of distant metastasis, with a distant control rate of 93% and a locoregional control rate of 95%. This data was confirmed by a recent prospective phase 2 trial that reported a 2-year progression-free survival of 96% and overall survival of 96% in a subset of patients who had HPV-positive OPSCC with T1-3N0-2c disease and less than 10-pack-year smoking history.45

Huang et al46 analyzed 573 patients with HPV-associated OPSCC and grouped them on the basis of tumor (T) and nodal (N) involvement into stage I, II, and III, known as RPA-based TNM stage grouping. The 5-year median survival was 82%, 76%, and 54%, respectively, reflecting a better survival for patients with less than T4 and N3 OPSCC. **Table 3** summarizes the results of the 3 RPA analyses risk-stratifying patients with OPSCC on the basis of TN stage and smoking status.43,44,46

Patients with HPV-positive OPSCC are younger than those with HPV-negative OPSCC, otherwise healthy, highly functional, and socially active, and preserving maximum quality of life after all treatment is a priority. It is possible that these patients are overtreated and unnecessarily exposed to short- and long-term treatment effects of standard approaches (open surgery or radiation and high-dose cisplatin). The current generation of trials for HPV-positive patients focuses on careful dein- tensification of radiation or systemic therapy with the goal of maintaining the excellent survival outcomes achieved with standard treatment (Table 4). On the basis of the available data, cisplatin concurrent with full-dose radiation remains
the standard of care for locally advanced HNSCC. Cetuximab with radiation is reserved for patients who cannot receive cisplatin because of poor renal function, hearing loss, neuropathy, poor performance status, or elderly and frail status. Neither intensifying cisplatin with RT for HPV-negative patients nor deintensification of the radiation dose is recommended outside clinical trials.

**Induction Chemotherapy**

The concept of IC with cisplatin and 5-fluorouracil followed by RT in locally advanced HNSCC was investigated in numerous trials between 1965 and 2000. A meta-analysis revealed a nonsignificant absolute benefit of 2.2% with IC before RT compared with RT alone.26 More recently, a 3-drug combination of taxane added to cisplatin and 5-fluorouracil has become the standard induction regimen when such treatment may be indicated. Trials directly comparing induction cisplatin and 5-fluorouracil with taxane, cisplatin, and 5-fluorouracil revealed a significant improvement in progression-free survival and overall survival for the taxane triple-drug regimen.47,48 A meta-analysis of the IC trials comparing cisplatin and 5-fluorouracil with or without taxane reported superior overall survival (HR, 0.79; 95% CI, 0.70-0.89; P<.001), progression-free survival (HR, 0.78; 95% CI, 0.60-0.87; P<.001), locoregional failure (HR, 0.79; 95% CI, 0.66-0.94; P=.007), and distant failure (HR, 0.63; 95% CI, 0.45-0.89; P=.009) for cisplatin, 5-fluorouracil, and taxane.49

In the treatment of laryngeal cancer, sequential therapy was not found to be feasible in a phase 2 trial comparing docetaxel plus cisplatin and 5-fluorouracil induction followed by randomization to cisplatin and RT or cetuximab and RT. Both treatments were associated with substantial toxicity, and the dropout rate from severe or life-threatening toxicity encountered with induction docetaxel plus cisplatin and 5-fluorouracil was unacceptably high.50

To define a role for IC, trials were designed to compare induction with taxane, cisplatin, and 5-fluorouracil followed by chemoradiation to chemoradiation alone. At interim analysis, 2 phase 3 trials investigating the sequential therapy approach—the PARADIGM44 and DeCIDE (Docetaxel-Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer)52 trials—found no appreciable trend in

### TABLE 3. Risk Stratification of Oropharyngeal Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Risk group</th>
<th>Variable</th>
<th>No. of patients</th>
<th>3-Year outcome (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang et al, 2010 (N=266)</td>
<td>Low risk for death</td>
<td>HPV+, &lt;10 py</td>
<td>88</td>
<td>OS: 93% (88.3%-97.7%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk for death</td>
<td>HPV+, &gt;10 py, N0-2a</td>
<td>26</td>
<td>OS: 70.8% (60.7%-80.8%)</td>
</tr>
<tr>
<td></td>
<td>High risk for death</td>
<td>HPV+, &gt;10 py, N2b-3</td>
<td>64</td>
<td>OS: 60.2% (51.5%-69.8%)</td>
</tr>
<tr>
<td></td>
<td>High risk for death</td>
<td>HPV+, &gt;10 py, T2-3</td>
<td>15</td>
<td>OS: 46.2% (34.7%-57.7%)</td>
</tr>
<tr>
<td></td>
<td>High risk for death</td>
<td>HPV+, &gt;10 py, all T4</td>
<td>73</td>
<td>OS: 46.2% (34.7%-57.7%)</td>
</tr>
<tr>
<td>O’Sullivan et al, 2013 (N=505)</td>
<td>HPV+, low risk for DM</td>
<td>T1-3N0-2c</td>
<td>286</td>
<td>DC: 93% (89%-95%)</td>
</tr>
<tr>
<td></td>
<td>HPV+, high risk for DM</td>
<td>T4</td>
<td>63</td>
<td>DC: 78% (65%-84%)</td>
</tr>
<tr>
<td></td>
<td>HPV-, low risk</td>
<td>T1-2N0-2c</td>
<td>33</td>
<td>DC: 83% (75%-91%)</td>
</tr>
<tr>
<td></td>
<td>HPV-, high risk</td>
<td>T3-4N3</td>
<td>56</td>
<td>DC: 72% (56%-82%)</td>
</tr>
<tr>
<td>Huang et al, 2015 (N=573)</td>
<td>HPV+, stage I</td>
<td>T1-3N0-2bM0</td>
<td>335</td>
<td>OS: 5-y median, 82% (77%-86%)</td>
</tr>
<tr>
<td></td>
<td>HPV+, stage II</td>
<td>T1-3N2cM0</td>
<td>91</td>
<td>OS: 5-y median, 76% (68%-86%)</td>
</tr>
<tr>
<td></td>
<td>HPV+, stage III</td>
<td>T4 or N3M0</td>
<td>147</td>
<td>OS: 5-y median, 54% (46%-63%)</td>
</tr>
<tr>
<td></td>
<td>DC = distant control; DM = distant metastasis; HPV = human papillomavirus; LRC = locoregional control; OS = overall survival; py = pack-year smoking; + = positive; - = negative.</td>
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</tbody>
</table>
favor of initial treatment with taxane, cisplatin, and 5-fluorouracil before chemoradiation. This finding resulted in early termination of these trials, and the published final results did not document benefit for any end point. In terms of further evaluation of the sequential therapy approach, a subset analysis in the DeCIDE trial revealed some separation of the survival curves (P = .19) for overall survival in patients with bulky nodal disease (N2c-3) favoring IC followed by chemoradiation.

Further investigation in this patient group may be warranted.  

The role of IC in HNSCC has yet to be defined, and its use is limited to laryngeal cancer followed by RT alone. The use of initial IC (in sequence with chemoradiation) may be justified in certain patient-specific situations such as very advanced, bulky primary or nodal disease or patients who are symptomatic and a delay in initiating chemoradiation is expected.

<table>
<thead>
<tr>
<th>TABLE 4. De-escalation Trials in HPV-Positive OPSCC†</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
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<tr>
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<tr>
<td>Cmelak et al,44 phase 2</td>
</tr>
<tr>
<td>RTOG 1016, phase 3 (clinicaltrials.gov identifier: NCT01302834)</td>
</tr>
<tr>
<td>ECOG 3311, phase 2 (clinicaltrials.gov identifier: NCT01898494)</td>
</tr>
<tr>
<td>Quarterback Trial, phase 3 (clinicaltrials.gov identifier: NCT01706939)</td>
</tr>
<tr>
<td>ADEPT, phase 3 adjuvant trial (clinicaltrials.gov identifier: NCT01687413)</td>
</tr>
<tr>
<td>TROG 12.01, phase 3 (clinicaltrials.gov identifier: NCT01855451)</td>
</tr>
<tr>
<td>De-ESCALaTE, phase 3 (clinicaltrials.gov identifier: NCT01874171)</td>
</tr>
</tbody>
</table>

†ADECaT = Adjuvant Therapy De-intensification trial for Human Papillomavirus-related, p16+ Oropharynx Cancer; CR = complete response; DC = distant control; De-ESCALaTE = Determination of Epidermal Growth Factor Receptor-inhibitor (Cetuximab) Versus Standard Chemotherapy (Cisplatin) Early And Late Toxicity Events in Human Papillomavirus-positive Oropharyngeal Squamous Cell Carcinoma; DFS = disease-free survival; DM = distant metastasis; ECOG = Eastern Cooperative Oncology Group; ECS = extracapsular spread; HPV = human papillomavirus; IC = induction chemotherapy; IMRT = intensity-modulated radiotherapy; ISH = in situ hybridization; LRC = locoregional control; MDASI-HN = M. D. Anderson Symptom Inventory - Head and Neck module; OPSCC = oropharyngeal squamous cell carcinoma; OS = overall survival; PFS = progression-free survival; PR = partial response; py = pack-year smoking; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; TORS = transoral robotic surgery; TPF = docetaxel, cisplatin, and 5-flourouracil; TROG = Trans-Tasman Radiation Oncology Group; + = positive.  
§T1-2N0-N1 negative margins.  
¶Clear/close margins, <1mm ECS, 2-4 metastatic lymph node.  
¶¶Positive margin, >ECS or >5 metastatic lymph nodes.  

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Targeted Therapy for HNSCC

Treatments targeting specific cell membrane growth factor receptors or downstream signaling pathway mutations in patients with metastatic disease are currently under investigation. Surface receptors of interest are \( \text{EGFR} \) overexpression, \( \text{EGFR} \) gene amplification, up-regulation of \( \text{HER2} \) and \( \text{HER3} \) \( \text{MET} \) overexpression (>80%), \( \text{MET} \) gene amplification (13%), and \( \text{MET} \) point mutation (14%). Among signaling pathways, agents targeting the \( \text{NOTCH1} \), \( \text{MET-PK3CA-MTOR} \), \( \text{EGFR-RAS-RAFI-MEK} \), and \( \text{WNT/\beta-catenin} \) pathways are under investigation. Within the cell overexpression of \( \text{MTOR} \), \( \text{HIF 1 alpha} \), \( \text{HDAC1} \) and \( \text{HDAC2} \) have been associated with poor prognosis. Within the cell nucleus, \( \text{EGFR} \) overexpression and \( \text{STAT3} \) overexpression are also indicators of poor prognosis in HNSCC. To date, there has been no breakthrough targeted therapy in HNSCC. The response rates of available single-agent targeted therapy have been in the range of 10% to 15%, with no meaningful clinical benefit. Whole-exome sequencing of HNSCC provides valuable information and insight into potential therapeutic targets to investigate.

CONCLUSION

The growing burden of OPSCC in the United States has important public health and clinical implications. It is important to recognize HPV-negative and HPV-positive HNSCC as 2 biologically and clinically distinct entities, with HPV-positive tumors having more favorable survival outcomes. This difference has resulted in the formulation of risk stratification parameters for prognosis. Current clinical trials are using risk stratification to define eligibility for evaluation of deintensification strategies in the treatment of OPSCC. The optimal management of locally advanced HNSCC based on risk and molecular biomarkers is being defined in clinical trials, and this direction for treatment represents a more personalized approach. Enrollment in these clinical trials is critical to move the field forward. In the meantime, standard approaches using chemoradiation as definitive treatment for most locally advanced HNSCCs or single-modality treatment for early-stage disease should be followed. Multidisciplinary evaluation and accurate staging are essential.

Abbreviations and Acronyms: \( \text{CT} = \) computed tomography; \( \text{HNSCC} = \) head and neck squamous cell carcinoma; \( \text{HPV} = \) human papillomavirus; \( \text{HR} = \) hazard ratio; \( \text{IC} = \) induction chemotherapy; \( \text{IHC} = \) immunohistochemical; \( \text{IMRT} = \) intensity-modulated radiotherapy; \( \text{ISH} = \) in situ hybridization; \( \text{OPSCC} = \) oropharyngeal squamous cell carcinoma; \( \text{PCR} = \) polymerase chain reaction; \( \text{PET} = \) positron emission tomography; \( \text{RPA} = \) recursive partitioning analysis; \( \text{RT} = \) radiation therapy; \( \text{RT0G} = \) Radiation Therapy Oncology Group; \( \text{TORS} = \) transoral robotic surgery.

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The Symposium on Neoplastic Hematology and Medical Oncology will continue in an upcoming issue.

REFERENCES

HEAD AND NECK SQUAMOUS CELL CARCINOMA


