Over the past decade, it has become apparent that head and neck squamous cell carcinoma (HNSCC)—including cancers of the mouth, throat, and larynx—is actually two separate diseases. As the incidence of “classic” tobacco/alcohol–induced HNSCC has declined, sharply increasing numbers of patients with HNSCC caused by the human papillomavirus (HPV) have forced us to rethink our approach to the diagnosis and treatment of patients with head and neck cancer.

HPV-related HNSCC most commonly occurs in the tonsils and base of the tongue, a region known as the oropharynx. Patients with HPV-related oropharyngeal cancer (HPVOPC) tend to present with advanced-stage disease due to spread to the lymph nodes of the neck, but paradoxically have a far better prognosis than patients with classic HNSCC. This creates a dilemma for treating physicians: how to personalize treatment of this unique patient population in an evidence-based fashion.

De-escalation of Nonsurgical Therapy
Since surgical approaches to OPC prior to the advent of robot-assisted surgery involved splitting the mandible, chemoradiation has become the standard-of-care treatment for OPC at most centers. While HPVOPC generally has an excellent response to chemoradiation, with a >80% cure rate for patients with stage III-IV disease at many institutions, the side effects of combination therapy regimens can be severe and leave a significant minority of patients with lifelong speaking and swallowing dysfunction. In the minds of many practitioners this raises the question: Are we over-treating the majority of patients with HPV-related head and neck cancer?

At the Icahn School of Medicine at Mount Sinai (ISMMS), we feel that this question is best answered in the context of well-designed clinical trials, rather than ad hoc treatment de-escalation. One such trial is the ongoing Quarterback Trial (principal investigator [PI]: Marshall Posner, MD), designed to determine the comparative rates of progression-free survival and locoregional control in HPVOPC patients treated with standard or reduced-dose chemoradiotherapy.

In this trial, stage III-IV HPVOPC patients who responded to induction chemotherapy are randomized to treatment with reduced-dose radiation, carboplatin, and Erbitux, versus standard-dose radiation plus carboplatin alone. The results of this study, conducted at ISMMS and several other...
Robot-Assisted Surgery as a Tool for Risk-Based Adjuvant Treatment

While all patients with cancer are clinically staged prior to initial therapy, only surgical treatment allows pathological information about negative prognostic factors (number of cancer-containing lymph nodes, extracapsular nodal extension, margin status, and presence of lymphovascular or perineural tumor extension) to risk-stratify patients and identify those who require adjuvant chemoradiation. The advent of transloral laser microsurgery (TLM) and transoral robotic surgery (TORS), which avoids the morbid lip- and jaw-splitting open surgical approaches of prior eras, has renewed interest in surgery for HPVOPC.

Pathological information obtained by analysis of the resected primary tumor and lymph nodes obtained at the time of neck dissection can be used to justify withholding chemotherapy and/or radiation in patients without adverse prognostic features or intensifying treatment of patients with high-risk disease who require triple-modality therapy (Laryngoscope. 2011;121[8]:1668-1674). While retrospective studies suggest that TORS and TLM can be used to drive risk-based adjuvant therapy for HPVOPC, this has not been tested in a prospective trial.

The upcoming Sinai Robotic Surgery (SIRS) trial (PI: Brett Miles, MD, DDS) will enroll early-stage to mid-stage HPVOPC patients with T1-3/N1-2B disease to determine whether pathological data can be used to personalize adjuvant therapy. All patients will receive TORS plus a neck dissection (where clinically indicated), and pathological data from the primary tumor and neck dissection specimen will be used to assign patients to low- (observation only), mid- (low-dose postoperative radiation only), and high- (chemoradiation) risk groups. Rates of locoregional control, overall survival, and use of salvage chemoradiation in the observation group will be calculated and compared with historical data to determine whether pathological risk stratification can be used to enhance disease control and minimize toxicity by delivering the right treatment regimen to the right patients.

Immune-Based Therapies as a Toxicity-Sparing Treatment Approach

The presence of immunologically foreign viral antigens in HPV-related tumors provides unique opportunities for development of immune-based therapies targeting this potential Achilles heel of virally associated cancers. Like chemotherapy, immunotherapy can act systemically to target microscopic or disseminated foci of residual disease following tumor-ablative surgery or radiation. However, the overall toxicity of tumor vaccines and other immune-based treatment approaches is much less than that of chemotherapy. Thus, combining upfront surgery to remove the tumor and involved lymph nodes with immunotherapy targeting subclinical residual disease is an attractive strategy for obtaining durable control while minimizing toxicity.

The high control rates of HPVOPC obtained with conventional therapeutic approaches suggest that initial clinical trials of immunotherapy in this patient population will be conducted in combination with existing standard-of-care treatments. However, almost nothing is known about whether the effect of chemoradiotherapy or surgery on the host immune response to HPV-related tumors is immune-stimulating or immunosuppressive.

The Biomarkers of Immune Activation and Suppression (BIAS) trial (PI: Andrew G. Sikora, MD, PhD) is an ongoing observational trial designed to profile the systemic antitumor immune response in HPVOPC patients before therapy and at multiple points during and after treatment. Data collection for the chemoradiation cohort has been completed, and collection for the surgical cohort is underway. The results of this trial will provide an extremely granular view of the peaks and troughs of the immune landscape during therapy, and guide integration of immunotherapy with existing standard-of-care treatments.

An upcoming complementary interventional trial at ISMMS will move the focus from systemic immunity to the very front lines of antitumor immunotherapy: the tumor microenvironment itself. An investigator-initiated, neoadjuvant vaccine trial for HPVOPC patients sponsored by Advaxis Pharmaceuticals (PI: Sikora) will determine the ability of a recombinant listeria-based vaccine carrying HPV antigens to induce a potent immune response in the tumor microenvironment, as well as systemic responses.

In the trial, patients with HPVOPC will be vaccinated prior to standard-of-care TORS resection of their tumor, and the profile of immune cells infiltrating the blood, tumor, and draining lymph nodes will be assessed, along with HPV antigen-specific immune responses. The results of this study will determine whether immune responses in the blood correlate with those in the tumor, and whether vaccination can drive antitumor T cells into the tumor itself, where they can do the most good.

In summary, HPV-related head and neck cancer is an epidemiologically and clinically unique disease, and a personalized approach to treatment of patients with HPVOPC can help optimize the balance of risks and benefits. However, rigorously designed clinical trials are the best way to obtain the knowledge base needed to develop personalized therapy for HPVOPC that minimizes toxicity without sacrificing our currently excellent oncologic outcomes in this population. At ISMMS, we are deeply committed to conducting clinical trials today that will shape tomorrow’s standard-of-care treatments for this unique patient population.