



Shrujal Baxi, MD, MPH

Shrujal Baxi, MD, MPH, is a medical oncologist who cares for patients with head and neck cancers. Her research focus is on the long-term and late effects of treatment, optimizing surveillance strategies, and better understanding the competing causes of mortality in long-term survivors of head and neck cancer. She is involved in both health services and quality-of-life research.

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Ten Years of Progress in Head and Neck Cancers

Shrujal Baxi, MD, MPH; Matthew Fury, MD, PhD; Ian Ganly, MD, PhD, FRCS (Edin), FRCS (Glas), FRCS-ORL (Edin); Shyam Rao, MD, PhD; and David G. Pfister, MD

Squamous cell carcinoma of the head and neck (HNSCC) is a heterogeneous disease characterized by complex clinical and pathologic presentations constituting approximately 90% of all head and neck cancers. The past decade has seen important advances in our understanding of the epidemiology, pathogenesis, and management of HNSCC. It is a disease increasingly managed by a multidisciplinary team of providers, as reflected in the updates of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers (to view the most recent version of these guidelines, visit NCCN.org).

Epidemiology

The incidence of HNSCC has remained relatively stable over the past 10 years in the United States, despite declining rates of smoking, which is the major risk factor for this disease.^{1,2} This discrepancy is at least partially explained by the emerging role of infection with high-risk subtypes of human papillomavirus (HPV), a risk factor for cancer of the oropharynx.^{3,4} HPV viral oncogenes E6 and E7 inactivate tumor suppressor genes *p53* and *Rb*, respectively.⁵ A substantial and growing proportion of oropharynx cancers—for example, an increase in HPV-positive tonsillar cancer in a Swedish Cancer Registry study from 23.3% in the 1970s to 68% approximately 30 years later—are now attributed to high-risk subtypes of HPV.^{6,7} NCCN recommends that all oropharynx tumors be tested for HPV using either immunohistochemical staining for *p16* overexpression, a reliable marker for HPV gene integration,^{8,9} or in situ hybridization testing for detection of virus.

Numerous studies have shown that patients with HPV-related oropharynx squamous cell carcinoma show an improved response to treatment and overall survival, after adjusting for traditional prognostic factors. However, smoking remains an independent predictor; patients with an HPV-related tumor and a smoking history (10 pack years was the cut off used in a recent important study) have a worse prognosis than patients with HPV-related tumors and no smoking history.¹⁰⁻¹² In an analysis of patients with stage III or IV, M0 disease treated on RTOG 0129, patients with HPV-related HNSCC had 3-year overall survival rates of 82.4% compared with 57.1% in patients with HPV-negative tumors ($P < .001$).

This trend has led investigators to research de-escalation of treatment for patients with HPV-related HNSCC. For example, a phase III trial (RTOG 1016) is currently underway randomizing patients with locally or regionally advanced disease to concurrent chemoradiation with cisplatin versus cetuximab in HPV-positive patients. Although HPV status of the tumor is considered in the management of occult primary cancers, treatment recommendations in the NCCN Guidelines for the most part are currently based on stage and anatomic location of the tumor. However, the results of ongoing trials will hopefully enable integration of HPV status into treatment algorithms in a more substantial way.

Novel Therapeutics

Advances in our understanding of the genetic instability and progression of disease in HNSCC are identifying new prognostic markers and therapeutic targets. Ongoing studies

are examining inhibitors of the vascular endothelial growth factors, platelet-derived growth factors, inhibitors of the mammalian target of rapamycin (mTOR), and other cellular pathways, either as single agents or in combination with cytotoxic chemotherapy.

In 2006, the FDA approved cetuximab, a human-mouse chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR), as a single agent in patients with recurrent or metastatic HNSCC who had undergone prior platinum-based therapy, or for concomitant use with radiation in the primary treatment of locally or regionally advanced HNSCC. In a phase III study, cetuximab and concurrent radiation prolonged median overall survival by 19.7 months when compared with radiation alone in patients with locoregionally advanced tumors ($P = .03$); the estimated 5-year survival rate improved by 9.2% on the cetuximab arm.^{13,14} Among patients treated with cetuximab, the development of a grade 2 or greater acneiform rash was associated with improved overall survival ($P = .002$).

The FDA expanded the indication of cetuximab to include its combination with chemotherapy for patients with recurrent or metastatic disease based on the results of the EXTREME study.¹⁵ In that study, patients with recurrent or metastatic disease were randomized to receive either combination cetuximab with chemotherapy (cisplatin or carboplatin and 5-FU) or chemotherapy alone. Patients receiving cetuximab with chemotherapy lived an average of 10.1 months, compared with 7.4 months for those receiving chemotherapy only ($P = .04$).¹⁵ The identification of molecular and clinical predictors of response to anti-EGFR-based therapy is an active area of investigation.

A small minority (< 5%) of patients receiving cetuximab experience a severe hypersensitivity reaction, typically with the first dose. In this regard, higher rates of hypersensitivity reactions have been identified in patients living in certain states, particularly in the Southeast United States, and appear to be associated with the pretreatment presence of IgE antibodies against galactose- α -1,3-galactose.¹⁶ The regional exposure that might explain the development of this antibody is not yet clearly defined.

Chemotherapy

The results of a meta-analysis combining the outcomes of 87 trials and 16,485 participants helped clarify the role of chemotherapy as part of definitive treatment for HNSCC.¹⁷ The hazard ratio of death was 0.88 ($P < .0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years. A significant interaction ($P < .0001$) was seen between chemotherapy timing (adjuvant, induction, or concomitant) and outcomes. In trials studying the addition of concurrent chemotherapy to radiation, the hazard ratio was 0.81 ($P < .0001$) with an absolute benefit of 6.5% at 5 years. A decreasing effect of chemotherapy was seen with age.

In 2004, the results of 2 pivotal trials evaluating concurrent chemoradiation in the adjuvant setting for locally or regionally advanced, resected tumors were published. Both the RTOG 9501 and EORTC 22931 studied the impact of concurrent cisplatin, 100 mg/m², on days 1, 22, and 43 with postoperative radiation versus radiation alone, following resection of advanced disease with high-risk surgical or pathologic features.^{18,19} In a meta-analysis combining these study results, the authors noted that patients with pathologic evidence of extracapsular extension or positive surgical margins had a statistically significant improvement in both locoregional control and overall survival when treated with adjuvant concurrent chemoradiation compared with radiation alone.²⁰ Patients who had neither of these factors did not appear to benefit from adjuvant chemoradiation (EORTC 22931, $P = .33$; RTOG 9501, $P = .78$). No significant impact on distant control was seen in either study, and the addition of cisplatin did increase acute severe adverse events.



Matthew Fury, MD, PhD

Matthew Fury, MD, PhD, is a medical oncologist who cares for people with tumors of the head and neck. His central research focus is the clinical study of new therapies for patients with squamous cell cancer of the head and neck, and he also is involved in phase I research. Dr. Fury serves on NCCN's Scientific Review Committees for several investigational chemotherapy drugs and is a member of the NCI's Task Force for Recurrent and/or Metastatic Head and Neck Cancer.

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Ian Ganly, MD, PhD, FRCS (Edin), FRCS (Glas), FRCS-ORL (Edin)

Ian Ganly, MD, PhD, FRCS (Edin), FRCS (Glas), FRCS-ORL (Edin), received his training in general surgery and otolaryngology in Scotland, UK, and in head and neck surgical oncology at Memorial Sloan-Kettering Cancer. He was an attending head and neck surgeon at the University of Edinburgh, Scotland, UK, from 2005-2008 before moving to his present position as attending head and neck surgeon at Memorial Sloan-Kettering Cancer Center in 2008. He has expertise in all aspects of multidisciplinary care of cancer of the head and neck but has a special interest in minimally invasive surgery carrying out endoscopic laser resection of tumors of the larynx and pharynx and robotic surgery for cancers of the base of tongue and tonsil. He also has an interest in basic science research, achieving his PhD in head and neck molecular oncology in 1999. He collaborates with scientists at Memorial Sloan-Kettering on the oncogenomics of head and neck and thyroid cancer.

The debate regarding the role of induction chemotherapy continues. Randomized phase III studies have shown that the addition of docetaxel to cisplatin and 5-FU as induction therapy before locoregional treatment can improve locoregional control, larynx preservation, and overall survival compared with the use of cisplatin and 5-FU alone as an induction regimen.²¹⁻²³ The regimen of paclitaxel, cisplatin, and 5-FU also appears to have added efficacy compared with cisplatin and 5-FU alone, but this combination is less well studied.²⁴ However, concerns regarding the potential negative impact of induction chemotherapy on the delivery of definitive concurrent chemoradiation remain, as does uncertainty as to whether its incorporation improves survival compared with use of state-of-the-art concurrent chemoradiotherapy alone. In 2010, the preliminary results of a 3-arm phase III study evaluating chemoradiation alone versus 2 different induction chemotherapy regimens followed by chemoradiation were presented in abstract form. Although the study found improved time to progression in the induction arms, no overall survival benefit was seen, and methodological flaws preclude firm conclusions regarding the efficacy and tolerability of induction chemotherapy in that study.²⁵ Two recently presented phase III studies similarly failed to demonstrate improved overall survival with the incorporation of induction chemotherapy prior to concurrent chemoradiation compared with chemoradiation alone.^{26,27}

Innovations in Surgery and Radiation Therapy

Head and neck surgery has also evolved over the past decade. For example, use of transoral resection robotic surgery using the da Vinci surgical robot for the resection of oropharynx tumors is growing.²⁸ The goal of minimally invasive procedures is to decrease surgical morbidity and reduce hospitalizations with the same overall survival as traditional open surgery and organ-preserving, nonsurgical treatments. Although minimally invasive procedures have been shown to be feasible, clinical trials are needed to assess which patients benefit from less-invasive surgical approaches and to compare outcomes with those of standard therapeutic options.²⁹ Given the high degree of skill necessary, robotic procedures should be performed at high-volume centers by experienced physicians.

Head and neck reconstruction has also seen significant advances, allowing for improved functional and quality-of-life outcomes. Some of the major advances in reconstructive surgery include newer techniques for free tissue transfer, integrated bone and dental rehabilitation, and motorized tissue transfer. Surgical advances will require more complex discussions with patients regarding all available therapeutic options and expected outcomes, recognizing that the data to guide these decisions are currently incomplete.

Advances in radiation oncology are aimed at improving or maintaining tumor control while minimizing the dose of radiation to surrounding normal tissue. In HNSCC in particular, the use of intensity-modulated radiation therapy (IMRT) is the major innovation in radiation delivery over the last decade. IMRT provides more conformal delivery of radiation to tumor target volumes and improved sparing of normal tissues.³⁰ In a multi-institutional phase III study, patients with pharynx cancers treated with parotid-sparing IMRT had lower rates of xerostomia than those treated with conventional radiation ($P = .005$).³¹ At 12 months, the rates of local tumor control appeared equivalent, but longer-term outcomes with IMRT versus conventional radiation are pending. Questions remain as to whether the aggressive sparing of normal tissue may contribute to the occurrence of marginal failures caused by undertreatment of high-risk volumes.

At the same time, advancements in normal tissue sparing can allow for better tumor control through improved coverage of tumor target volumes and potentially

dose escalation, because compromises for normal tissue dose limitations are avoided (e.g., limiting spinal cord dose to prevent myelopathy). An alternative treatment approach that is attractive in head neck cancer is proton therapy, which could further decrease normal tissue doses compared with standard photon-based treatments, including IMRT. Published experience with proton therapy from the limited number of centers is growing, and availability is also expected to grow.³² The results from multi-institutional studies will help clarify the benefits of this newer, more expensive technique.

Conclusions

Head and neck cancer is a heterogeneous disease with a changing epidemiology. Important progress in therapeutic options has occurred over the past decade. Effective therapy requires coordination, communication, and individualized care delivered by multidisciplinary oncology and other providers. In the next 10 years, as our understanding of the molecular pathogenesis of cancer deepens, the need for clinical trials to identify optimal therapy will only increase. These studies will be critical to identifying further advances in care and deserve our support.

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Shyam Rao, MD, PhD

Shyam Rao, MD, PhD, is a radiation oncologist who cares for patients with head and neck cancers. His research focuses on the role of the tumor microenvironment in modulating response to radiation therapy. He is also interested in the evaluation of strategies intended to decrease the late toxicities of radiation treatment.

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David G. Pfister, MD

David G. Pfister, MD, is Chief of the Head and Neck Oncology Service within the Department of Medicine and Co-leader of the Head and Neck Cancer Disease Management Team at Memorial Sloan-Kettering Cancer Center, and Professor of Medicine at Weill Medical College of Cornell University. Dr. Pfister is an internationally recognized expert in the management of head and neck malignancies. He co-chairs the Metastatic-Recurrent Disease Task Force for Head and Neck Cancer at the National Cancer Institute, is a member of the Board of Directors for the International Thyroid Oncology Group, and is on the Medical Advisory Board for Support for People with Oral and Head and Neck Cancer. He is currently a member of the NCCN Board of Directors and NCCN Guidelines Steering Committee, and chairs the NCCN Clinical Practice Guidelines in Oncology Head and Neck Cancers Panel.

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