HEAD AND NECK CANCER

Locally Advanced Head and Neck Cancer

CHAIR
Anthony Cmelak, MD
Vanderbilt-Ingram Cancer Center
Nashville, TN

SPEAKERS
Ralph William Gilbert, MD
Princess Margaret Hospital
Toronto, ON, Canada

Robert I. Haddad, MD
Dana-Farber Cancer Institute/Harvard Medical School
Boston, MA
Locally Advanced Head and Neck Cancer

Anthony J. Cmelak, MD, Kyle Arneson, MD, Nicole G. Chau, Ralph W. Gilbert, MD, and Robert I. Haddad

OVERVIEW

Treatment of locally advanced head and neck squamous cell carcinomas requires a multidisciplinary approach to be able to offer patients definitive therapy while aiming to preserve organ function and minimize acute and long-term toxicities. Advances in surgical techniques will be reviewed for both primary sites and the neck and also in the salvage settings. Recent data on concurrent versus sequential chemoradiotherapy in these patients will be reviewed, with emphasis on identification of appropriate patients for sequential chemoradiotherapy. Finally, advances in modern radiotherapy modalities that have resulted in improved dosimetry and quality of life following treatment will be reviewed.

Locally advanced disease includes advanced T stage (T3 and T4) and advanced neck disease (N2 or greater). In an era of nonsurgical organ preservation approaches, primary and salvage surgery remains an important option in the management of primary head and neck malignancies. In this section, we will review the role of surgery by tumor site, summarizing the current state of evidence and consensus in the management of the various primary sites and the management of regional neck disease.

THE ROLE OF SURGERY

Oral Cavity

The primary treatment approach for the majority of oral primary mucosal malignancies remains surgery and appropriate adjuvant therapy (radiotherapy or chemoradiation). Surgical approaches include trans-oral resections or trans-oral laser surgery, with more advanced and posteriorly placed tumors of the oral cavity treated with access procedures including mandibular osteotomies or lingual release techniques. Regional management of the neck is based on the extent of neck disease with some controversy over the extent of neck dissection (i.e., selective, limited neck dissection) to high-risk and involved sites of disease, usually levels I to IV or comprehensive neck dissection including levels I to V. The majority of advanced oral cavity resections will be considered for reconstruction of the oral tongue, mandible, or maxilla. Modern options usually include a free tissue transfer by either a fasciocutaneous flap or an osteocutaneous flap. The broad application of these reconstructive techniques have dramatically improved the functional results for this group of patients. Patients with the most advanced tumors requiring total glossectomy or glossectomy and laryngectomy should be considered for organ preservation approaches, including chemoradiation with induction and/or sequential therapy.

Oropharynx

The current standard for the treatment of advanced oropharyngeal carcinoma in both HPV +ve and HPV –ve patients is a nonsurgical organ preservation approach. These include induction chemotherapy and radiotherapy, radiotherapy alone, or primary chemoradiation. In patients with early-stage primary disease of the tonsil or tongue base and advanced neck disease, controversy exists over the role of minimally invasive surgical approaches including Trans-oral Laser Excisions (TOL) and Trans-oral Robotic Surgery (TORS) with integrated neck dissection. The rationale for minimally invasive approaches is the potential of improved function as a result of de-escalation of adjuvant treatment and the promise of reduced functional disabilities associated with minimally invasive approaches. No randomized trials have specifically addressed this question, with treatment approaches advocated according to institutional bias and provider preference. A trial for early-stage disease is currently under consideration by the RTOG (Radiation Treatment Oncology Group). Large retrospective series appear to suggest that de-escalation to altered fractionation with radiation alone or surgery combined with moderate dose adjuvant therapy appear to produce local regional control rates comparable to chemoradiation in early-stage disease.

Larynx

Treatment of laryngeal carcinoma has been defined by a number of well-designed clinical trials. Most prominent

From the Vanderbilt-Ingram Cancer Center, Nashville, TN; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University of Toronto, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada.

Authors’ disclosures of potential conflicts of interest are found at the end of this article.

Corresponding author: Anthony J. Cmelak, MD, Department of Radiation Oncology, The Vanderbilt Clinic, B-1003 PRB, 2220 Pierce Ave., Nashville, TN 37232-5671; email anthony.cmelak@vanderbilt.edu.

© 2013 by American Society of Clinical Oncology.
among these is the RTOG-9111 trial, which demonstrated a clear benefit to chemoradiation and induction protocols followed by surgery or radiotherapy based on response to induction. For patients with locally advanced tumors with extralaryngeal disease (T4a) or patients with advanced destruction of the laryngeal framework and a nonfunctional larynx, the current consensus is primary total laryngectomy with appropriate neck management followed by adjuvant radiotherapy or chemoradiotherapy (for patients with positive margins or extracapsular extension). In patients with advanced glottic disease involving the paraglottic space bilaterally but without cricoarytenoid fixation, there is interest both in North America and Europe in the supracricoid partial laryngectomy with either cricothyroidopexy (CHP) or cricothyroid-epiglottopexy (CHEP). This operation removes the paraglottic space, laryngeal framework, and both vocal folds, preserving both arytenoids, and produces functional voice results in the majority of patients. It is particularly useful in patients who will not need adjuvant radiotherapy (N0 or N1), as the functional results following adjuvant treatment are problematic.

**Hypopharynx**
The treatment for advanced hypopharyngeal disease remains controversial. Some centers prefer induction chemotherapy, usually taxane-based regimens, selecting patients for organ preservation approaches while others advocate chemoradiation. Patients with extensive or circumferential involvement of the hypopharynx are problematic for all organ preservation approaches, as a significant number of these patients will either stricture completely or have very poor swallowing outcomes following treatment. Primary surgery should be considered for patients with T4a disease and resectable regional disease, or circumferential involvement where poor swallowing results can be anticipated. Current surgical options for pharyngeal reconstruction include the free cutaneous tube flap, the gastro-omental flap, and the free jejunum. The first two options are associated with excellent swallowing outcomes and tracheo-esophageal speech comparable to standard laryngectomy.

**Salvage Neck Management**
Given the prevalence of HPV +ve oropharyngeal tumors in our population of patients, the management of regional neck disease has changed dramatically over the past decade. In patients with HPV +ve, most centers advocate pretreatment and post-treatment PET/CT (at 12 weeks or greater). Patients with residual CT abnormalities of less than 1.5 cm and negative PET scans are observed with low rates of regional neck failure. Many patients with HPV +ve disease will involute their neck disease slowly, and many centers advocate observation of residual CT abnormalities for longer than 3 months. In HPV -ve disease, most centers advocate a similar approach but residual neck disease of >1.5 cm or a +ve PET would be indications for salvage neck dissection. The extent of neck dissection in this population of patients should be based on the original extent of disease. However, current evidence suggests that less than radical neck dissection with preservation of the accessory nerve is an option in a significant number of patients.

**Salvage of Organ Preservation Approaches**
The salvage of the failure of organ preservation approaches, particularly chemoradiation, represent a difficult challenge for the head and neck surgical oncologist. Selecting patients for salvage procedures is difficult, and the majority of patients undergoing surgery will require complex adjunctive reconstruction to avoid severe wound-healing problems. The current salvage literature clearly indicates a role for the salvage of recurrent, resectable, hypopharyngeal and laryngeal primary tumors. Salvage of oropharyngeal recurrences post chemoradiation remains controversial, with relatively poor disease-related outcomes and functional results being observed in patients with advanced recurrent disease. Evidence would suggest that the best results are observed in patients with recurrent (not persistent) disease and patients with early-stage disease at the primary site (T1 or T2).

---

**KEY POINTS**

- Major advances in microsurgery and reconstruction have dramatically improved functional and esthetic results for patients with locally advanced disease.
- Sequential chemoradiotherapy with docetaxel, cisplatin, and fluorouracil (TPF) is a reasonable approach in patients with locally advanced disease who have advanced nodal stage disease and who are in need of immediate therapy and organ preservation.
- Larynx preservation study updates (RTOG 91-11) show a clinically meaningful benefit for induction chemoradiotherapy over chemoradiotherapy in 10-year overall survival.
- Advances in computers and imaging technology have resulted in improved targeting of tumors with better sparing of normal tissue.
- Sparing organs at risk for chronic radiation injury, such as the parotid glands and pharyngeal constrictors, has allowed for better long-term functional outcome and quality of life.

**CHEMOTHERAPY**

**Induction: Inducing Controversy in Locally Advanced Head and Neck Cancer**
A discussion about induction chemotherapy (IC) cannot occur in the head and neck oncology community without triggering heated debate and controversy. Concurrent chemoradiotherapy (CRT) consisting of bolus cisplatin 100 mg/m² is a standard approach in locally advanced head and neck cancer (LAHNC). The addition of chemotherapy concomitant with radiation improves survival and locoregional control over radiation alone. No studies have shown superiority of CRT over IC in head and neck cancer.

So what is the rationale for IC in LAHNC? Sequential chemoradiotherapy (ST) integrates induction chemotherapy...
followed by concurrent CRT to theoretically confer further reduction in distant recurrence and maximize local regional control and organ preservation. Patients who may benefit from ST are those considered at high risk for distant or local failure, including those with large primary tumors (T4) and/or advanced nodal involvement (N2, N3), those with significant local symptoms, and those with anticipated delay in initiation of radiotherapy (Table 1). Good performance status (ECOG 0–1) is a prerequisite in addition to careful consideration of comorbidities.

The optimal induction chemotherapy regimen has been defined by two major phase III trials, TAX 323 and TAX 324, which demonstrated improved survival and progression-free survival (PFS) with docetaxel, cisplatin, and 5-FU (TPF) compared to PF in patients with resectable and unresectable LAHNC. Another phase III trial has also confirmed the superiority of TPF over PF induction in larynx preservation. Thus TPF has largely replaced PF and remains the IC regimen for comparison in randomized trials evaluating IC as part of ST compared with CRT.

**Evidence for ST versus CRT**

Four phase III randomized trials using TPF IC have been launched to compare ST with CRT. Three have been reported in abstract form to date. Two studies, PARADIGM and DeCIDE, lacked statistical power for their primary endpoint, overall survival, due to early closure and a higher than expected survival in the control arm (3-year overall survival [OS] 78% compared to 55% at the time of study design), which was likely related to a large proportion of patients with HPV-related oropharyngeal primaries.

PARADIGM is a randomized phase III trial of three cycles of TPF followed by CRT, compared with CRT in patients with LA HNSCC. The trial closed with only 145 patients of 300 planned patients enrolled. Patients who achieved complete clinical response at the primary site following IC received weekly carboplatin (AUC 1.5) and daily radiation fractionation, while the remaining patients received weekly docetaxel (20 mg/m²) with accelerated RT. The CRT arm consisted of two cycles of bolus cisplatin with accelerated concomitant boost over 6 weeks (as in RTOG 0129). No difference in PFS (HR 1.07; CI:0.59–1.92, p = 0.82) or OS (HR1.09; CI:0.59–2.03, p = 0.77) was detected. ST did not significantly reduce distant recurrence rates. Patients who did not achieve complete clinical response to IC appeared to have much poorer survival.

The DeCIDE trial is a multicenter phase III study of 280 patients (initially planned for 400 patients) with N2 and N3 disease randomized to CRT consisting of docetaxel, hydroxyurea, 5-FU, and hyperfractionated radiotherapy (DFHX), compared with two cycles of TPF induction followed by DFHX. No significant difference was identified between the two arms for the primary endpoint, OS (HR0.91; CI:0.59–1.41, p = 0.68), or for recurrence-free survival or distant failure-free survival. The cumulative incidence of distant metastases appeared improved in the IC arm. Toxicities were greater in the IC arm with increased severe neutropenia during CRT (14% compared with 4%, p = 0.023) and more deaths during treatment (13 deaths [13.5%] in IC arm compared with four deaths [3.8%] in CRT arm).

The Spanish Head and Neck Cancer Cooperative Group conducted a phase III trial of 439 patients with unresectable LAHNC comparing TPF followed by CRT compared with PF followed by CRT compared with CRT alone. The study was designed before the establishment of TPF as superior to PF and was not powered to show a difference in survival. Compared to CRT alone, IC had improved the median time to treatment failure (primary endpoint defined as time from randomization to progression, recurrence, surgery, death, withdrawal due to adverse events or no locoregional control) from 5 months to 12.5 months; however no formal statistical comparison was made between the TPF and PF arms. Intent to treat analysis was not presented and results remain unpublished.

Finally, the GSTTC Italian Collaborative Group is conducting a phase III trial (NCT01086826) comparing TPF followed by CRT vs. CRT alone; it has completed accrual and is awaiting sufficient follow-up before reporting. This study uses a factorial design with randomization to TPF compared with no TPF followed by second randomization to CRT consisting of PF compared with radiotherapy with cetuximab. It is preceded by a randomized phase II trial comparing TPF followed by CRT vs. CRT alone using PF concurrent with radiotherapy in both arms. ST demonstrated superiority in the primary endpoint, complete radiographic response, compared to CRT (50% vs. 22%).

Taken together, randomized phase III trials directly comparing TPF induction as part of ST compared with CRT, have to date not definitively answered which approach is superior in improving survival or PFS in LAHNC. It does appear from

---

**TABLE 1. Potential Advantages and Disadvantages of Induction Chemotherapy as Part of Sequential Chemoradiotherapy for LAHNC**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early symptom management (e.g., trismus, dysphagia, hoarseness, pain) may improve function prior to CRT</td>
<td>Prolongs total duration of therapy</td>
</tr>
<tr>
<td>Rapid tumor shrinkage may reduce the need for urgent interventions (e.g., urgent tracheostomy for airway obstruction, PEG tube for swallowing dysfunction)</td>
<td>Delays the start of definitive chemoradiation</td>
</tr>
<tr>
<td>Bridge to definitive treatment when immediate initiation of radiotherapy is not possible</td>
<td>Side effects may reduce or compromise the intensity of definitive chemoradiation</td>
</tr>
<tr>
<td>Early systemic treatment of micrometastases</td>
<td></td>
</tr>
</tbody>
</table>

In vivo assessment of response provides prognostic information, which may permit earlier initiation of tailored aggressive treatment for nonresponders.

Abbreviations: CRT, concurrent chemoradiotherapy; LAHNC, locally advanced head and neck cancer; PEG, percutaneous endoscopic gastrostomy.
these four studies that both CRT and ST are highly active modalities in treating locally advanced disease. A cost benefit or quality-of-life analysis has yet to be performed for any of these studies.

**Larynx Preservation**

Larynx cancer management is distinct from other sites as the larynx is anatomically complex providing critical functions. Hence, clinical trials in locally advanced laryngeal cancer include patients who would be suitable for total laryngectomy but for whom an alternative approach could be reasonably performed. IC and CRT are both validated in locally advanced laryngeal cancer.

Induction chemotherapy as part of an organ preservation strategy was embraced following the landmark Department of Veterans Affairs Laryngeal Cancer Study Group larynx trial in 1991, which randomized 332 patients with locally advanced laryngeal cancer to either three cycles of IC with PF followed by definitive RT or primary surgery followed by postoperative RT.15 Patients without at least a partial response and those with any evidence of disease progression during or after induction were managed with surgery and postoperative RT. The 2-year survival rate was equal in both treatment groups (68%), and the larynx preservation rate was 64% in the IC arm.

Concurrent chemoradiotherapy subsequently was evaluated as an alternative to IC followed by RT alone in the RTOG 91–11 study.16 This study randomized 547 patients with T2, T3, or low-volume T4 supraglottic or glottic larynx cancer to IC using PF for up to three cycles followed by RT alone in responders, or CRT with bolus cisplatin, or RT alone. Definitive RT in all three groups consisted of 70 Gy in 35 fractions. The initial report in 2003 concluded CRT was superior to IC followed by RT or RT alone for the larynx preservation rate (88% vs. 75% vs. 70%, respectively) at 2 years. For the primary endpoint of laryngectomy-free survival, CRT and IC were equivalent. Based on this and similar OS rates in all three groups; CRT was adopted in North America while IC continued to be favored in Europe.

In contrast, long-term results of RTOG 91–11 reported recently support a more favorable role of IC over CRT.17 The 10-year laryngectomy-free survival rate (LFS) and OS rate for CRT and IC were similar, and both were superior to RT alone. Of note, the Kaplan-Meier curves for LFS and OS at 10 years show clear separation favoring IC over CRT (IC: CRT 39% vs. 28% for OS), albeit not statistically significant. Those numbers though are clinically meaningful, as most patients will favor OS over any other endpoint. CRT improved the larynx preservation rate over IC; however, it came with a statistically significant increase in nonlarynx cancer–related deaths in the CRT over IC arm.

Larynx preservation is often cited as a primary endpoint; however, it is imperfect. Success cannot be claimed if many patients succumb to acute and late-treatment toxicity that compromises the function of a preserved larynx or ultimately survival. Recognizing this, an international consensus panel has created a new endpoint of laryngoesophageal dysfunction (LED)-free survival, which includes the events of death, local relapse, total or partial laryngectomy, tracheotomy at \( > 2 \) years, or feeding tube at \( > 2 \) years.18 We strongly support this in conjunction with quality-of-life indicators for future clinical trials.

Sequential chemoradiotherapy has not been compared with concurrent CRT in adequately powered randomized trials in laryngeal cancer. Therefore, it remains unclear if a ST approach using modern IC regimens of TPF would result in greater survival benefit or reduction in distant metastases compared to CRT alone. The superiority of TPF over PF induction in larynx preservation5 and feasibility of induction TPF as part of sequential CRT has been established in patients with locally advanced larynx/hypopharynx SCC.19

**MODERN RADIOTHERAPY**

**Imaging and Treatment Planning**

Three dimensional imaging such as computed tomography (CT scans), positron emission tomography (PET), and magnetic resonance imaging (MRI) during treatment planning has allowed identification of tumor location(s) and the relationship to normal structures/organs at risk (OAR). Three dimensional conformal radiation therapy (three dimensional-CRT) utilizes these image sets, often fused for optimal targeting, to design radiation treatment fields that spare OAR. The patient undergoes CT simulation in their treatment position. Customized immobilization devices (e.g., thermoplastic masks) created during treatment planning are used daily during treatment improving daily patient positioning reproducibility and minimize patient movements. Because diagnostic scans are often obtained in a nontreatment position, commercial products are currently available that provide deformable image registration that minimize uncertainty between image sets.

**Altered Fractionation**

Local recurrence remains the most common scenario for treatment failure in patients with HNC. In an attempt to decrease this risk, two main radiation approaches have been studied. Hyperfractionation delivers two fractions a day with a reduced dose per fraction. This approach facilitates the delivery of 10% to 15% higher total radiation dose with the expectation of decreasing the risk of late normal tissue toxicity. The second approach is accelerated fractionation, delivering more than five fractions of treatment per week by treating on weekends or delivering two or more fractions on one weekday. Accelerated fractionation shortens the delivery time period of radiation, potentially reducing the accelerated repopulation of tumor clonogens that occur 3 to 4 weeks after initiating treatment. Some clinical trials have combined both of these approaches to formulate both hyperfractionated and accelerated treatment regimens.20,21 The costs in terms of acute toxicity have been higher, with grade 3 or higher acute toxicities, according to the Radiation Therapy Oncology Group (RTOG) criteria, increasing from 33% to 55% compared with conventional fractionation.22,23 These altered fractionation approaches
have also shown clinical benefit in terms of improved locoregional control that have led to a small but significant benefit in 5-year survival of 3.4% (2% for accelerated, 8% for hyperfractionation) over the standard fractionation. The benefit of altering fractionation is greater in local tumor control than in regional (nodal) control and has a bigger benefit in younger patients, particularly that patients less than 50 years of age. It has no effect on the development of distant metastases.

**IMRT: Indications, Clinical Trials, Outcomes**

Intensity-modulated radiation therapy (IMRT) uses x-rays of differential fluence to protect normal tissue surrounding target tumor. Brahme and colleagues described the concept 25 years ago, and IMRT has been progressively introduced into the clinics over the past 10 to 15 years. IMRT was first used to spare salivary gland tissue in patients with head and neck in phase I/II studies performed at the University of Michigan. Radiation dose to the contralateral parotid gland was 32% compared with 93% for the standard plans. This resulted in patients recovering 63% of their stimulated saliva by 1 year. The role of IMRT in parotid gland sparing is now well established, with subsequent studies from other institutions establishing similar threshold doses, and a mean dose threshold for reduction in salivary output to less than 25% of the baseline was found for both stimulated (26 Gy) and unstimulated (24 Gy) saliva flow rates. A randomized study with 51 patients with nasopharyngeal cancer receiving either IMRT or conventional RT showed 83% of patients in the IMRT group had recovered parotid salivary flow compared with 9.5% in the conventional group at 1 year. The global QOL was significantly better in the IMRT group compared with the conventional group. Local control and disease-specific survival were equivalent to patients treated with conventional treatment.

**RapidArc: Technical Aspects, Benefits, and Drawbacks**

Volumetric-modulated arc therapy (VMAT) consists of one or more arcs of the linear accelerator gantry around the patient. The treatment planning computer can modulate the beam with moving multileaf collimators, with variable dose rates, and with variable gantry rotation speeds to inversely calculate a highly conformal treatment plan. VMAT provides the advantage of a significantly reduced treatment time, meaning less time for the patient on the treatment table and improved clinic throughput. VMAT also requires an overall lower number of total monitor units as compared to static field IMRT to deliver an equivalent treatment, which reduces integral dose to the patient. This benefit, along with its rapid delivery of treatment (2 to 3 minutes compared with 10 to 12 minutes for fixed-gantry IMRT) has driven the use of this technology in LAHNC patients.

**IGRT: Indications, Clinical Utility**

The advances in three-dimensional radiation treatment planning and delivery provided by IMRT and VMAT have made it so daily patient treatment positioning has increased importance. There is known daily set-up variation even with use of custom immobilization devices, requiring treatment volumes to have an additional margin to ensure tumor coverage. Linear accelerators have historically provided the ability to review low-image-quality megavoltage radiographs to help confirm daily patient positioning. More recently, however, linear accelerators are being fitted with kilovoltage x-ray tubes (OBI) to allow near diagnostic quality films for better visualization of bony anatomy and more certain patient alignment. The term image-guided radiation therapy (IGRT) has been coined to emphasize that daily patient alignment is being determined and treatment delivery is being confirmed with this near-diagnostic quality imaging. IGRT, therefore, has allowed for a smaller daily set-up error in the treatment-planning process. This could be critically important when a tumor abuts a critical OAR such as the spinal cord where position verification is critical to ensure normal tissue constraints.

Linear accelerator OBI has further evolved to allow for the acquisition of serial axial images with kilovoltage cone beam computed tomography (CBCT). CBCT has the advantage of being able to assess both bony and soft tissue anatomy in three dimensions as compared to portal MV imaging and nonrotational KV OBI. This allows for patient alignment to be further refined based on three-dimensional landmarks and additional reduction in daily set-up error. These methodologies will allow for more precise and accurate daily treatment positioning.

**Adaptive Radiotherapy (ART)**

IMRT plans are typically based on a pretreatment CT that provides a snapshot of the patient's anatomy. Nevertheless, patient variations may occur during the course of treatment because of set-up error and anatomic modifications. Therefore, the accuracy of IMRT delivery for head and neck cancer may be compromised during the treatment course, potentially affecting the therapeutic index. Adaptive radiotherapy involves obtaining a new CT during the treatment course to create a new treatment plan based on the patient's current anatomy and tumor volume. These dosimetric data support the concept of identifying patients with bulk node disease likely to respond (shrink) during treatment, patients with tumors involving larger air cavities/sinuses, or patients with significant weight loss. This practice could potentially identify changes over target volumes and organs at risk for injury, such as the spinal cord and brain. A recent Chinese study utilized planned adaptive radiotherapy to generate a one re-optimized treatment plan part way through treatment for 86 patients being receiving IMRT for nasopharyngeal SCCa and compared them to the 43 enrolled patients who declined a repeat CT simulation. The patients for whom adaptive radiotherapy was utilized had better reported quality-of-life measures as well as better 2-year local regional control. Beltran and colleagues utilized cone-beam CT during treatment at the 15th and 25th fractions to determine changes in actual dose delivery to sensitive structures in the treatment region in relation to the initial IMRT plan generated from the pretreatment CT. Contralateral and ipsilateral parotid gland
mean doses increased by 6.1% (range: −5.4, 23.5%) and 4.7% (range: −9.1, 22.3%), respectively, by the 25th fraction. Additionally, the maximum absorbed dose to the spinal cord by the 15th fraction had increased by 1.8 Gy. Others have shown similar results. Hansen and colleagues found the maximum dose (Dmax) to the spinal cord increased in all 13 HNC patients studied (range, 0.2–15.4 Gy; \( p = 0.003 \)), and the brain-stem Dmax increased in 85% of patients (range, 0.6–8.1 Gy; \( p = 0.007 \)).

Proton Beam Therapy: Indications, Utilization, Clinical Trials, Drawbacks

Proton beam therapy provides the advantage over that of photons as depth of proton penetration is determined by its Bragg peak. At the Bragg peak the proton deposits a great majority of its energy at that depth in a relatively small volume. This phenomenon ensures that there is essentially no exit dose to normal tissue as well as a low-entrance dose. These physical properties would allow for the design of highly conformal proton beam treatment plans. Custom patient-specific compensators need to be designed to modulate depth of penetration in a “scattering” proton beam. A “scanning” proton beam can vary its energy and intensity while it scans a treatment volume allowing for the development of an intensity modulated proton therapy (IMPT) treatment plan. The goal of IMPT, as in IMRT, is to deliver a highly conformal dose to the tumor while minimizing dose to OAR. Proton therapy may prove very useful in settings where a critical OAR is deep to the tumor as there is minimal exit dose, as well as in children as proton therapy allows for a lower integral radiation dose and thus has the theoretical potential to lower their long-term risk of secondary malignancy. Drawbacks include the lack of randomized data proving equivalence or superiority to photon/IMRT treatment, increased expense, and paucity of long-term data assessing treatment related toxicities.

Neutron Beam Therapy: Indications, Utilization, Clinical Trials, Drawbacks

Neutrons have relatively similar depths of penetration as photons, and neutrons have the advantage of a much higher linear energy transfer (LET), meaning it will deposit a significantly greater amount of energy along its path than photons. This unfortunately can result in increased dose to OAR. Investigation into the use of neutron beams to treat SCCHN did show similar tumor control rates as photon beams, but significantly increased late normal tissue toxicity. Neutron therapy has shown a significant local control benefit when compared to photon/electron beam treatment in inoperable or recurrent salivary gland tumors, and the study was stopped early as this significance (10-year local control rates of 56% vs. 17%) was shown after only 32 patients.

Brachytherapy

As advances have been made in the delivery of highly conformal external beam radiation, the need for and use of brachytherapy has fallen. It is recommended that these complex brachytherapy procedures be performed by those clinicians who have maintained a certain volume of these specialized treatments procedures in their practice. Recommendations for brachytherapy for SCCHN were recently published by the Head and Neck Working Group of the European Brachytherapy Group–European Society for Therapeutic Radiology and Oncology (GEC-ESTRO).

CONCLUSION

Surgery continues to play an important role in the management of primary mucosal malignancies of the head and neck. Recent developments in minimally invasive approaches including robotics along with major developments in reconstructive approaches and microsurgery have dramatically improved the functional and esthetic results for this group of patients.

Concurrent chemoradiation remains a standard of care for the treatment of LAHNC; however, greater therapeutic efficacy demands we must evolve from a “one size fits all” treatment approach. Both PARADIGM and DeCIDE studies did not show an advantage of IC. The reasons for this are not clear as both studies did not complete the planned accrual. We also strongly believe that both suffered from a change in the epidemiology of head and neck cancer where HPV-related oropharynx cancer has become the main cause of head and neck cancer in the United States. These patients have an excellent prognosis, and it is possible that for those patients a less-intense therapeutic approach is warranted. We would caution, though, not to interpret PARADIGM and DeCIDE results to mean that IC is inferior or suboptimal. They do not.

The optimal treatment of LAHNC requires personalized consideration of individual patient factors and multidisciplinary assessment. We believe that IC as part of ST remains an appropriate therapeutic option for select patients, including those with significant local symptoms or at high risk of distant or local failure (large T4 or N2–3 disease) or as part of an organ-preservation strategy.

The recent publication of RTOG 91–11 long-term results raises serious concerns about the initial benefits and significant toxicities noted with CRT, and at a minimum, an argument should be made that for patients with larynx cancer both IC and CRT should be equally recommended. In fact, we call on national organizations to explicitly make this recommendation based on this newly published data. Centers that are not familiar with IC regimens or do not possess the expertise necessary to deliver high-dose chemotherapy with TPF should continue to use CRT. Significant expertise and resources are needed to deliver ST, and those are not available in most centers. A multidisciplinary team is absolutely essential and should be in place when ST is chosen as the initial treatment approach. The benefit of such a team is to allow a close monitoring of the patient during IC and the ability to move the patient immediately to CRT when IC is complete or if IC is not effective or too toxic. Avoiding delays in starting CRT are essential to maintain high cure rates. Further
investigation is required to determine the patient subset for whom ST is superior to CRT. To improve cure rates and minimize toxicity, we must define appropriate subsets of patients for treatment intensification or de-intensification strategies. To this end, future studies must incorporate HPV status, patient-specific characteristics, and tumor tissue correlative studies.

The field of radiation oncology continues to advance in conjunction with the advances in linear accelerator and imaging technology. The acute and long-term side effect profiles will continue to improve without compromise in tumor control for SCCHN provided we can consistently deliver highly conformal treatment plans while sparing OAR. In the near future, this will be through increased utilization of IGRT and adaptive radiotherapy. With increased computational power and reliable deformable registration, there is the potential to alter a treatment plan on a more frequent basis to account for daily patient set-up variation and small anatomic/volumetric changes in tumor and OAR. If the CBCT on the linear accelerator could be used to obtain the updated threedimensional image set, adaptive radiotherapy could be accomplished without the patient ever having to leave the treatment table. The ability to deliver highly conformal radiation treatment plans accurately and reliably may allow for tumor dose escalation without a corresponding increase in short- and long-term side effect profiles. But as with any advance in medicine, randomized clinical trials will need to form the basis to allow clinical integration of each of the current and upcoming technological or multidisciplinary advances in the treatment of SCCHN.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


References


HEAD AND NECK CANCER

Molecular Pathways in Head and Neck Cancer

CHAIR
Amanda Psyrrri, MD
University of Athens
Athens, Greece

SPEAKERS
Tanguy Y. Seiwert, MD
The University of Chicago Medicine and Biological Sciences
Chicago, IL

Antonio Jimeno, MD, PhD
University of Colorado, Denver
Aurora, CO
Molecular Pathways in Head and Neck Cancer: EGFR, PI3K, and More
Amanda Psyrri, MD, PhD, Tanguy Y. Seiwert, MD, PhD, and Antonio Jimeno, MD, PhD

OVERVIEW

The treatment of head and neck squamous cell carcinoma (HNSCC) is set to undergo rapid changes, as novel treatment targets informed by genomic profiling and novel molecularly targeted therapies continue to make strides. In this review we provide an overview of the latest developments regarding (1) EGFR targeting for HNSCC, (2) PI3K as a novel treatment target, and (3) newly described key genetic events in HNSCC such as NOTCH1 mutations and emerging candidate targets including ALK1 and hedgehog. The first molecular targeting strategy to demonstrate a survival advantage for patients with HNSCC has emerged in the context of EGFR biology. Cetuximab remains the only U.S. Food and Drug Administration (FDA)-approved targeted therapy available for HNSCC, but EGFR as a target has not been individualized in this disease. The PI3K-AKT pathway is downstream of EGFR and is emerging as potentially one of the most important pathways in HNSCC. PIK3CA is the most frequently mutated oncogene for HNSCC (approximately 20%) and may play a role for both HPV-negative and HPV-positive tumors. Multiple therapeutic strategies targeting PI3K are being explored, and multiple agents either alone or in combination are in development. NOTCH1 is a key tumor suppressor gene and its genetic alterations lead to abnormal pathway activation. ALK1 is a novel target involved in angiogenesis, and efficacy in patients with HNSCC was documented in an early inhibitor trial. The hedgehog pathway modulates EGFR dependence and epithelial to mesenchymal transition (EMT), a key invasion and drug-resistance mechanism in HNSCC.

The treatment of head and neck squamous cell carcinoma (HNSCC) is set to undergo rapid changes, as molecular targeted therapy continues to make strides. HNSCCs are characterized by substantial heterogeneity, at the clinical and molecular level, which challenges their consideration as a single disease entity. Comprehensive exploration of the mutational landscape of HNSCC, provided by two whole-exome sequence studies which have been conducted independently by two groups,1,2 as well as the pending release of data from the Cancer Genome Atlas Project (TCGA), promises to shed light and mechanistically inform novel as well as existing molecular targets, and to set the stage for translating these discoveries into therapies for patients.

EGFR: NEW DATA AND BEST USE OF INHIBITORS

The first molecular targeting strategy to show a survival advantage for patients with HNSCC has emerged in the context of epidermal growth factor receptor (EGFR) biology. EGFR is a member of a family of receptor tyrosine kinases whose other members include ERBB2, ERBB3, and ERBB4. Targeted disruption of the members of the EGFR family has demonstrated that these receptors play a major role in the regulation of a host of cellular activities including cell division, differentiation, and migration.3 Furthermore, over-expression or deregulation of the EGFR family members has been implicated in various human cancers, such as breast cancer, glioblastoma, and squamous cell carcinomas.4 Grandis and colleagues first demonstrated that EGFR over-expression is an early and very frequent molecular change in HNSCC, and further work revealed that the intensity of its expression is associated with reduced survival.5,6 It is now well established that EGFR in HNSCC is activated by natural ligand-induced (EGF, amphiregulin, and transforming growth factor alpha-TGFα) conformational change in EGFR. This leads to receptor dimerization (homo- or heterodimerization with other EGFR family members), which in turn triggers a sequence of signal transduction events that include activation of the Ras/Raf/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase 3-kinase (PI3K)–Akt, and signal transducer and activator of transcription pathways.7 Phosphorylated MAPK translocates into the nucleus, where it phosphorylates various transcription factors that activate expression of specific target genes, which promote angiogenesis, proliferation, metastasis, and invasion.8 EGFR is commonly targeted either by small molecule...
Cetuximab remains the only U.S. FDA-approved therapy for HNSCC. Cetuximab is a chimeric IgG1-human monoclonal antibody against the extracellular domain of EGFR, which exerts its antineoplastic properties by blocking ligand binding to the receptor. Preclinical studies evaluating cetuximab in human cancer cell lines in vitro and human tumor xenografts in vivo have shown its potent antitumor activity. The clinical efficacy of cetuximab appears to involve several mechanisms, including inhibition of cell cycle progression, induction of apoptosis, inhibition of angiogenesis, inhibition of metastasis, and its ability to enhance the response to chemotherapy and radiation.

In 2006, the FDA approved the addition of cetuximab to radiation for the treatment of locally advanced HNSCC. Cetuximab was also approved as a single agent for the treatment of patients with recurrent or metastatic HNSCC in whom platinum-based therapy had failed. In locally advanced disease, cetuximab combined with radiotherapy was compared with radiotherapy alone in a multinational randomized study. After a median follow-up of 54 months, the median survival time was 49 months in patients treated with cetuximab plus radiotherapy compared with 29.3 months in those treated with radiotherapy alone (p = 0.018). Specifically, the addition of cetuximab to radiotherapy led to an increase of 9.2% in absolute survival compared with radiotherapy alone (45.6% vs. 36.4%). Cisplatin chemoradiotherapy remains the current standard of care for locally advanced, unresectable HNSCC, since no direct comparison between cetuximab radiotherapy and cisplatin chemoradiotherapy has been performed. Cetuximab is also being studied as a substitute to cisplatin in locally advanced HPV-associated oropharyngeal cancers (OSCC) in an attempt to de-intensify treatment. Two ongoing phase III studies compare cetuximab combined with intensity modulated radiation therapy (IMRT) with cisplatin chemoradiotherapy in HPV-associated locally advanced oral squamous cell carcinoma (OSCC); Radiation Therapy Oncology Group (RTOG) 1016 and DE-ESCALATE. In the latter, only low-risk patients with HPV-positive OSCC will be included. The Eastern Cooperative Oncology Group (ECOG) phase II study (E1308) evaluated whether the increased response to platinum-based induction chemotherapy can be used to select patients who can safely receive a lower dose of intensity-modulated radiation therapy (IMRT). The protocol includes three cycles of induction chemotherapy with cisplatin, paclitaxel, and cetuximab and identifies only those who attain complete response as eligible for receiving low-dose IMRT (54 Gy/27 fractions) with concomitant cetuximab. On the other hand, patients in whom therapy fails to achieve a complete response receive standard-dose (60.3 Gy) IMRT with concurrent cetuximab. The study is closed to accrual.

In vitro studies in HNSCC cell lines have shown a synergistic effect of cetuximab with cisplatin, and clinical data in the recurrent/metastatic setting confirm the activity of this combination. RTOG 0522 was conducted to test the hypothesis that the addition of cetuximab to cisplatin chemoradiotherapy in locally advanced HNSCC will improve progression-free survival (PFS) compared with standard cisplatin-based chemoradiotherapy. A total of 895 patients were randomly assigned to receive cetuximab plus cisplatin/radiotherapy or cisplatin/radiotherapy. At a median follow-up of 2.4 years, no significant difference in survival parameters (PFS or overall survival [OS]) was observed between the study arms. A proposed explanation for the lack of survival gain from the addition of cetuximab to cisplatin chemoradiation is that cetuximab and cisplatin share the same mechanism of action. It has therefore been postulated that other agents such as docetaxel might be better partners to cetuximab/radiotherapy, and this combination represents an arm of an upcoming RTOG study.

Cetuximab has also been shown to improve the outcome of chemotherapy in the recurrent/metastatic setting. Burtness and colleagues reported improved response rates with the addition of cetuximab to cisplatin in ECOG 5397. In another study, conducted by Vermorken and colleagues, 442 eligible patients with previously untreated recurrent or metastatic HNSCC were randomly assigned to receive cisplatin (100 mg/m²) or carboplatin (area under the curve of 5 mg/mL/min) plus 5-fluorouracil (1 g/m² per day for 4 days) every 3 weeks or the same chemotherapy plus weekly cetuximab for a maximum of six cycles. Patients who attained at least stable disease (SD) with chemotherapy plus cetuximab continued

KEY POINTS

- EGFR is overexpressed in the majority of HNSCC and can be targeted by both small molecules and antibody-based therapies.
- A consistent mechanism of resistance to EGFR-targeted therapies has not been described in HNSCC.
- A critical question is whether HPV-associated HNSCC derives benefit from the addition of cetuximab to chemotherapy, as retrospective analyses of randomized studies yielded conflicting results.
- PI3K is a key signaling pathway in cancer, including head and neck cancer.
- Genetic alterations in PI3K-related genes are common in HNSCC (e.g., PIK3CA mutations in up to 20% of tumor).
- Multiple PI3K inhibitors are currently in clinical testing for HNSCC.
- NOTCH1 genetic alterations lead to abnormal pathway activation.
- ALK1 is a novel target involved in angiogenesis.
- The hedgehog pathway modulates EMT.
with cetuximab until disease progression or unacceptable toxicity. The addition of cetuximab to platinum-based chemotherapy with fluorouracil resulted in improvement in median OS from 7.4 to 10.1 months (p = 0.04). The median PFS was significantly prolonged from 3.3 to 5.6 months (p < 0.001), and the response rate increased from 20% to 36% (p < 0.001). This was the first time that survival improvement was demonstrated with a combination therapy in the setting of recurrent/metastatic HNSCC.

Panitumumab is a fully human monoclonal antibody against EGFR. Two phase II randomized studies, CONCERT 1 and 2, have been conducted in the unresectable locally advanced setting. CONCERT 1 was a randomized phase II study of chemoradiotherapy with and without panitumumab. CONCERT 2 was a randomized comparison of panitumumab radiotherapy to cisplatin chemoradiotherapy. Both studies failed to show superiority of the panitumumab arm, and the addition of panitumumab to cisplatin chemoradiotherapy was associated with increased toxicity. The SPECTRUM study, a randomized phase III trial of chemoradiotherapy with cisplatin/5-fluorouracil with or without panitumumab in patients with recurrent/metastatic HNSCC, also did not meet its primary endpoint, which was OS.

EGFR TKIs have been tested in HNSCC but none have received FDA approval to date. A phase II trial of gefitinib in patients with recurrent or metastatic HNSCC resulted in an overall response rate with gefitinib of only 11%.21 As skin toxicity is considered a predictor for response to EGFR-targeted therapies, a phase II study evaluated adaptive dose-escalation to skin toxicity in the recurrent/metastatic setting.22 Dose escalation up to 750 mg of gefitinib per day was performed. Higher gefitinib trough levels correlated with higher likelihood for attaining disease control; however, dose escalation was not associated with increased activity. A phase III randomized study, ECOG-E1302, compared docetaxel to docetaxel plus gefitinib in patients with recurrent or metastatic HNSCC with a performance status of 2 or who had been previously treated. The study was terminated early because of an interim analysis in December 2008 showed that it was highly unlikely that it would reach its primary endpoint. The docetaxel/gefitinib arm was associated with longer median time to tumor progression (3.5 vs. 2 months; p = 0.047), but no statistically significant improvement in response rate, PFS, or OS compared with the docetaxel arm. The study was criticized for including patients who were heavily pretreated or who had a poor performance status. A phase I study of chemoradiotherapy with lapatinib, a dual inhibitor which also disrupts the HER2 pathway, for locally advanced HNSCC reported an overall response rate of 81%.23 Lapatinib in the recurrent/metastatic setting has little activity in EGFR inhibition–naïve or –refractory subsets. Heterodimerization of EGFR with other HER family members is involved in aberrant EGFR signaling and is one of the mechanisms implicated in resistance to EGFR inhibitors. Aftatinib (BIBW2992) is an irreversible dual inhibitor of EGFR and HER2 TKI, which binds to Cys773 of EGFR and Cys805 of HER2. A property of BIBW2992 is its broad activity against multiple receptors in the HER family, making it theoretically more effective against tumor cells bearing several ErbB family members and heterodimerizations. A randomized phase II study compared weekly cetuximab (400 mg/m² loading dose and 250 mg/m² thereafter) with 50 mg of afatinib daily in 74 patients with recurrent or metastatic HNSCC in whom platinum-based therapy had failed.24 Treatment was continued until disease progression or undue side effects (stage I), with a cross-over design after disease progression (stage II). Of 34 patients randomly assigned to afatinib, six (18%) had a partial response, 18 (53%) attained stable disease, and 10 (30%) had disease progression. Of 40 patients randomly assigned to cetuximab, three (8%) had a partial response, 20 (50%) had stable disease, and 17 (43%) had disease progression. Preliminary safety analysis showed a side effect profile consistent with other EGFR inhibitors, with diarrhea and rash. A preliminary efficacy analysis based on the response rates demonstrates that afatinib has activity in patients with recurrent/metastatic HNSCC in whom platinum-based therapy has failed and compares favorably to cetuximab. A randomized phase III study comparing methotrexate to afatinib as a second-line therapy in recurrent/metastatic setting is ongoing, while another study comparing afatinib to placebo as maintenance therapy following definitive platinum-based chemoradiotherapy for locally advanced HNSCC is also underway.

A fundamental problem in EGFR-targeted therapy in HNSCC is patient selection, since a consistent mechanism for resistance has not been identified. EGFR as a molecular target has yet to be individualized for HNSCC. In non–small cell lung cancer (NSCLC), patients with activating mutations in the EGFR tyrosine kinase domain demonstrate significantly better response to EGFR TKIs. Mutations in EGFR tyrosine kinase domain are rare in HNSCC. Some investigators report detection of the type III mutated variant (EGFRvIII) in a variable proportion of HNSCC ranging from 0% to 40%,25 but its existence remains controversial.

EGFRvIII mutated variant is characterized by an in-frame deletion from exons 2 through 7 in the extracellular domain, which is hypothesized to affect the intracellular domain conformation and the ATP pocket leading to constitutive activation of the receptor and resistance to targeting by monoclonal antibodies directed against the extracellular domain of EGFR. Irreversible EGFR inhibitors such as afatinib in preclinical studies are effective against EGFRvIII.

Resistance to EGFR inhibition might also be mediated by activation of alternative and/or downstream pathways that bypass EGFR and activate extracellular signal-regulated kinase 1/2 (ERK1/2). Yonesaka and colleagues26 recently showed that activation of ERBB2 amplification or through heregulin upregulation, induces persistent ERK 1/2 activation and acquired cetuximab resistance. Depletion of ERBB2 or disruption of ERBB2/ERBB3 heterodimerization restored cetuximab sensitivity in vitro and in vivo, underscoring the importance of ERBB2...
signaling in maintenance of the resistant phenotype. Overexpression of ERBB2-induced gefitinib resistance, and the combination of pertuzumab (which targets HER2) with gefitinib in HNSCC cell lines resistant to gefitinib resulted in increased inhibition of cell growth. 

In colon cancer, mutations which constitutively activate key signaling mediators downstream of EGFR, particularly KRAS, have been associated with cetuximab resistance. Mutations in KRAS are extremely rare in HNSCC, although HRAS mutations have been reported.

MET overexpression was found in 84% of HNSCC cases; MET mutations and gene amplification were reported in 13.5% and 13% of the cases, respectively. A combination of a MET inhibitor with erlotinib resulted in greater-than-additive inhibition of cell growth by ErbB3/AKT signaling.

EMT has also been implicated in resistance to cetuximab. A recent study demonstrated that targeting of antioxidant systems that allow stem-like cancer cells to avoid oxidative stress may sensitize the remaining surviving cells to EGFR inhibition.

Another critical question is whether HPV-associated HNSCC derives benefit from the addition of cetuximab to chemotherapy. A retrospective analysis of the SPECTRUM study suggested that the addition of panitumumab to chemotherapy was associated with clinical benefit only in patients who are p16-negative. On the contrary, retrospective analysis of the EXTREME study showed that both p16-positive and p16-negative patients derive clinical benefit from the addition of cetuximab to chemotherapy. These discordant results might be explained by the different immunohistochemical cutpoints used to define p16 positivity in the two studies. It should be emphasized, however, that in both studies, p16-positive tumors represented a small minority of the study population, and thus these findings should be interpreted with caution.

Future research will need to identify factors that correlate with response (or lack thereof) to EGFR-targeted therapies and the underlying genotype-phenotype relationship that dictates this response.

**PHOSPHATIDYLINOSITIDE 3-KINASE PATHWAY**

**BIOLOGY AND INHIBITORS**

**The PI3K-AKT-mTOR Pathway and Physiology**

Phosphoinositide 3-kinases (PI3Ks) are a family of related enzymes that play a pivotal role in important cellular regulatory mechanisms. PI3Ks are capable of phosphorylating the 3′-OH position of phosphoinositide lipids (PIs) generating lipid second messengers. Their function has been linked to the regulation of numerous biologic processes, including cell growth, differentiation, survival, proliferation, migration, and differentiation. According to structural and substrate specificity PI3Ks are divided into 3 classes (Fig. 1):

Class 1 is currently the only clinically relevant subgroup and can be further divided into A and B subtypes:

- Class 1 A enzymes are activated by receptor tyrosine kinases (RTKs) and G-protein coupled receptor (GPCRS), as well as some oncogenes such as RAS. These are heterodimers consisting of p110 catalytic subunit and p85 regulatory subunit, with p110alpha (PIK3CA gene product) and p110beta (PIK3CB gene product) being most commonly involved in cancer-related signaling. In response to growth factor stimulation and activation of RTKs, PI3Ks move to the membrane by direct interaction of its p85 subunit with tyrosine phosphate motifs on activated receptors or to adaptor proteins (IRS). p110 activation generates phosphatidyl inositol-3,4,5 triphosphate, which activates various products downstream.

- Class 1 B enzymes are regulated by GPCRS. It is a heterodimer with catalytic subunit p110 gamma and regulatory subunit p101. p110 gamma is activated by GPCRs through its regulatory subunit.

Class 2 consists of a single catalytic subunit. There are three isoforms of class 2 PI3Ks, which are activated by RTKs, cytokine receptors, and integrins.

Class 3 consists of a single catalytic subunit VPS34 (homolog of yeast vacuolar proteins sorting associated proteins 34, also known as PIK3C3). VPS34 has been shown to function as a nutrient-regulated lipid kinase that mediates signaling through mTOR, and contributes to cell growth.

PI3-kinases have been linked to an diverse group of cellular functions, including cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking (Fig. 2). Many of these functions relate to the ability of class 1 PI3-kinases to activate protein kinase B (PKB, also commonly known as AKT). AKT, a serine-threonine kinase, has three different isoforms (AKT1, AKT2, AKT3). AKT activation is initiated by translocation to the plasma membrane. AKT phosphorylation is carried out by 3-phosphoinositide-dependent protein kinase 1 (PDK1) and PDK2. It is thought that mTOR–rictor (rapamycin insensitive companion of mTOR) complex 2 (mTORC2) is the primary source of PDK2 activity under most circumstances (Fig. 2).

There are few AKT-independent pathways, but their role in cancer is not well defined. Once activated, AKT is a phosphorylating source for many proteins, including glycogen synthase phosphate 3 and FOXOs, regulating diverse cellular functions (Fig. 2). Thus, in most cancers, AKT activation by PI3K is either by tyrosine kinases (RTKs) or by somatic mutations.

PI3K-AKT signaling plays a pivotal role in normal and cancer physiology through multiple downstream targets (Fig. 2). Cyclin D1 influences cell cycle progression and proliferation, inhibition of GSK3 leads to increased glucose metabolism, inhibition of Forkhead influences both proliferation and antiapoptosis, and signaling by mTOR/TSC1/TSC2 influences protein metabolism and cell growth.

In normal physiology and many cancers, PI3K (specifically Class IA PI3K) signaling is usually initiated by upstream RTK signaling. The p85 regulatory subunit is vital in mediating class IA PI3K activation by RTKs. Aberrant activation of PI3K (e.g., HER2 amplification) is, to a large degree,
mediated by PI3K signaling, and class IA PI3K inhibitors may be active in HER2-amplified tumors.34

**PTEN loss.** Activated class I PI3-kinases generate PtdIns(3,4,5)P3, which acts as a key second messenger that drives several downstream signals and regulates cellular processes. The cellular levels of PtdIns(3,4,5)P3 are tightly regulated by the opposing activity of the tumor suppressor PTEN (phosphatase and tensin homolog). PTEN functionally antagonizes PI3K activity through its intrinsic lipid phosphatase activity that reduces the cellular pool of PtdIns(3,4,5)P3 by converting PtdIns(3,4,5)P3 back to phosphatidylinositol-4,5-bisphosphate (PtdIns[4,5]P2). Loss of PTEN results in unrestrained signaling by the PI3K pathway, leading to cancer. PTEN loss is common in head and neck cancer and many other malignancies.31,35 Interestingly, tumors with PTEN loss appear to signal primarily using the p110beta (PIK3CB), which is important for the selection of appropriate inhibitors.33 It has been reported that loss of tumor suppressors such as PTEN commonly occurs, although mutations may not be the primary mechanism of PTEN loss in HNSCC.36

**Genetic Alterations in the PI3K Pathway in Head and Neck Cancer**

**PIK3CA mutations.** Several reports indicate that genetic aberrations of the PI3K pathway are common in head and neck cancer. In particular, mutations of the PIK3CA gene have been reported in 6% to 20% of head and neck tumors.1,2,36,37 Furthermore, it was suggested that well-established oncogenic (canonical) PIK3CA mutations are particularly common in HPV-positive head and neck cancers.37 PI3K appears to be active in patients with breast and/or gynecologic malignancies if tumors harbor PIK3CA mutations.38 It appears that PIK3CA is commonly amplified, although a “low-level” copy number increase is characteristic.1,36,37

Other genetic aberrations in the PI3K pathway have been reported in various cancers including PIK3RI mutations,
INPP4/PHLPP tumor suppressor loss, AKT mutations and amplification, TSC1/2 or PDK1 aberrations, or loss of NF2. It remains unclear whether such changes occur in HNSCC. It should also be noted that upstream amplification of certain RTKs leads to PI3K dependence (e.g., ErbB2). For EGFR, which is amplified in 10% to 15% of HNSCC, signaling may not solely rely on PI3K.

**Translational Implications**

It has been shown in vitro that PI3K mutations may confer increased resistance to EGFR inhibition. Two head and neck cancer cell lines with canonical PIK3CA mutations were largely insensitive to inhibition with the EGFR inhibitor gefitinib and showed persistent activation of pAKT. It will be important to further validate such findings in clinical studies, and PIK3CA may therefore be a candidate biomarker of EGFR resistance.

**PI3K INHIBITORS IN CLINICAL TESTING AND TRIALS IN HNSCC**

Three classes of PI3K inhibitors can be differentiated:

1. Combined inhibitors of PI3K/mTOR. Examples include NVP-BEZ235 and GDC-0980. GDC-0980 is currently being evaluated in a phase I study, while development of NPV-BEZ235 has been somewhat delayed because of reformulation of the drug.

2. Pan-Class I PI3K inhibitors. Examples include NVP-BKM120, GDC-0941, and PX-866. Both NVP-BKM120 and PX-866 are currently being evaluated in head and neck cancer in phase II studies in combination with cetuximab.

3. Alpha-specific (p110alpha specific) inhibitors. An example is NVP-BYL719, which is currently in phase II testing for HNSCC in combination with cetuximab.

It remains unclear which type of PI3K inhibitors are most promising for head and neck cancer, as well as which agent to potentially combine with PI3K inhibitors, and which biomarkers to use. Nevertheless, the abundance of genetic aberration in the PI3K pathway and early clinical data suggest that PI3K may be a promising target for HNSCC.

**NEW SIGNALING PATHWAYS AND TARGETS IN THE HNSCC HORIZON**

**NOTCH**

The NOTCH family consists of 4 receptors (NOTCH1–4), which interact with the Delta-like (Dll1, Dll3 and Dll4) and Jagged (Jag1 and Jag2) families of ligands, which are normally bound to the cell membrane. Ligand binding is followed by two cleavages of the NOTCH receptor by ADAM metalloprotease and gamma-secretase complex, leading to the release of the NOTCH intracellular domain (NICD). NICD association with the CSL/MAM complex is able to bind DNA and promote transcription. NOTCH signaling had previously been implicated as pro-tumorigenic—by virtue of activating mutations and translocations observed in the genes for NOTCH receptors or their regulators, in T-cell acute lymphoblastic leukemia (T-ALL), chronic lymphocytic...
leukemia, and diffuse large B-cell lymphoma. NOTCH1 heterodimerization (HD) domain mutations that result in ligand independent proteolytic activation were found to drive proliferation in T-ALL.41 These activating mutations result in ligand, and lung squamous cell carcinomas (SCC).1,2,43 Unlike T-ALL, mutations found across SCC primarily fell within the EGF-repeats domain and were predicted to be inactivating by disruption of ligand binding.

The tumor suppressor role of NOTCH signaling in SCCs is still being characterized. However, NOTCH signaling does promote terminal differentiation of keratinocytes and is negatively regulated by the EGFR pathway. EGFR-activated c-Jun suppresses p53 and NOTCH1 in keratinocytes and skin SCC, while blockade of EGFR induces keratinocyte differentiation through NOTCH.44 Thus the interest in NOTCH signaling in HNSCC may lie in identifying the pathways that become dysregulated after NOTCH inactivation and that confer a proliferative and/or a pro-survival advantage.

ALK1
The activin receptor-like kinase 1 (ALK1) is a type I receptor belonging to the transforming growth factor-beta (TGFβ) superfamily and is selectively expressed on activated endothelial cells in response to injury or disease.45 ALK1 is involved in the maturation phase of angiogenesis and has been hypothesized to play a key role in the development of functional vasculature.

ACE-041 is a recombinant and soluble fusion protein consisting of the extracellular domain of human ALK1 linked to the Fc portion of human immunoglobulin G1 (IgG1). ACE-041 binds to the ligands bone morphogenetic protein (BMP) 9 and BMP10 and inhibits their interaction with ALK1, thus blocking ALK1-mediated signaling. ACE-041 binding inhibits vascular endothelial cell maturation and disrupts the process of vascular development.46 As opposed to other angiogenic agents that block the proliferative phase of angiogenesis, ACE-041 modulates the maturation phase of angiogenesis.

ACE-041 was studied in a dose-escalation phase I study to determine its safety, tolerability, optimal dosing strategy, and antitumor activity in patients with advanced solid tumors.46 ACE-041 was well tolerated, with the main toxicity being edema and fluid overload that were dose-dependent and responded to diuretic therapy. Six heavily pretreated patients (NSCLC,47 small bowel, carcinoid, rectal) had stable disease on ACE-041 and one patient with HNSCC had a partial response. This has prompted an ongoing phase II clinical trial of ACE-041 in patients with refractory relapsed/metastatic (NCT01458392).

Hedgehog Pathway
The hedgehog pathway (HhP) is a validated anticancer target, and vismodegib (a small molecule that inhibits the HhP) is approved for use in patients with advanced basal cell carcinoma of the skin. Ligand activation by sonic hedgehog (SHH) leads to a cascade of signaling, leading to glioma-associated oncogene family zinc finger 1 (GLI1) expression, which in turn modulates numerous cancer target genes. HhP signaling may also be crucial in the survival and characteristics of cancer stem cells and is a likely candidate for drug resistance.48,49 EGFR and HhP and have been implicated as key drivers of proliferation and survival of cancer cells.

EGFR and HhP signaling converge and/or synergize upstream of GLI1 through the MEK/ERK signaling pathway in cancer cells and during keratinocyte oncogenic transformation.50-52 Epidermal growth factor (EGF) stimulates expression of GLI1 and target genes BCL2 and PTCH1 in gastric cancer,53 and the HhP ligand sonic hedgehog (SHH) signals through MAPK and PI3K to increase expression of HhP specific targets in renal cancer.54

Both pathways have been closely linked to EMT.55,56 In this process, epithelial cells gain a more spindle- or fibroblast-like phenotype and become more mobile and invasive. Molecularly, EMT is characterized by expression of the pro-EMT ZEB, SNAIL, and TWIST transcription factors, loss of E-cadherin (E-CAD), and increased levels of vimentin (Vim).57 The ability of cells to alter their morphology is often associated with drug resistance, allowing tumor cells to escape from cytotoxic and pathway-targeted therapies.58-60 Recently, reports have described an EGF-induced EMT-like state in EGFR-dependent HNSCC and prostate cancer cell lines.61,62 On the other hand, chronic gefitinib treatment was found to generate a mesenchymal drug-resistant population in HNSCC cells independent of EGFR activation.63 The dichotomy of these EGFR-dependent and -resistant states and the role of HhP signaling have yet to be clarified in HNSCC.

GLI1 has been demonstrated to be a key driver of tumor growth and metastasis in multiple cancers.64,65 In HNSCC, nuclear GLI1 expression levels were determined in tumors from patients enrolled on RTOG 9003, a radiation fractionation trial.66 The results were also correlated with previously determined EGFR expression, and assessed in relation to time to metastasis (TTM), time to disease progression (TDP), and OS. Of 1,068 eligible patients, data on GLI1 and EGFR were available in 339 and 300 patients, respectively. GLI1 was associated with poorer outcomes, adjusted for age, tumor/node/metastasis staging system stages, and performance status, and the significant influence persisted in a multivariable analysis (TTM hazard ratio [HR], 2.7; 95% CI, 1.5 to 4.9; TDP HR, 1.6; 95% CI, 1.1 to 2.5; OS HR, 1.9; 95% CI, 1.4 to 2.7; p < 0.001). Although these data suggest that GLI1 could serve as a marker in HNSCC, several pathways other than HhP converge and modulate GLI1, and thus the regulatory mechanisms and oncogenic significance need further investigation.
Based on preclinical data using an array of in vitro and patient-derived in vivo models of HNSCC and the HhP inhibitor IPI-926, the interplay between EGFR and HhP is being explored in a dose-escalation, proof-of-concept clinical trial in which patients with refractory relapsed or metastatic HNSCC receive sequential therapy with cetuximab and IPI-926 (NCT01255800). The study is a pilot trial with three sequential tumor biopsies (baseline, after cetuximab, and after combination) aiming at interrogating cancer stem cell subpopulation dynamics, EMT, HhP signaling, and whole transcriptome analysis to determine the molecular mechanisms underlying EGFR acquired resistance and how HhP modulation may modulate such EGFR dependence.

In conclusion, many novel pathways and treatment approaches are being explored for head and neck cancer, including ways to enhance EGFR activity and overcome resistance, targeting PI3K signaling, which is central to HNSCC and frequently genetically altered, as well as identifying new candidate treatment targets such as NOTCH, ALK1, and hedgehog signaling.

ACKNOWLEDGMENT

The authors would like to acknowledge the contribution of Theodoros Rampias, Wanda Shen, Saad Mansoos, and Stephen B. Keysar.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


References


HEAD AND NECK CANCER

Salivary Gland Cancer

CHAIR
Lisa F. Licitra, MD
Fondazione IRCCS Istituto Nazionale dei Tumori
Milan, Italy

SPEAKERS
Göran Stenman, DMD, PhD
University of Gothenburg
Gothenburg, Sweden

David Raben, MD
University of Colorado, Denver
Aurora, CO
Salivary Gland Cancer: An Update on Present and Emerging Therapies

Julie Carlson, MD, Lisa Licitra, MD, Laura Locati, MD, David Raben, MD, Fredrik Persson, MD, PhD, and Göran Stenman, DMD, PhD

OVERVIEW

Malignant salivary gland tumors make up a small proportion of malignancies worldwide, yet vary widely in terms of histology, patterns of spread, and recurrence. A better understanding of this variability will guide appropriate treatment recommendations and lead to improved outcomes. Recent molecular genetic studies have uncovered a translocation-generated gene fusion network in salivary gland carcinomas that can be used for diagnosis, treatment decisions, and development of specific targeted therapies. The gene fusions encode novel fusion oncoproteins that function as transcriptional coactivators, tyrosine kinase receptors, and transcription factors involved in growth-factor signaling and cell-cycle regulation. While surgery currently is the primary therapy for operable tumors, radiation plays an important role in the postoperative setting, as well as in the definitive setting for inoperable lesions. An awareness of the risk factors for tumor recurrence and spread is important for both adjuvant therapy referrals and for radiation treatment planning purposes. Additionally, chemotherapy is being used increasingly in both the concurrent setting as a radiosensitizer, as well as in the palliative setting for metastatic tumors. Future trials investigating concurrent chemotherapy and radiation, as well as the use of targeted agents based on evolving molecular discoveries, will elucidate optimal personalized approaches for this challenging disease.

Malignant tumors of salivary glands are uncommon: the world annual incidence rates are between 4 and <0.05 per 100,000.1 In Europe SGC has an incidence of 1.2 per 100,000, according to Surveillance of Rare Cancers in Europe (www.rarecare.eu). The causes are not fully understood. Diet, prior irradiation, past history of cancer, and genetic predisposition may play a role. Workers employed in rubber manufacturing companies, in beauty shops, and those exposed to nickel compounds, have an increased risk of salivary gland cancer (SGC). Chronic inflammation of salivary glands is not clearly defined as a risk factor.

ANATOMY

Salivary glands include the three paired major salivary glands—the parotid, submandibular, and sublingual—and the minor salivary glands. The head and neck contain about 450 to 750 minor salivary glands, widely distributed throughout the upper respiratory tract and do not contribute to saliva. However, they are often included in papers on salivary gland cancer.2

GENE FUSIONS AND MUTATED ONCOGENES AS EMERGING MOLECULAR TARGETS FOR THERAPY

Recent studies have shown that chromosome translocations resulting in fusion oncoproteins are typical features not only of hematologic malignancies and sarcomas but also of several types of carcinomas.3 Many of these fusions are now recognized as important diagnostic and prognostic biomarkers and as novel molecular targets for therapy.

Molecular genetic studies have revealed that several histologic subtypes of SGCs are characterized by tumor-type specific gene fusions.4 The major targets of the translocations are transcriptional coactivators, tyrosine kinase receptors, and transcription factors involved in growth factor signaling and cell cycle regulation. The discovery of these gene fusions and their downstream targets and activated signaling pathways opens new avenues for improved diagnosis, classification, and, most importantly, development of new targeted therapies. Moreover, studies of mutated oncogenes and activated signaling pathways have contributed new knowledge about potential therapeutic targets in SGCs.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (ACC) is an aggressive but slow-growing cancer with an often fatal outcome. ACC is characterized by a tumor-type specific t(6;9)(q22–23;p23–24) translocation resulting in a fusion of the MYB oncogene to the transcription factor gene NFIB.5 MYB is a transcription factor involved in the control of cell proliferation, apoptosis, and differentiation that is highly expressed in...
immature, proliferating cells and is downregulated as cells become differentiated.\(^4\) The MYB-NFIB fusion oncogene, which is highly overexpressed in ACC, activates transcription of several important MYB target genes, including BCL2, KIT, CD34, BIRC3, MYC, and MAD1L1.\(^5\)

More than 80% of ACCs have MYB activation by gene fusion or other mechanisms and because the fusion is not found in any other type of SGC, it is regarded as a key oncogenic event and hallmark of ACC.\(^4\) In addition to being an important diagnostic biomarker, MYB and its downstream targets are also novel potential therapeutic targets. Studies are now in progress to identify drugs that can inhibit/down-regulate the MYB-NFIB fusion and/or the signaling pathways activated by the fusion using both patient-derived ACC-xenograft models and newly developed ACC-based in vitro systems for drug screening.\(^4\)

Studies of hematopoietic progenitor cells have shown that fibroblast growth factor (FGF) 2 can cooperate with v-Myb and maintain these cells in an undifferentiated proliferative state.\(^6\) In the absence of FGF2, these cells differentiate into mature erythrocytes, suggesting that the FGFR signaling pathway may be a possible molecular target in ACC. Indeed, there is an ongoing phase II study using the FGFR kinase inhibitor dovitinib in patients with ACC who have progressive disease.

The TrkC/NTRK3 signaling pathway was recently shown to be activated in ACC;\(^7\) in vivo studies of ACC-xenografts revealed growth inhibition of the TrkC kinase inhibitor AZD7451, suggesting that Trk kinase inhibition may be a potential therapeutic option in ACC. Similarly, a subset of ACC was recently shown to have mutations in RAS pathway genes, including BRAF and HRAS, suggesting that the BRAF inhibitor vemurafenib may be effective in patients with activating BRAF kinase mutations.\(^8\)

The role of epidermal growth factor receptor (EGFR) kinase inhibitors in ACC is unclear. EGFR mutations are very rare in ACC, but the gene is activated in about one-third of the tumors.

**MUCOEPIDERMOID CARCINOMA**

Mucoid epidermoid carcinoma (MEC), the most common subtype of SGC, is characterized by a t(11;19)(q21–22;p13) translocation resulting in a CRTC1-MAML2 gene fusion. CRTC1 encodes a CREB (cAMP response element-binding protein) coactivator and MAML2 a coactivator for Notch receptors, and in the fusion protein, the Notch-binding domain of MAML2 is replaced by the CREB-binding domain of CRTC1. The fusion oncogene has transforming activity and activates transcription of cAMP/CREB target genes, including AREG, PEPCK1, MMP10, IL6, and NR4A2/3.\(^9\) Preliminary studies using small molecule inhibitors of the EGFR (AREG-ampiregulin) or PKA (cAMP-dependent kinase) pathways have shown that they can inhibit the proliferation of MEC cell lines in vitro, suggesting that targeting these pathways may offer a new approach to systemic treatment of CRTC1-MAML2 positive MECs.\(^10\)

The CRTC1-MAML2 fusion is a clinically important biomarker that distinguishes true MECs from fusion-negative MEC-like tumors.\(^11\) There is ample evidence to suggest that the latter tumors are not true MECs but instead represent poorly differentiated adenocarcinomas or adenosquamous carcinomas. We therefore suggest that patients with histopathologically confirmed or suspected MECs should be screened by RT-PCR and/or FISH for the CRTC1-MAML2 fusion before being enrolled in clinical trials using MEC-specific anticancer agents.

**MAMMARY ANALOG SECRETORY CARCINOMA**

Mammary analog secretory carcinoma (MASC) of the salivary glands is a recently described SGC with strong morphologic and genetic resemblance to secretory carcinoma of the breast.\(^12,13\) Both tumor types share a t(12;15)(p13;q25) translocation, resulting in an ETV6-NTRK3 gene fusion. The fusion is found in more than 90% of MASCs and is an important biomarker that defines this. Recent studies have demonstrated that ETV6-NTRK3-mediated transformation of mammary epithelial cells is blocked by targeting the IGF1R signaling pathway.\(^14\) Thus, the dual-specificity IGF1R/insulin receptor (INSR) kinase inhibitors BMS-536924 and BMS-754807 were shown to block ETV6-NTRK3 induced cell transformation in vitro and to significantly reduce tumor growth in vivo. These data indicate that the IGF1R/INSR
signaling pathway is a novel molecular target and that it may be possible to treat ETV6-NTRK3-positive SGCs with IGF1R/INSR inhibitors.

**CARCINOMA EX PLEOMORPHIC ADENOMA**
Carcinoma ex pleomorphic adenomas (Ca-ex-PA) are often high-grade, aggressive tumors. The malignant component of Ca-ex-PA is frequently a poorly differentiated adenocarcinoma or undifferentiated carcinoma but may be any other subtype of SGC (e.g., MEC, salivary duct carcinoma, or ACC). Previous studies have shown that Ca-ex-PA express pleomorphic adenoma (PA) specific gene fusions involving PLAG1 and HMGA2. In addition, amplification of genes in 12q13–15, in particular MDM2 and HMGA2, mutation of p53, and amplification of HER2 have been shown to be of importance for malignant transformation of PA. The findings of p53 mutations or amplifications of MDM2 suggest that targeting the p53-pathway may be one way of treating tumors with these molecular abnormalities. Such treatment may include small-molecule inhibitors of MDM2 (e.g., MI-219 and Nutlin-3 analogs), which can reconstitute p53-function in tumors with MDM2-amplification/overexpression. The majority of Ca-ex-PA with HER2 amplification/overexpression are salivary duct carcinomas developing within PAs. There are anecdotal reports showing that these patients may significantly benefit from anti-HER2 treatment with trastuzumab.

**ACINIC CELL CARCINOMA**
Acinic cell carcinoma (AciCC) is typically a slow-growing, low-grade tumor which occasionally may undergo high-grade transformation. So far, no recurrent chromosome rearrangement, gene fusion, or common mutation has been encountered in these tumors. However, a recent study unexpectedly showed that conditional inactivation of the Apc and Pten tumor suppressor genes in mouse salivary glands caused a synergistic activation of canonical Wnt and mTOR signaling and rapid development of salivary gland tumors morphologically similar to human AciCCs. Treatment of tumor-bearing mice with the mTOR inhibitor rapamycin resulted in complete regression of the tumors. Studies of human AciCC specimens confirmed that mTOR signaling is also activated in human AciCCs. Taken together, these results indicate that the mTOR pathway may be a relevant molecular target in AciCC.

**CLINICAL PRESENTATION**
**Major Salivary Gland Tumors**
Malignant neoplasms in these sites usually appear clinically indistinguishable from benign tumors. Consequently, every painless swelling of a salivary gland must be suspected, especially in the absence of inflammation. Pain is not typical. Malignant tumors account for 15% to 32% in the parotid gland, 41% to 45% in the submandibular gland, and 70% to 90% in the sublingual gland. Malignant salivary tumors show a range of biologic behaviors. In approximately 40% of cases, these tumors are indolent growing lumps. In approximately 40% of cases, such tumors are also aggressive (especially in elderly patients); facial palsy may be a presenting sign with an evolving mass.

Nodal metastases depend on histotype and grading more than primary tumor site. A rapid growth and sometimes ulceration of a preexisting parotid mass is seen in one-third of patients with carcinoma ex pleomorphic adenoma. Soft palatal fullness may also be present, in the case of tumors invading the parapharyngeal space. Trismus, fixation of the tumor to overlying skin, ulceration, and fistulas are signs of very advanced disease.

**Minor Salivary Gland Tumors**
A greater proportion of malignancies occurs in the minor salivary glands than in the major counterpart. In over 50% of cases, minor salivary gland tumors are intraoral: a painless submucosal swelling is usually present, sometimes accompanied by ulceration of the overlying mucosa. In case of nasopharyngeal or nasal cavity infiltration, facial pain, nasal obstruction, or bleeding may be present. Tumors occurring in the larynx or trachea may cause hoarseness, voice change, or dyspnea.

**DIAGNOSIS**
Physical examination represents the main diagnostic tool for major SGCs. Approximately 80% of salivary gland tumors arise in the parotid and the majority of them are benign, an initial differential diagnosis between cancer and other benign diseases should be done.

Ultrasoundography is characterized by high sensitivity and low cost, and it is always recommended as a preoperative examination given that approximately 90% of tumors arise in the superficial lobe of the parotid gland. MRI has a sensitivity of 87% with a specificity of 94%, and it is particularly useful in visualizing the tumor interface and surrounding tissues for correct surgical planning, especially in the case of larger tumors (more than 4 cm), tumors arising in deep structures and/or involving them, and for tumors originating from the minor SGCs. In particular, MRI with contrast enhanced and with fat-suppressed T1-weighted image results are useful if there is perineural invasion.

Tissue biopsy is indicated in those cases when an evidence of malignancy has been assessed and extensive surgery, such as neck dissection and total parotidectomy, is needed.

More controversial are indolent cancers mimicking a benign tumor. A fine needle aspiration cytology (FNAC) is the best treatment choice. FNAC is highly sensitive and specific with an accuracy of 87% to 96%, although it is an operator-related modality. Sensitivity rates range between 73% and 86% both in malignant and in benign tumors, whereas specificity proved better in benign than in malignant tumors (97% vs. 85%). Inadequate sampling may lead to a false-negative diagnosis, the most frequent error. In the case of a
periglandular nodule, FNAC is feasible to distinguish a primary salivary tumor from a pathologic lymph node. A proper diagnosis allows avoidance of unnecessary surgery. The procedural accuracy may be improved by the combination of ultrasonography and guided FNAC.

Open biopsy should be avoided because of the risk of seeding. In the presence of small malignant masses in minor salivary glands, punch biopsy (dermatologic punch) may be preferable to direct excision, unless the latter provides adequate margins. Frozen section diagnosis is still debatable. Accuracy is better for benign tumors than it is for malignant lesions (98.7% vs. 85.9%, respectively). If malignancy is not confirmed by FNAC, frozen section should always be performed in view of an immediate neck dissection. Histotype differentiation represents the major limit of this procedure.

NATURAL HISTORY AND PROGNOSIS

Initial spread of the major SGC is local invasion. Parotid tumors present fixation to surrounding structures in approximately 20% of cases, skin invasion in 10%, and facial nerve involvement in 25%.

Neck lymph node metastases are more common in the submandibular gland than in the parotid gland, about 40% vs. 25%, respectively. The frequency depends on T stage, site, and histotype.

Distant metastases at presentation are rare. At 10 years they account for approximately 30% to 40%, primarily depending on histologic type (ACC, squamous cell, undifferentiated, and salivary duct carcinoma). Lung and bone are the most common sites.

Survival is related to tumor stage, histotype, grading, facial nerve paralysis, extra-salivary gland tumor extension, and cervical node involvement. All these predictors may influence treatment outcome; among them, stage seems to be more important than grading. In addition to the abovementioned predictors of survival, patient age and presence of positive surgical margins are the most important factors predicting locoregional control in parotid gland cancer. Perineural invasion and solid histologic features are additional prognostic factors in ACC. Margin status, angiolymphatic invasion, tumor necrosis, and myoepithelial anaplasia are the major predicting factors of recurrence in epithelial-myoeepithelial carcinomas.

Patients with MEC of the parotid gland have a better prognosis than those with submandibular gland tumors, but these figures were not confirmed for other histotypes. No data suggesting different prognosis between major and minor salivary gland tumors are available.

The site of occurrence is a prognostic factor in the small subset of minor SGCs.

TREATMENT

Surgery

Major salivary glands. Both benign and malignant salivary gland neoplasms may be approached by the similar surgical techniques and strategies. In general, the tumor must be resected, together with normal tissue margins surrounding the neoplasm. The treatment plan may be influenced by tumor location, extension, and histology.

Partial or complete sacrifice of the facial nerve occurred in up to 40% of the patients treated for a parotid malignancy. The risk of clinically detectable nodal metastasis ranges between 14% and 20%. Occult metastases ranges between 12% and 52%. It increases in high grade and advanced T-stage, in the presence of extracapsular extension or facial paralysis, regardless of histology. In these cases, a selective prophylactic neck dissection including levels IB, II, and III, is appropriate.

Radiation Therapy

Although salivary gland tumors were historically thought to be radioresistant, a number of published reports suggest that radiation plays an important role in local control in both the postoperative setting and in the definitive setting for unresectable salivary gland tumors. In addition, technical advancements in radiation delivery have allowed for greater sparing of adjacent normal structures.

Postoperative Radiation

Although no randomized studies evaluate postoperative radiation (PORT) for salivary gland tumors, a number of institutional experiences suggest select high-risk patients may benefit from adjuvant radiation. From these reports, the indications for PORT include locally advanced tumor, pathologic T3 to T4 stage, invasion into adjacent structures, nodal involvement, high-grade histology, perineural invasion, angiolymphatic invasion, positive margins, and recurrent disease.

The Dutch Head and Neck Oncology Cooperative Group, in a series of 538 patients, found improved 10-year local control with PORT compared with surgery alone for patients with T3 to T4 tumors, close or positive margins, bone invasion, and perineural invasion, with the most pronounced effect in T3 to T4 tumors. In this analysis, no dose response was seen; median dose was 62 Gy. Older data from Memorial Sloan Kettering Cancer Center confirmed benefits of PORT retrospectively, except in patients with low-grade, early-stage cancers. Larger series from institutions such as MD Anderson Cancer Center have also demonstrated a 71% local control rate in 166 patients with the addition of radiation for resected tumors with close or positive margins. There was a trend toward improved local control with doses > 60 Gy for patients with positive margins or named nerve involvement.

McHugh and colleagues recently reviewed their experience in 125 patients, demonstrating a five-year overall survival and disease-free survival of 79.3% and 76.5%, respectively. Improved survival was noted in patients with low or intermediate-grade disease. As expected, negative prognostic markers included positive lymph nodes, extracapsular lymph node spread, and perineural invasion, with advanced stage and perineural invasion significant in multivariate analysis.
Patients with ACC treated with radiation at MD Anderson were also reviewed in 2012; although many of the patients presented with T1 to T2/N0 disease, 20% of the patients experienced distant metastasis (DM), with a median latency of 31.5 months. A solid tumor subtype and ECE were critical markers of DM.32

Lymph Node Treatment
Lymph node involvement varies with subsite. Tumor size and stage, histotype, and grade have also been associated with risk of nodal involvement.35,36 High-risk histologies include high grade adenocarcinoma, MEC, salivary duct, and squamous cell carcinoma.27 A scoring system has been developed to guide elective nodal irradiation treatment decisions based on T stage and histology.27

A SEER study published in 2010 evaluated factors associated with nodal involvement in minor salivary gland tumors.35 On multivariate analysis, the four factors that remained statistically significant included male gender, T3 to T4 primary, pharyngeal primary, and high-grade adenocarcinoma or high grade MEC. These factors were incorporated into a prognostic index.

Definitive Radiation
Surgical resection is still a mainstay of treatment; however, at times, because of patient or tumor-based issues, primary radiation therapy is needed. A clear dose-response relationship was seen, with significantly improved local recurrence free survival at doses ≥ 66 Gy, with 50% local control at five years.27 An RTOG study randomized patients with unresectable salivary gland tumors to neutron therapy compared with photon therapy.36 At 10 years locoregional control was significantly improved with neutron therapy, but late toxicities, including dysphagia, pain, necrosis, and poor taste, were reported.

Chemoradiation
The use of concurrent chemoradiation (cCRT) is under investigation within the cooperative group setting based in part on smaller, single institution studies evaluating concurrent platinum-based chemotherapy. A case control study evaluating cCRT compared with radiation alone in the postoperative setting for locally advanced tumors found a significant benefit in terms of local recurrence free survival and median overall survival with the addition of chemotherapy.37 Additional single institution experiences suggest improved outcomes in terms of local control with cCRT in both the postoperative setting in high-risk patients and in the definitive setting.38-40 A currently enrolling RTOG randomized phase II study will hopefully provide further insight into the efficacy of cisplatin-based chemoradiotherapy. RTOG 1008 randomizes patients with resected high-risk malignant SGCs to radiation alone to 60–66 Gy compared with radiation with concurrent cisplatin at 40 mg/m² weekly. This should reach completion by 2014 or sooner with an intent to move forward in a phase III trial if this approach appears promising.

Radiation Technique
As in many other head and neck cancer sites, intensity modulated radiation therapy (IMRT) is being increasingly used rather than 3-D conformal radiation therapy (3DCRT) to decrease dose to critical structures. Past approaches used a direct en face electron-photon mix or two angled beams called a wedged-pair technique; both covered larger areas and were relatively unsophisticated. IMRT affords the ability to soften the fluence or strength of the radiation beams and incorporates sophisticated software planning platforms that include inverse optimization whereby normal organs or tissue are treated as avoidance structures. In the sites where salivary gland tumors reside, primary organs at risk include cochlea, brain, oral cavity, visual pathway, uninvolved salivary glands, and spinal cord.

PORT fields encompass the tumor bed with adequate margin to account for microscopic disease. Preoperative imaging, operative reports, and physical exam should be used to delineate tumor extent. Working closely with surgeons is extremely helpful for delineating high-risk regions. In the case of perineural invasion, institutional experiences and patterns of failure have shown the importance of tracking the nerve to the base of the skull, with PORT encompassing the base of the skull reducing the risk of local recurrence.41,42 Recommended postoperative doses range from 60 Gy to 66 Gy depending on the presence of risk factors.

Neutron therapy for many years was considered the optimal approach to treating locally advanced unresectable SGCs. Because of toxicity and lack of availability of neutron therapy,27 standard treatment for unresectable salivary gland tumors is photon radiation to a total dose of ~70 Gy to the primary tumor with consideration of elective nodal radiation, depending on tumor characteristics and imaging information, as in the postoperative setting. Proton therapy is available in more centers throughout the United States; however, there is no Level 1 evidence that protons are superior to photon-based radiation in terms of local control or survival.

Nodal radiation coverage depends, in part, on primary site location, as well as the level of lymph node basins involved radiographically or pathologically. In clinically node-negative patients, ipsilateral level I to III lymph nodes are at highest risk for submandibular primaries, and ipsilateral periparotid and level I and II to III lymph nodes are at highest risk in parotid primaries. For patients who are node-positive, including the next echelon nodal region is recommended. Typical doses for postoperative or elective neck treatment are in the range of 45 Gy to 50 Gy. Most SGCs are well-lateralized and therefore require ipsilateral neck treatment only. In the case of central minor salivary gland tumors, a large primary crossing midline, or multiple ipsilateral involved nodes, contralateral neck nodal treatment should be considered.

Systemic Treatments
Chemotherapy is employed almost exclusively with a palliative aim. Many regimens have been tested, although no randomized studies have been conducted that define the
best therapeutic choice in this setting.2 A platinum-based chemotherapy seems to be associated with the best response rate, both as a monotherapy and as a combined regimen, although it is still not clear whether a combination chemotherapy has any advantage over a single-agent chemotherapy. In general, activity is below 30%, and even less for ACC (10% to 15%).

Chemotherapy activity seems to be histotype driven. Patients with adenocarcinoma, ACC, AiCC, and malignant mixed tumors are reportedly similarly sensitive to the CAP regimen. In patients with MEC and undifferentiated tumors, however, a better response seems to be obtained to those drugs that are active against squamous cell carcinomas (e.g., cisplatin, 5-FU, methotrexate).43 No response was seen in patients with ACC who were treated with paclitaxel alone compared with some responses observed in MEC and adenocarcinoma. For this reason, a combination of carboplatin + paclitaxel is used in these latter histotypes.44 Also gemcitabine proved ineffective in ACC.45 No benefit, in terms of survival, has been observed in patients responding to chemotherapy over patients who had no response. For this reason, chemotherapy could be reserved for asymptomatic patients and/or those with a rapid progressive disease. A watchful waiting is, instead, preferable for indolent disease or for patients with just a few symptoms. Phase II trials have been conducted. One long-lasting partial response was reported with trastuzumab in a case of HER2 3 + MEC,46 but no activity has been recorded for imatinib, gefitinib, cetuximab, lapatinib, and bortezomib.47-50 Rare objective responses to imatinib were recorded,51 favored in the case of strong c-kit immunostaining.52 A single response was observed in a patient with ACC enrolled in a phase II study with sorafenib.53 Case reports on antihormonal treatment in selected histotypes have been also reported.54 Targeted agents are currently recommended only in clinical trials.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

Employment or Leadership Position: None. Consultant or Advisory Role: Lisa F. Licitra, Amgen; BMS; Boehringer Ingelheim; GlaxoSmithKline; Lilly; Merk-Serono; Boehringer Ingelheim; Pfizer. Stock Ownership: None. Honoraria: None. Research Funding: Lisa F. Licitra, Exelixis. Expert Testimony: None. Other Remuneration: None.

References


HEAD AND NECK CANCER

Supportive Treatment for the Patient with Head and Neck Cancer

CHAIR
Stephen Sonis, DMD, DMSc
Brigham and Women's Hospital
Boston, MA

SPEAKERS
Susanne Singer, MD, MSc
University of Mainz
Mainz, Germany

Jan S. Lewin, PhD
The University of Texas MD Anderson Cancer Center
Houston, TX
Assessing and Improving Quality of Life in Patients with Head and Neck Cancer

Susanne Singer, PhD, Johannes Langendijk, MD, and Noam Yarom, MD

OVERVIEW

Health-related quality of life (QoL) indicates the patients' perception of their health. It depends not only on disease- and treatment-related factors but also on complex inter-relationships of expectations, values and norms, psychologic distress, and comparison with other patients. This article introduces methods and challenges of QoL assessment in patients with head and neck cancer, as well as ways to overcome measurement problems and ways to improve their QoL.

In daily life, we often do not realize how important simple things like swallowing, speaking, and eating are for us. Only if a severe disease, such as a head and neck neoplasm, deteriorates these functions do we appreciate the importance of oral health and the related quality of life (QoL).

Mr. Brown and his wife come to my office at the Psychosocial Counseling Centre for Cancer Patients and Relatives. He moves slowly, his body is very thin, and he nearly loses his trousers. One can see that this patient does not have much time left. The couple takes a seat and, before they start talking, his wife gives him a plastic bag, which he uses put his thick, sticky saliva in. He is not able to swallow it because it is too viscous and his energy too low. It takes a while to empty his mouth. Then he starts crying and says how humiliated he feels because of this scene.

What is QoL? The World Health Organization (WHO) has defined it as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.”1 This concept includes several dimensions of life (i.e., physical health, psychologic well-being, and social relationships). The level of independence from others and features of the environment can be considered additional dimensions.

In the context of oncology, the term “health-related QoL” usually does not indicate that an overall satisfaction with life is of interest, but rather a more specific domain of QoL. For ease of reading, we will only use “QoL” in this chapter when speaking about “health-related QoL.”

ASSESSMENT

Because of the multidimensional nature of health-related QoL, most measurement tools are multidimensionally constructed.

Another important conceptual issue is the point of view from which the assessment is made. In most concepts, it is implied that the patient is evaluating his well-being; thus, QoL is considered to be similar to self-perceived health. However, some authors, often implicitly, use the same term for objective measurements, i.e., for an assessment performed by physicians, nurses, or proxies. Often, this is measuring toxicity or function (e.g., performance status). For reasons of comparability, it is recommended to use the term “quality of life” only when self-assessment is meant in accordance with the WHO definition.

A physician who wants to include QoL in his treatment considerations has to decide the aims of the assessment. From a holistic perspective, QoL focuses on the subjective suffering of the patient and on his or her individual needs and wishes, depending on the context in which the patient lives. On the other hand, in the analytic approach, a (virtual) norm is set and the degree of deviance from this norm is assessed. The latter approach is commonly applied in clinical trials, while the former is often used by a physician in practice.

Assessment Tools

The two main methods of psychometric assessment in general are interviews and questionnaires. As a frequent application of QoL instruments is in clinical trials, self-administered questionnaires are used most often because of their brevity and ease of analysis.
The questionnaires can be classified into generic and specific instruments, whereby the former measures general aspects of QoL along the main dimension outlined by WHO (e.g., physical fitness, pain, anxiety) and the latter are developed for specific conditions or problems, such as head and neck cancer, high-dose chemotherapy, or fatigue.

The development of QoL questionnaires is mostly conducted in several phases. First, the relevant issues of a specific health problem are collected and rated regarding their importance. Second, items are formulated from the issues and a provisional questionnaire is tested in a group of patients. Eventually, after rephrasing and shortening, the final questionnaire is validated, preferably in different clinical and cultural settings. The involvement of patients from the first phase on is considered crucial in this process to ensure that the questionnaire validly measures QoL domains that are of high importance to patients. Some frequently used questionnaires are displayed and described in Table 1.

One of the earliest scales developed to measure QoL is the Karnofsky Performance Status, known as the “Karnofsky Index.” This instrument, published in 1949, assesses the patient’s physical functioning abilities to care for him- or herself. Although this is one of the most frequently used scales, its reliability and sensitivity to change are poor; therefore, it should be administered only in conjunction with more comprehensive and reliable tools.

### Challenges in Assessing QoL

It may be common sense that the perceived quality of our life is an important predictor of satisfaction and thus relevant in health care planning. However, quality of life is still not routinely measured in clinical practice. In clinical trials, assessing QoL is becoming more and more common, but the analysis of these data is often unsatisfactory. Why?

First, it might be that the investigators do not have enough knowledge on how to analyze the questionnaires used. They may be discouraged by the multidimensionality of the instruments, which results in multiple outcomes, something that is usually considered negative in clinical trials. As a consequence, investigators sometimes calculate total scores from different scales that are psychometrically and clinically unrelated, resulting in meaningless outcomes.

### TABLE 1. Frequently Used Quality-of-Life Instruments

<table>
<thead>
<tr>
<th>Title</th>
<th>Developed by</th>
<th>Number of items</th>
<th>Short form</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>World Health Organisation Quality of Life Assessment Instrument (WHOQOL)</td>
<td>WHO QoL Group (collaboratively in several culturally diverse areas)</td>
<td>100</td>
<td>WHOQOL-BREF (26 items)</td>
<td></td>
</tr>
<tr>
<td>36-Item Short-Form (SF-36)</td>
<td>Medical Outcomes Study</td>
<td>36</td>
<td>SF-12, SF-8</td>
<td>Computer-administered version available</td>
</tr>
<tr>
<td>EuroQol Questionnaire (EQ-50)</td>
<td>EuroQol Group (collaboratively in several culturally diverse areas)</td>
<td>5 plus visual analogue scale</td>
<td>Not available</td>
<td>Licensing fees are determined by the EuroQol Executive Office on the basis of the information provided</td>
</tr>
<tr>
<td><strong>Specific for Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)</td>
<td>EORTC Group (collaboratively in several culturally diverse areas)</td>
<td>30</td>
<td>EORTC QLQ-C15</td>
<td>Free of charge for academic users</td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy (FACT-G)</td>
<td>FACIT Group</td>
<td>27</td>
<td>Not available</td>
<td>Different version for the general population available</td>
</tr>
<tr>
<td><strong>Specific for Head and Neck Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-H&amp;N35)</td>
<td>EORTC Group (collaboratively in several culturally diverse areas)</td>
<td>35</td>
<td>Not available</td>
<td>Free of charge for academic users</td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy, Head and Neck Module (FACT-HN)</td>
<td>FACIT Group</td>
<td>39</td>
<td>Not available</td>
<td>Free of charge for academic users</td>
</tr>
<tr>
<td>University of Washington Quality-of-Life Instruments (UW-QOL-R)</td>
<td>Hassan &amp; Weymuller</td>
<td>10</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN)</td>
<td>Rosenthal</td>
<td>28</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

---

**KEY POINTS**

- Quality of life is a multidimensional construct.
- Measurement of quality of life should always be based on the patient’s perspective.
- Understanding psychologic processes of adjustment and coping can help to solve problems in the assessment and improvement of quality of life.
Second, the doctor may be puzzled by the psychologic nature of self-assessments in general. QoL is a conglomerate of expectations, perceptions, and comparisons with other people. Whether we are satisfied in a certain situation or not depends, on the one hand, our expectations and, on the other hand, the assessment of our reality—the level to which those expectations are fulfilled. If we do not expect to live without suffering, we can bear more health problems than others. In other words, if a patient tells us he or she has no problems with the side effects of a certain treatment, this can mean that there are really no side effects or that the patient does not consider them to be a problem worth mentioning to the doctor. Another facet of the psychologic adjustment process is the comparison with other people. If, for example, a patient who has undergone radiation in the head and neck region that resulted in parotid gland dysfunction meets other patients who have received the same treatment and who are worse off than him or her, that patient might praise fate for having fewer side effects, and will probably indicate a better health status compared to a patient who meets only fellow patients who have fewer problems. This phenomenon is called top-down or bottom-up comparison.

Third, it has been shown that patients tend to report only problems they consider relevant to their disease. For example, a patient with cancer who is asked whether he or she has experienced pain during the past week might consider only the tumor pain to be relevant, but not the migraine he or she suffered the day before. This “selective reporting” can lead to an underestimation of the health problems of patients. Therefore, it makes more sense to compare subgroups of patients rather than patients with general population samples. The sometimes surprising results of QoL measurement can be understood when all of these psychologic processes are taken together; for example, the so-called “satisfaction paradox,” whereby patients with severe diseases indicate better QoL than healthy subjects. These challenges sometimes lead to confusion and frustration on the part of the investigator; however, that does not mean that QoL measurements are invalid. After consulting QoL experts, many of the above-mentioned challenges can be detected, understood, and addressed.

Another methodologic challenge is the compliance of patients in completing QoL questionnaires. It is often assumed that patients are unwilling to do so. However, only a few authors have reported on completion rates in their studies. We performed a systematic review of all publications based on one of the most frequently used QoL instrument in patients with head and neck cancer, the EORTC QLQ-H&N35, and we found that out of 125 papers, only 23 reported on percentages of missing values. The completeness of the questionnaire varied from 66% to 99%. Scales with missing values included Sexuality, Speech, Teeth, and Weight Gain, with average percentages of missing values of 11.5%, 7.0%, 2.7%, and 2.0% respectively. Regarding the Teeth and Sexuality scales, some authors reported that it may remain unclear whether a nonanswer was because the patient was unwilling to answer or because the item did not apply to his or her status.

Another interesting point to consider in the analysis of QoL results is the difference between statistical significance and clinical relevance. Simply speaking, statistical significance is a function of the number of patients included. If a study is large, small differences between groups will become statistically significant; if the study is small, even large differences will not become significant. Therefore, instead of only looking at the p value of a finding, it is also important to interpret the size of the effect (be it a difference or an association). Only an effect size that is clinically meaningful should be used for clinical decision making.

**IMPROVEMENT OF QoL IN PATIENTS WITH HEAD AND NECK CANCER**

A clinician who wants to improve his or her patients’ QoL must consider the following:

1. What are the most important QoL domains for the patient?
2. What domains usually deteriorate because of the treatment or the disease, and for how long?
3. What factors influence the patient’s QoL?

**TABLE 2. Quality-of-Life Domains of High Priority to Patients**

| Worry that cancer will come back |
| Problems that new cancer might develop |
| Problems swallowing solid food |
| Problems with sense of taste |
| Trouble eating |
| Problems with talking |
| Problems with articulation/speaking clearly |
| Voice quality |
| Problems with chewing |
| Problems with wound healing |
| Edema/swelling in head and neck |
| Problems with sense of smell |
| Problems swallowing liquids |
| Sticky saliva |
| Dry mouth |
| Soreness in mouth |
| Trouble enjoying meals |
| Pain in mouth |
| Painful throat |
| Problems swallowing pureed food |
| Problems because of loss of teeth |
| Dizziness |
| Tingling and numbness of feet or hands |
| Problems with teeth |
| Rash |
| Trouble talking to other people |
What QoL Domains Are Important for the Patients?

There are three ways to answer this question. First, it is possible to compare mean scores of different QoL domains. The scales with the highest scores (or lowest, depending on the direction of scoring) can be considered the most important. This method is not without problems, because scales are often not constructed to be directly comparable with each other.

The second option is to ask patients, “How important is [QoL domain] for you?” Within the European Organisation for Research and Treatment of Cancer QoL Group, we have done this in a group of 137 patients with head and neck cancer who come from eight different countries. They were asked to indicate, from a list of 92 different issues, the 25 they would prefer to include in a questionnaire. The issues most frequently mentioned are displayed in Table 2. It appeared that fear of tumor progression, swallowing, talking/voice quality, swelling in the neck, and sense of taste are the most important QoL domains. Similar results were found by List et al.\textsuperscript{10,11}

The third way is to ask the patients to give their opinion of what constitutes a tolerable level of suffering from symptoms that affect their QoL. This method is a bit more sophisticated and more difficult for the patients. An advantage, however, is that it acknowledges the fact that QoL is changed after an oncologic treatment and that this can imply a certain amount of suffering. Thus, the important question is not which QoL domain is most frequently deteriorated but which deterioration is most problematic for the patient. For example, a moderate increase in pain might be more problematic than a large increase in problems with smelling.

We used this method in a group of patients after total laryngectomy.\textsuperscript{13} The results showed that patients are most accepting of sensory impairments, coughing, and dyspnea; constipation, nausea and vomiting, and diarrhea were rated as being the most troublesome symptoms.

Typical Course of QoL in Patients with Head and Neck Cancer

The course of QoL during and after treatment depends, in addition to individual factors, on the tumor entity and on the treatment the patient receives (Fig. 1). There is, however, a common pattern that occurs across different groups of patients: QoL decreases during treatment, improves slowly about 6 months after baseline, and improves again after 12 months. Frequently though, it does not achieve pretreatment levels of QoL. In particular, dry mouth and swallowing problems (especially after radiotherapy) as well as speech problems (especially after surgery) are long-lasting issues (S. Singer, PhD, et al, unpublished data, February 2013).\textsuperscript{14-18}

When investigating the course of QoL, clinicians should be aware that differential drop-out is a problem in prospective studies.\textsuperscript{19} Patients who drop out of the study because of death or health problems differ from those who continue to participate, and this is true for the baseline scores as well. Therefore, if only the QoL of patients who complete all time points is analyzed, the scores are usually over-optimistic (S. Singer, PhD, et al, unpublished data, February 2013).

FIG 1. Quality of life over time in patients with different types of cancer and treatment.

Displayed are the mean scores of the EORTC QLQ-H&N35. Data sources (from left to right): Bjordal et al, 2001 (375 patients, Sweden and Norway)\textsuperscript{12}; Fang et al, 2008 (203 patients, Taiwan)\textsuperscript{13}; Oates et al, 2007 (4 patients, Australia)\textsuperscript{16}; Yoshimura et al, 2009 (56 patients, Japan)\textsuperscript{14}; Schliephake et al, 2002 (53 patients, Germany)\textsuperscript{15}; Singer et al, 2013 (174 patients, Germany; S. Singer, PhD, unpublished data, February 2013).

Abbreviations: HNCa, heterogeneous group of patients with head and neck cancer; Nasopha, nasopharyngeal cancer; OC, cancer in the oral cavity; LaCa, laryngeal cancer; diff Tx, different treatments; RT, radiotherapy; CRT, chemoradiotherapy; BL, at baseline before treatment; Tx, during treatment; 1/2y, 6 months after baseline; 1y, 1 year after baseline.
Predictors of QoL
Knowledge of factors that can influence the course of QoL after head and neck cancer treatment is crucial for clinicians, especially if these factors can be changed. To date, we know that certain features of the treatment (for example, sparing of the parotid gland during radiation) can improve certain QoL domains (for example, dry mouth and swallowing). There is also good evidence that the course of QoL is highly related to the mental health of the patient (S. Singer, PhD, et al, unpublished data, February 2013). This calls for professional psychologic support in patients with head and neck cancer, which is frequently insufficient.

In conclusion, QoL is an important outcome to be considered in clinical trials and in routine treatment. Its assessment can be challenging at times; however, there are reliable and valid tools available and clinicians can use them meaningfully if they know how to apply them and how to interpret their scores.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References


Oral Mucositis in Head and Neck Cancer: Risk, Biology, and Management

Stephen T. Sonis, DMD, DMSc

OVERVIEW

Of the toxicities associated with conventional forms of treatment for head and neck cancers, probably none has such a consistent legacy as oral mucositis. Despite the fact that mucosal injury was noted as far back as Marie Curie’s first forays into therapeutic radiation, an effective intervention has yet to be developed. In addition to its historic link to radiation, new therapeutic strategies including induction chemotherapy often produce mucositis, and targeted therapies appear to alter mucositis risk and its severity and course.

The symptomatic effect of oral mucositis is profound. Disabling oral and oropharyngeal pain prevents patients from eating normally, requires opiate analgesics, and in some cases results in alteration or discontinuation of anticancer therapy. Furthermore, the health and economic consequences of oral mucositis are far from trivial. The incremental cost of oral mucositis in patients with head and neck cancer exceeds $17,000 (USD).

Although the incidence of mucositis has been described as almost ubiquitous among patients with head and neck cancer treated with conventional chemoradiation regimens, there are clearly differences in the frequency and severity of its manifestations. The lack of uniform scoring criteria, variability of reporting thresholds (some studies only report grades 3 or 4), differences in the biologic challenge as a consequence of variations in chemoradiation treatment regimens, radiation fields, and tumor location have resulted in inconsistent incidence reporting. Furthermore, there continues to be a disconnect between health care professionals and patients relative to their assessments of the presence, severity, and effect of mucositis. The rate, symptom severity, and influence of mucositis on quality of life is routinely perceived as being greater among patients than the medical literature would suggest. This might reflect the common and understandable attitude among those charged with treating the cancer that a marginally tolerable level of collateral damage to normal tissue is an acceptable price for tumor eradication. It is unclear what the acceptable level is from a patient’s perspective, and it probably varies from patient to patient. Couple all of this with the realization that not all patients are at equal risk for mucositis, and it becomes easier to understand the reported range of mucositis frequency from as low as 30% to 40% to almost 100% when all severities of mucositis are evaluated.

Mucositis incidence data surrounding intensity-modulated radiation therapy (IMRT) is illustrative of the lack of consistent reporting. Many studies report mucositis incidence in patients being treated for head and neck cancers. While some reports are limited to cancers of the mouth, others are less restrictive in their inclusion criteria and include patients with cancers of the nasopharynx, sinuses, hypopharynx, and larynx as well as the mouth and oropharynx. Interpretation of results must account for this variation because it appears that the risk of significant (this definition varies from including all ulcerative mucositis to only grades 3 and 4) mucositis is markedly influenced by tumor location, as it affects the volume of oral mucosa that is exposed to radiation. The use of concomitant chemotherapy, now the standard of care, enhances mucositis risk and apparently, so does the concomitant use of targeted agents.

Regardless of the criteria used to assess the presence of mucositis in patients with head and neck cancers, it is clear there is a cohort of patients who go through treatment relatively unscathed by the toxicity. This observation has fueled speculation and studies on the topic of mucositis risk determinants. Approximately 30% of radiation therapy-induced side effects are attributable to therapy-related or patient-specific factors. A radiation dose–response analysis recently described by Bhide et al demonstrated the effect of different dose-response schedules on the development of mucositis. In general, the volume of oral mucosa that receives weekly cumulative doses of 9.5 Gy to 10 Gy is likely to determine overall mucositis risk among susceptible patients. But even at this dose, about one-third of patients will not develop the condition. Likewise, among patients receiving cycled induction chemotherapy, almost one-half develop ulcerative...
mucositis, while the other half survive three cycles of treatment with no appreciable mucosal injury. Consequently, one must conclude that risk is largely a function of patient-related, not treatment-related, factors.11

The pursuit of understanding patient-related mucositis risk factors is not new. Historically, it has centered on gender, body mass, age, comorbidities, and lifestyle.12 Although there is some data to support each of these, it is sparse and far less convincing than one might expect given the discrepancies in mucositis frequency. More recently, the potential role of genetics has surfaced as a more likely explanation.11

Genetic risk factors for regimen-related mucositis have been primarily studied in patients with non-head and neck cancer. Both individual and clusters of pathway-related single nucleotide polymorphisms (SNPs) have been reported to increase mucositis risk. In contrast, to date, studies of genetic risk of mucositis in head and neck cancer have been limited to evaluating radiosensitivity and its relationship to DNA repair. The genome-wide association study methodology or more sophisticated forms of analysis have not yet been applied. Rather, candidate gene/SNP studies have been the norm and have identified polymorphism associated with the XRCC1 as being predictive of mucosal injury.13,14 Given the successes of SNP-based toxicity risk prediction studies in patients undergoing stem cell transplant or cycled chemotherapy, it seems likely that a broader look at both genes and SNPs that takes into account gene/SNP interacting networks should be fruitful in identifying actionable elements of mucositis risk prediction.

THE ORAL ENVIRONMENT AND MUCOSITIS

The pathogenesis of mucositis is a study of multiple sequential biologic events coupled with the influence of the oral environment and microbiome.1 The majority of pathways that lead to mucositis are the same whether the initiating event is chemotherapy (as in induction), radiation, or concomitant chemoradiation. However, the schedule of biologic challenges is clearly different. Whereas patients being treated with cycled chemotherapy receive an acute challenge that is administered systemically, patients undergoing radiation receive a succession of fragmented (fractionated) radiation doses, which, even in small increments, trigger a cascade of biologic events. Although radiation is considered to be focially administered (vs. systemic), the biologic events it triggers are detectable systemically with resulting constitutional effects. In both cases, what has been described as “bystander” events result in collateral injury when products or signals from one cell (potentially the targeted tumor) negatively affect normal adjacent cells.15

The oral mucosa shares its neighborhood with a multitude of microorganisms: bacteria, viruses, and fungi. Although the modulating influence of microbes has been studied relative to cancer regimen-related toxicities in other areas of the gastrointestinal tract, studies of their effect on oral mucositis have been largely limited to descriptions of quantitative or qualitative changes.1,16 Mucositis is not an infectious disease. Its frequency is not affected by decolonization or antimicrobial strategies. The kinetics of bacterial colonization follows, rather than precedes, mucositis development.1 Although there are changes in the composition of the bacterial flora in patients who are myelosuppressed and were first described almost 40 years ago, modifying the oral bacterial composition has not proven to be an effective mucositis deterrent. Furthermore, antibacterial strategies for mucositis interventions have been ineffective.17

The role of viruses, particularly herpes simplex (HSV), in the etiology of radiation-induced mucositis remains questionable. Advocates for such a relationship cite observations of culturable HSV in a limited proportion of patients who have clinically significant oral mucositis.18 They also suggest that treatment with standard antiviral therapy favorably affects the subsequent course of mucositis. Since over one-half of patients have latent HSV-1 infection, it is not unexpected that virus, activated by radiation or local tissue injury, would be detectable in some patients with mucositis. Consequently, although not a primary driver of mucositis, HSV-1 presence in a secondary infection could affect the course of the condition. The effectiveness of prophylactic administration of antiviral medication to patients who are seropositive and on radiation-induced mucositis has not been adequately investigated.

The oral environment is also unique relative to the presence of saliva. The fluid is a rich mix of enzymes, antibodies, and proteins that play an important role in maintaining the homeostasis of the oral mucosa and limiting microbial colonization. Because patients being treated with head and neck radiation routinely demonstrate signs of xerostomia, it was not unreasonable to suspect that a change in either the quantity or quality of saliva might affect the course of mucositis. However, this does not appear to be the case to any significant extent and certainly not in the context of a potential interventional strategy. In fact, the course of mucositis has been unaffected when saliva production–stimulating agents have been tested.19,20

Nonetheless, additional studies are probably justified to determine the true effect of saliva on tissue. For example, are patients with preexisting conditions that lead to xerostomia more likely to develop mucositis?

KEY POINTS

- Oral mucositis is among the most common toxicities of standard chemoradiation regimens used to treat head and neck cancers.
- Risk of mucositis is largely determined by genetic factors.
- The pathobiology of mucositis is complex. The mechanistic complexity of mucositis provides targets for intervention.
- Mucositis in patients being treated for head and neck cancer remains a substantive, unmet clinical need.
BIOLOGIC EVENTS THAT LEAD TO MUCOSAL INJURY AND EXAMPLES OF OPPORTUNITIES FOR MECHANISTICALLY BASED INTERVENTIONS

The conclusion that mucosal injury is the consequence of a multifactorial cascade of biologic events is relatively new. In the realm of radiation injury, direct cell damage culminating in DNA strand breaks is still relevant, but it’s not the only show in town. Although the basal cells of the epithelium are the consummate “end organ” leading to tissue destruction, the pathways that lead to their demise are multiple. Although the biologic stages originally noted to describe the sequence of mucositis remain fundamentally correct, accumulating data demonstrate that their complexity is more involved than was originally described. Also, although compartmentalization of the events associated with mucositis is undoubtedly a fantasy created for the convenience of explanation, the sequence can be divided into five stages: initiation, upregulation/activation, signal amplification, ulceration, and healing. The initiating biologic events that start the process were first attributed to oxidative stress and the generation of free radicals. Although still a critical event, we now know that activation of the innate immune response and Nrf2 provides alternative initiating pathways. Studies in which these pathways have been effectively interrupted demonstrate mitigation of downstream injury. From an interventional standpoint, the initiation phase is a ripe target as its attenuation affects the course of direct and indirect pathways of tissue damage.

The free-radical scavenger, amifostine, was among the first drugs used for mucositis intervention. Originally developed for the military, the clinical utility of its radioprotective effects were applied to mollify salivary gland damage and consequent xerostomia. Its application as a mucoprotective has generated interesting but inconsistent results. Especially interesting is the observation that amifostine is capable of activating genes associated with superoxide dismutase, itself capable of attenuating oxidative stress. Supporting a potential therapeutic opportunity have been results of preclinical studies in which superoxide dismutase mimetics have been effective in diminishing the intensity and course of radiation-induced mucositis and novel gene transfer studies that have reached the same conclusion. In a similar way, studies with n-acetyl cysteine—an established antioxidant with the ability to affect nuclear factor-kappa beta (NF-κB) activity—have demonstrated efficacy in both animal and human studies. Finally, as noted below, palifermin’s (keratinocyte growth factor 1) ability to reduce radiation-induced mucosal damage is likely due, in part, to the molecule’s effect on glutathione activity. Additional support for this hypothesis is the finding of increased risk of mucositis among patients who express SNPs associated with gene mutations associated with glutathione synthesis.

Following initiation, another series of cell-based events is triggered. At least 14 canonical pathways have already been associated with the development of mucositis in patients being treated with concomitant chemoradiation for head and neck cancers. Among the best studied is activation of the NF-κB pathway and consequent generation of proinflammatory cytokines. Although tissue and peripheral blood levels of proinflammatory cytokines—such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)—track well with the development of mucositis, it is unclear whether their role is one of mediating or messaging for injury or whether they are themselves true drivers of damage. This is especially true in the case of radiation-induced mucositis where repeated fractional challenges cause a challenge dynamic different from that associated with the acuity of chemotherapy. This is an area that requires more investigation, particularly in determining prevention and treatment strategies. Studies with agents known to mediate TNF production have been clinically tested with mixed results. Of potential importance is the finding that polymorphisms associated with TNF production are associated with chemotherapy toxicity risk prediction. It is well known that, in a variety of inflammatory diseases that result in mucosal injury (i.e., inflammatory bowel disease), an antagonistic group of cytokines—the anti-inflammatory cytokines such as IL-4, IL-10 and IL-11—likely have functional significance. Given the complexities of mucositis, it would be naïve to not consider the potential role of these molecules in the overall pathogenesis of the condition. However, there current data is limited.

In theory, pharmacologic or biologic that alter cytokine expression or levels represent a potential therapeutic approach, and a number have been evaluated. Benzydamine HCl (BZD) is an anti-inflammatory rinse that has been approved outside the United States for use in patients receiving radiation therapy. Its efficacy is modest and limited to patients receiving standard radiation regimens in the absence of concomitant chemotherapy. BZD has been reported to have a range of biologic activities that interfere with mechanisms thought to be of importance in the pathogenesis of radiation-induced oral mucositis. A study in a hamster model of mucositis—in which the effect of topically applied BZD on selected morphologic and biologic parameters was studied in temporal fashion—demonstrated that BZD modified epithelial proliferation, but not differentiation, and that the observed changes correlated with a reduction in tissue levels of IL-1β and TNF-α, but not IL-6. Preferential antiapoptotic activity was seen in epithelium and connective tissue of BZD-treated animals.

Another cytokine-based approach capitalized on the anti-inflammatory activities of IL-11. Subcutaneous injection of the cytokine favorably altered the course of mucositis induced by either chemotherapy (5-FU) or radiation in animal models. When studied in association with radiation-induced mucositis, it appeared that IL-11 suppressed the expression of genes associated with IL-1β, TNF-α, IL-2, and transforming growth factor-beta. Furthermore, the timing of modified gene expression corresponded with observed mucosal injury. Tissue levels of IL-1β and TNF-α were also suppressed in association with better clinical outcomes. A clinical trial in patients receiving autologous stem cell transplantation for breast cancer was stopped before accrual could be completed.
Two agents known to inhibit TNF-α production have been evaluated in preclinical and clinical studies of mucositis associated with chemotherapy. Pentoxifylline was effective in delaying clinical manifestations of chemotherapy-induced oral and intestinal toxicity in animal models and also ameliorated oral mucositis associated with conditioning regimens for stem cell transplant. However, it was also associated with a higher rate of infection, suggesting that the physiologic cost of such an approach in patients who are myelosuppressed may exceed its antimucositis benefit. Nonetheless, the observation does provide a glimpse of a potential intervention strategy.

Given the finding that multiple pathways simultaneously contribute to mucositis, it seems very likely that a truly effective agent will be characterized by mechanistic pleiotropism. Palifermin, keratinocyte growth factor-1, was approved for the prevention and treatment of oral mucositis in patients with hematologic malignancies who received stemotoxic conditioning regimens for hematopoietic stem cell transplants and serves as a prototype for a pleotropic antimucositis agent. The phase III trial on which palifermin’s approval was based on the mandated use of total-body irradiation as a conditioning regimen component. Subsequent trials of palifermin’s efficacy have not been as consistent, but in general, the overall trend speaks to its utility for a mucositis indication. For the purposes of this discussion, the collective biologic effects of the molecule are illustrative of a multitargeted biologic shotgun. As related to initiation, palifermin has the ability to upregulate enzymes associated with the disruption of reactive oxygen species. In particular, glutathione-S-transferase and glutathione peroxidase are favorably impacted. And indirectly, palifermin’s ability to upregulate Nrf2—which itself has been shown to reduce oxygen free radical damage—has been observed. Palifermin likely affects clonogenic cell death by preventing DNA strand breaks through its activation of DNA polymerases and its antiapoptotic effects implemented during the upregulation phase (probably through NF-κB) through Bcl-2, Bax, and p53 enhanced cell survival. Although palifermin resonates as a growth factor, its ability to modulate both pro- and anti-inflammatory cytokines provides a means for it to actively attenuate the cytokine-mediated tissue-damaging and amplifying effects. There is also evidence to suggest that palifermin has the potential to mitigate the effect of reduced epithelial turnover, and this is manifested in reductions in the atrophic and ulcerative changes that characterize mucositis. As one would predict based on its fundamental growth factor activity, it appears likely that palifermin favorably affects events associated with epithelial injury. However, the inconsistencies reported in palifermin’s clinical efficacy seem puzzling given its biologic robustness and point to some of the challenges in developing an effective mucositis intervention.

Clinical data for palifermin as a mucositis intervention now exist for conditioning regimens for both autologous and allogeneic hematopoietic stem cell transplantation; chemotherapy used for the treatment of colorectal cancer, head and neck cancer, and sarcoma; and a smattering of regimens for hematologic malignancies. Positive efficacy signals have been reported for most but not all. The variability of responsiveness is confusing and might reflect individual dose response, responsiveness to keratinocyte growth factor or a range of other possibilities. What seems clear is that, as shown with other mechanistically based approaches to mucositis treatment, not all patients respond in the same way, and to optimize efficacy, a personalized approach to intervention—understanding risk and response/nonresponse—is highly desirable.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

Employment or Leadership Position: Stephen T. Sonis, Biomodels (L). Consultant or Advisory Role: Stephen T. Sonis, ActoGeniX; Axaxia Biologicals; Galera Therapeutics (U); Inform Genomics; Izun Pharmaceuticals; Merck; Novartis; Pfizer; Polymedix (U); ProCertus; SciClone. Stock Ownership: None. Honoraria: None. Research Funding: None. Expert Testimony: None. Other Remuneration: None.

References

5. Mortensen HR, Overgaard J, Specht L, et al. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 68/7


32. Ferrà C, de Sanjose S, Lastra CF, et al. Pentoxifylline, ciprofloxacin and prednisone failed to prevent transplant-related toxicities in bone marrow transplant recipients and were associated with an increased incidence of infectious complications. *Bone Marrow Transplant.* 1997;20:1075-1080.