NIH Symposium Summary: Organ Preservation Therapies for Squamous Cancers of the Head and Neck

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Abstract

This symposium, sponsored by the NIH Office of Rare Diseases, the National Cancer Institute, the National Institute of Deafness and Other Communication Disorders, and the National Institute of Dental and Craniofacial Diseases, reviewed the current status of organ preservation therapies for head and neck cancers, as well as promising newer approaches for therapy and for toxicity amelioration.

Introduction

In the last decade, combination chemotherapy and radiation has been increasingly used as an “organ preservation” alternative to primary surgery for locally advanced squamous cancer of the head and neck. Randomized clinical trials of sequential chemotherapy followed by radiation in cancer of the larynx and hypopharynx have demonstrated that such an approach is feasible, with survival equivalent to that obtained with surgery followed by radiation (1, 2). Increasingly, concomitant chemotherapy and radiation (radiochemotherapy) approaches are being considered for surgically curable squamous tumors of the larynx and hypopharynx, as well as other sites. The correct choice of treatment for a given patient, the role of surgery in organ preservation regimens, the optimal radiochemotherapy regimen(s), and the effect of organ preservation strategies on organ function and overall quality of life obtained by non-surgical versus surgical primary treatment regimens remain controversial. This multidisciplinary panel discussion symposium, held September 7 and 8, 1999, reviewed the current state of the art, toxicities, functional outcomes, new advances, and promising new therapeutics in organ preservation treatment of squamous cancers of larynx, hypopharynx, and head and neck.

Panel Discussion 1: What Have We Learned about Organ Preservation from Clinical Trials?

Dr. Gregory Wolf reviewed completed randomized clinical trials. The pioneering Veterans Administration Laryngeal Cancer Study (1) randomized patients with advanced laryngeal cancer to either standard treatment of surgery followed by radiation or to neoadjuvant cisplatin and 5-fluorouracil, followed by radiation in chemoradiation responders. Patients refractory to chemotheraphy received standard treatment, and patients with residual or recurrent disease after radiation underwent salvage surgery. A similar approach was used by the European Organization for Research and Treatment of Cancer for pyriform sinus/hypopharyngeal cancer (2). In both studies, organ preservation was achieved in about two-thirds of the survivors, with no significant survival difference between treatment arms. Discussion participants stressed that the current challenge is to refine patient selection for organ preservation or surgery to limit added morbidty of multimodal therapy and reduce complications associated with salvage surgery. Functional morbidity, quality of life, and survival obtained with organ preservation regimens should be compared to those obtained with optimal surgical reconstructive methods in non-laryngeal and hypopharyngeal sites.

Dr. William Mendenhall addressed clinical trials of chemotherapy and radiation. To date, induction chemotherapy has not improved survival or local control (1–3), but response to chemotherapy may portend successful organ preservation (1, 2). Several small, randomized trials, as well as meta-analyses (4–6), suggest that chemotherapy added to radiation results in increased survival in patients with advanced head and neck cancer, compared to treatment with radiation alone. Studies of altered fractionation radiation have also improved locoregional control but not survival (7) and have increased toxicity. Identification of patients responsive to radiation was attempted at the University of Florida in supraglottic laryngeal cancer patients. Three-dimensional tumor volume correlated with radiation response (8). However, discussion participants pointed out that this method has not been tested for all anatomical primary sites or for concurrent radiochemotherapy and may not be sufficient to account for adenopathy, tumor growth patterns, or tumor biology.

Dr. Everett Vokes addressed chemotherapy plus radiation versus surgery for organ preservation. The goals of organ preservation trials are to improve survival, preserve organ function, and manage toxicity. Sequential chemotherapy and radiation...
potentially results in accelerated repopulation, which may be circumvented by concomitant radiochemotherapy. Trials at the University of Chicago and Northwestern University with a concomitant radiochemotherapy regimen of paclitaxel, 5-fluorouracil, oral hydroxyurea, and hyperfractionated radiation administered every other week demonstrate 2-year survival rates of up to 70% in stage IV patients (9). Concomitant radiochemotherapy regimens demonstrated a 20% survival benefit compared to radiation alone in patients with advanced disease (10–13). Recent trials show: (a) favorable overall and progression-free survival rates, especially with concomitant radiochemotherapy; (b) successful organ preservation in most patients, although many have prolonged compromised speech and swallowing; (c) a shift in the failure pattern from locoregional to distant failure; and (d) significant toxicities, which were manageable by experienced teams. Discussion participants stressed that such aggressive radiochemotherapy regimens could prove dangerous in settings without adequate experience. Studies are needed on the effect of different chemotheraphy and radiation regimens on organ function, site-specific organ preservation, the optimal role of surgery, and the assessment of quality of life and functional end points. Predictors of response would aid physicians in advising patients whether to have surgical or nonsurgical treatment.

Dr. C. Rene Leemans addressed the role of surgery in organ preservation. The success of any organ preservation protocol depends on the potential for successful surgical salvage. The results of the Veterans Administration laryngeal trial (14, 15) show a strong correlation between residual disease in the neck after induction chemotherapy and the need for salvage neck dissection. In this study, most deaths were attributed to uncontrolled neck disease, even after salvage neck dissection, suggesting that salvage neck dissection at clinical recurrence failed to control disease. Complications after neck dissection are more common after concomitant radiochemotherapy than after chemotherapy or radiation alone (16, 17). Current practice is either (a) planned neck dissection in all patients without complete response in the neck or (b) planned neck dissection for all patients initially presenting with >N2 disease, regardless of response to nonsurgical organ preservation therapy. No randomized trials exist comparing timing and/or types of neck dissections in organ preservation regimens. Discussion participants agreed that current imaging techniques cannot diagnose neck metastases reliably; the usefulness of positron emission tomography, computed tomography, or magnetic resonance imaging for this purpose needs evaluation.

Panel Discussion 2: Controlling Toxicity for Aggressive Organ Preservation Regimens

Dr. David Brizel discussed the efficacy of amifostine for amelioration of radiation toxicity. This agent, initially developed by the United States Army, was recently approved by the United States Food and Drug Administration for salivary gland protection in patients receiving once daily postoperative adjuvant radiation for head and neck cancer. However, its efficacy versus xerostomia in altered fractionation regimens, organ preservation therapies, and combination radiochemotherapy regimens is currently unknown. No significant effect on mucositis severity has yet been demonstrated with amifostine administration. Subset analysis and Phase II trials suggest that a reduction in mucositis may be possible with either an increased amifostine dose or a smaller field size (18), but this needs confirmation. Importantly, amifostine has not been associated with decreased locoregional control, progression-free survival, or survival (19).

Dr. Stephen Sonis discussed new approaches to treat salivary dysfunction and mucositis. The biology of xerostomia suggests several possible approaches: (a) free radical scavengers, such as amifostine or glutathione (18); (b) inhibition of free radical formation by depletion of heavy metals from the salivary gland [pilocarpine, cyclo-octidine, and zinc-desferrioxamine (20, 21)]; (c) stimulation of gland function with pilocarpine or isoproterenol (22); or (d) stimulation of proliferation of the cellular components of the gland parenchyma with keratinocyte growth factor (23). Other approaches include gene therapy or alteration of signal transduction pathways or cytokine production (24). The biological complexity of mucositis has only been recently appreciated (25). The hypothesis that mucositis is due solely to DNA damage to basal epithelial cells has been supplanted by the understanding that proinflammatory cytokines (IL-1β, TNF-α) are major drivers of tissue injury. Modulators of these cytokines, such as IL-11 and benzydamine, appear to attenuate radiation mucositis (26, 27). Local bacterial colonization of injured mucosa results in the release of cell wall products that amplify local tissue cytokine production and hence injury. Consequently, effective topical antimicrobial therapy may be of benefit in mucositis treatment. Protegrins, naturally occurring antibacterial proteins, have demonstrated efficacy for chemotherapy-induced mucositis (28) and may also have a role in radiation-induced injury. Local inhibition of normal cell proliferation with transforming growth factor β may offer a different approach to mucositis prevention (29). The effects of granulocyte macrophage colony-stimulating factor or granulocyte colony-stimulating factor are inconclusive, although a number of recent studies suggest a possible role (30, 31). Their mechanism of action appears not to be limited to modulation of local immune response. The use of prostaglandin analogues has had mixed results (31).

Dr. Ralph Weichselbaum discussed technology and techniques to limit acute and chronic toxicity in aggressive radiochemotherapy approaches. Intensity modulated radiation therapy, which delivers a high-dose volume of radiation that closely conforms to the shape of the tumor and that varies the intensity of the radiation beam across the irradiated volume, maximizes the dose to the tumor while minimizing the dose to adjacent normal tissue. Although the technique is heavily computer and labor intensive, advances in automated treatment planning and control should improve performance and reduce time and costs. Other parotid-sparing radiation techniques have also been studied (32–35). One innovative therapy technique links a radiosensitive promoter to a gene for a diffusible cytokine, such as

3 The abbreviations used are: IL, interleukin; TNF, tumor necrosis factor; NF-κB, nuclear factor κB; RR, risk ratio; VEGF, vascular endothelial growth factor.
Angiostatin. TNF-α induces production of angiostatin. Angiostatin and radiation have at least additive effects, without additive toxicity (36). Radiation may also be useful to increase the replication efficiency of attenuated herpes viruses, another targeted and possibly less toxic therapeutic approach (37).

Dr. Jeri Logemann addressed measurement of speech and swallowing function and rehabilitation for head and neck squamous cancer patients. Many patients undergoing organ preservation protocols exhibit swallowing disorders that may worsen over time (38). Surgically treated oropharyngeal cancer patients often have poorer swallowing function compared to normal individuals or even to patients studied after stroke (39–41). Postoperative radiation further decreases swallowing efficiency and delays the recovery pattern (42). Swallowing function is measured by timing the swallow, by noting the amount of bolus (food) swallowed or aspirated into the airway, noting the ability to eat at least 50% orally, and by videofluorographic studies, including temporal measurement of various pharyngeal and laryngeal movements. The willingness to eat orally is dependent on the swallowing time. Organ function often underlies a patient’s behavior in eating or speaking, and more research is needed on the relationships between function and behavior. Protocol studies should include videofluorographic swallowing studies, high-fidelity recording of conversational speech, and quality of life assessments over time. Bias in such studies needs assessment; patients with the worst organ function, even if cured, tend to drop out of longitudinal studies of organ function (43). Better understanding of the pathophysiology of swallowing and speech dysfunction in head and neck cancer patients under various protocols will lead to more effective rehabilitation strategies.

Panel Discussion 3: Organ Preservation and Function

Dr. Ramon Esclamado detailed surgical advances in organ function preservation for cancers of the tongue and base of the tongue. A major challenge is to reconstruct the tongue with tissue that mimics its complex movement and shape. Both sensory and motor innervation are critical for oral tongue function. With base of tongue cancer, swallowing is severely impacted. Either a propulsive force or a pharyngeal clearing force needs to be preserved for swallowing to be successful after surgery (44). Tongue reconstruction methods include free flaps, regional flaps, and primary closure and depend on the size as well as the functional impact of the defect. Flaps are favored for exposed mandible or for planned postoperative adjuvant therapy. Free flaps (i.e., latissimus dorsi, pectoralis, rectus abdominis, or forearm) promote faster wound healing, resulting in a lower complication rate with adjuvant treatment. The effect of the source of the flap on functional recovery has not been studied extensively. In summary, total glossectomy with laryngeal preservation is feasible in selected patients. Functional outcome remains poor when laryngectomy plus total glossectomy is needed. Preservation of sensation and motor innervation of the remaining musculature is critical for optimal functional outcome.

Dr. Kian Ang discussed current practices and recent advances in radiotherapy. Refinements in organ preservation techniques include optimization of fractionation schedules, improvements in delivery, and combined chemotherapy with radiation. Hyperfractionation, i.e., increased number of reduced-dose treatments over the same overall time, improved local control for T3 oropharyngeal cancers (45). Accelerated fractionation schedules, i.e., radiation delivered at similar dose per treatment and total dose, over a shorter time, has also been studied. The concomitant boost technique, a type of accelerated fractionation in which the boost dose is given as a second daily treatment during the later part of radiation, resulted in a 75–80% disease-free survival in patients with T3 base of tongue cancers (46). Radiation Therapy Oncology Group 90-03 compared three experimental fractionation schedules to daily radiation and showed that patients with locally advanced squamous head and neck cancers treated with hyperfractionation or with the concomitant boost technique had improved locoregional control and increased acute toxicity compared to those treated with standard fractionation, although there was no significant difference in overall survival (7). Results of this trial will help optimize radiation regimens for organ preservation treatments. Meta-analyses (4–6) have shown that concurrent radiochemotherapy regimens provide an estimated 8% increase in absolute survival compared to radiation alone. However, mucositis, late toxicity, and treatment-related deaths were increased by factors of 2.9, 2.8, and 2.4, respectively. Studies of concomitant chemotheraphy with conformal (3-D CRT) or intensity-modulated radiation therapy treatment planning are needed to assess whether such approaches lessen toxicity compared to contemporary radiochemotherapy regimens. New radiochemotherapy treatments should be based on rationally derived additive or synergistic mechanisms of interaction determined preclinically. Two such experimental regimens are the use of fludarabine or epidermal growth factor receptor inhibitors with radiation (47, 48). Molecularly targeted therapies could also increase tumor specificity without increasing toxicity.

Dr. Susan Urba discussed the role of chemotherapy for organ preservation in laryngeal and nonlaryngeal sites. Early studies with neoadjuvant combination chemotherapy led to the hypothesis that response to a single induction chemotherapy course may identify patients who are likely to benefit from organ preservation. If confirmed, this approach could identify those patients “destined to fail” radiochemotherapy and prevent delay of a potentially curative surgical procedure. The probability of success of an organ preservation approach may be site specific; however, few studies have adequate statistical power for appropriate subset analysis by primary tumor site. Disease site-specific clinical trials would reduce the natural history differences between primary sites and allow for differences in stage and other predictive factors to be studied. Recently, Calais et al. (12) reported a randomized trial in oropharyngeal cancer in which patients with stage III and IV disease received either radiation alone or radiation concurrent with three courses of carboplatin and 5-fluorouracil. With a median survival of 35 months, a survival benefit (15.4 months versus 29.2 months, median survival) was noted in the combined radiochemotherapy

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4 R. Weichselbaum, unpublished data.
group, albeit with higher toxicity compared to radiation alone. At present, radiochemotherapy regimens are under study in patients with oropharyngeal cancer. Randomized trials of surgical versus nonsurgical therapy in patients with oropharynx cancer should be encouraged to assess any functional benefit for nonsurgical organ preservation.

Beth Solomon addressed rehabilitation evaluation in patients on organ preservation protocols. The major goal of rehabilitation is maximal functional independence. Rehabilitation specialists should see patients at presentation and periodically throughout treatment and follow-up. Rehabilitation specialists can also help ameliorate the effects of pain, impaired movement, edema, swallowing difficulties, and speech impairment. Other factors, such as stress, anxiety, effects of treatment, and work/life adjustment may impact organ function dynamically. A plan of rehabilitation measures and frequency of measures should be stipulated in all clinical trials. At the NIH, assessments are conducted at baseline, at 1–2 months, 3–4 months, 6–9 months, and at 1 year after radiochemotherapy in patients on organ preservation protocols. In each patient, an oral sensorimotor examination, a 21-item swallowing questionnaire, an oropharyngeal ultrasound examination and videofluoroscopic swallowing study, and a dysphagia functional outcome assessment are completed. We need to understand more about the long-term impact of swallowing and speech impairments on quality of life and to explore the differing organ function expectations of patients and caregivers. Quantitative studies of function correlating impairments with specific interventions or compensation strategies are needed to optimize rehabilitation efforts.

Dr. George Adams explored earlier stage disease as a laboratory to compare surgical and nonsurgical treatments. He noted that there are even fewer definitive answers regarding optimal treatment for early stage disease than for advanced disease. Questions that need to be studied include: (a) optimal primary treatment modality (radiation or surgery) for early cancers; (b) the relative efficacy of photodynamic therapies and laser surgery versus standard surgery or radiation; (c) the role of molecular alterations in predicting treatment response and prognosis; (d) how to study chemoprevention; (e) methods for early detection; (f) methods to predict recurrence or second primary cancers; (g) the role of the immune system; and (h) management of pan-oral abnormalities. Various properties of tumors, such as thickness, angiogenesis, angiogenesis, perineural infiltration, ploidy, allelic imbalance, apoptosis-related genes, telomerase, proliferation, cyclin D1, NF-κB, cellular antioxidants, free radical scavengers, cytokines, and differentiation, have been found to be predictive or prognostic in small studies (49–51). Definitive studies are needed to confirm the clinical usefulness of such molecular markers. Discussion participants suggested that early disease could serve as a model to study tumor biology and therapy. “Window of opportunity” studies, administering novel agents for a short time period before surgery, could evaluate the effect of such agents on their putative target and elucidate important biological pathways.

Panel 4: Molecular Medicine and Immunology

Markers of cancer behavior may predict which patients will respond to nonsurgical organ preservation therapy. Likewise, host factors, such as immune function, may predict response to treatment. The following speakers and discussion focused on these characteristics as possible ways to improve organ preservation in head and neck cancer.

Dr. Carol Bradford detailed correlative studies on molecular markers (p53, proliferating cell nuclear antigen, and Bcl-xL) and clinical parameters (T and N stage, tumor area, and growth pattern) from patients on the Veterans Administration Laryngeal Cancer Trial (52). In this exploratory study, none of the markers predicted for survival in the chemotheraphy arm. Among patients randomized to induction chemotheraphy, T stage (T1–3 versus T≥4), P = 0.01; RR, 5.6) predicted response. Laryngeal preservation was correlated with p53 overexpression (>20% nuclear staining, P = 0.03; RR, 3.4); proliferating cell nuclear antigen expression > 40% (P = 0.01; RR, 4.2), and T stage (P = 0.007; RR, 7.1). In the surgical arm, extranodal extension and growth pattern predicted survival and disease-free survival. In subset analysis, patients not responding to chemotheraphy tended to have normal p53 and high levels of Bcl-xL (“long” an inhibitor of p53-induced apoptosis), whereas patients who had successful organ preservation tended to have mutant p53 and low Bcl-xL. Such studies are too small to draw conclusions but suggest further testable hypotheses. During the discussion, the opinion was expressed that mechanisms of resistance may differ among various chemotherapeutics and radiation. In vitro and in vivo models, as well as sufficiently powered prospective clinical trials, are needed to test hypotheses.

Dr. Elizabeth Hammond addressed the practical obstacles to the clinical study of molecular markers in head and neck cancer. Tissue acquisition remains a major obstacle; only a portion of the patients entered into trials have submitted usable tissue blocks. Standard tissue handling, informed consent procedures, collaborations with pathologists, public and patient support, and standardization of methodology (fixation, staining, and cut points) are needed. Molecular studies should be robust, relevant, and likely to affect patient care. The population from which tissues are obtained should represent the study population, and there should be adequate tissue and the necessary number of failures to discern a marker effect. Appropriate sample size calculation requires an estimate of marker prevalence and its associated hazard rate. Presently, the literature contains a multitude of small trials, often with conflicting results, using tissue from small, select populations, different methods, different cut points for positivity, and different reporting formats, preventing comparison or meta-analysis of results. Standardized control tissues may allow aggregation of studies for more definitive answers. More data are needed on the effects of treatment interactions, tumor heterogeneity, and the relationship between gene expression and protein function. Proof of principle studies of marker effect should precede large validation trials. Tissue arrays could facilitate investigation of many markers in fewer patients.

Dr. Theresa Whiteside addressed the role of the immune system in head and neck cancer. Solid tumors are sensitive to natural killer cells, although this is not often demonstrated by the 51Cr release assay (53). Tumors may escape immune surveillance by (a) altering ligand binding pairs necessary for natural killer cell activation (53), (b) developing resistance to apoptosis mediated by Fas ligand, although Fas receptors are
expressed (54), or (c) down-regulating HLA expression or expression of costimulatory molecules (55). Increased proportions of activated T cells (Fas receptor positive), with high levels of caspase-3 activity, are detectable in peripheral blood of patients with head and neck cancer. The T-cell receptor-associated ζ chain, which is responsible for signal expression, is decreased or absent in T cells from these patients, both locally in tumor-infiltrating lymphocytes and in peripheral blood T cells (56). Studies in oral cancer patients indicate that the presence of T-cell receptor-associated ζ chain and dendritic cells (antigen-presenting cells) correlates with improved survival, whereas the presence of apoptotic tumor-infiltrating lymphocytes and peripheral blood T cells correlates with decreased survival (57). Such indicators of immune function may be prognostic markers. Other potentially interesting markers include the cytokine profile of tumor and host and the frequency of cytotoxic T lymphocytes (CTLs) or tumor-specific CD4 cells before and after therapy.

Dr. William McBride discussed cytokine response during treatment. Cytokines act as endogenous mediators of response. They work in cascades and integrate inflammatory processes, angiogenesis, regeneration, and wound healing. Cytokines such as TNF-α, IL-1, IL-6, basic fibroblast growth factor, VEGF, platelet-derived growth factor, and transforming growth factor β are particularly involved. The balance of these factors is critical. An imbalance may result in treatment-related fibrosis or other adverse effects. Radiation (58) and anticancer drugs (59) can initiate the pathway by inducing cytokines, such as TNF-α, and dysregulate it by causing selective cell loss. It may be possible to target cytokine pathways to reverse radiation fibrosis. Head and neck tumors themselves produce cytokines (60 – 62). These can interact with ongoing inflammatory responses and may be responsible for some of the toxicities of radiation treatment. A major pathway for the action of proinflammatory cytokines is through NF-κB, a survival factor for many cell types (63). Head and neck squamous cancers constitutively express NF-κB (64). This observation led to exploration of ways to decrease NF-κB, such as by inhibition of the degradation of its inhibitor (IκB). One approach is the use of proteasome inhibitors (65, 66). Because the proteasome is also responsible for degradation of p53, p21, and p27 proteins, this is an attractive therapeutic target. Understanding cytokine pathways and cascading downstream pathways should lead to rational therapeutic development.

Panel Discussion 5: Therapeutics for the Future—Possible Strategies for New Organ Preservation Regimens

Dr. Thomas Robbins presented data on the selective intraarterial administration of cisplatin concomitantly with daily radiation therapy for unresectable head and neck cancer (67). Thiosulfate is administered i.v. to ameliorate systemic cisplatin toxicity. Thus far, complete response rates at the primary site are approximately 90% for cancer of the hypopharynx and larynx and 69% for patients with invasion of bone and cartilage (67). Lymph node complete response rates are about 70%. Toxicity has been comparable to that of other radiochemotherapy regimens. A confirmatory trial in Amsterdam found similar response rates (68). The feasibility of the regimen is currently being studied in a multicenter cooperative group trial in the United States.

Dr. James Mitchell discussed hypoxia modifiers. Tumors may selectively shut off blood supply, perhaps transiently, creating a dynamic hypoxic area. Response to radiation is inversely related to hypoxia (69). Electrodes can measure hypoxia, but they are not practical for wide use. Noninvasive imaging techniques, such as BOLD magnetic resonance imaging, nitroimidazole positron emission tomography, and electron paramagnetic resonance imaging, are currently being developed to monitor hypoxia (70 – 74). Strategies to reduce hypoxia in tumors include high LET radiation, radiosensitizers, agents that deplete glutathione, nitric oxide, nitric oxide donors, carbogen, mitomycin C, and tirapazamine. Most of these methods have not made a large clinical impact, due to either unacceptable toxicity or inability to deliver the agent at effective concentrations. However, bioreductive agents, such as tirapazamine, show tremendous selectivity for hypoxic cells and appear promising (75). Hypoxia-inducible factor 1, a transcription factor that senses hypoxia and increases gene expression of VEGF when pO2 is low, has also been identified as a possible molecular target (76).

Dr. James Zwiebel discussed gene and related therapies. A number of gene therapy methods and other viral vectors are under study. Generally, intratumoral, intra-arterial, or intracavitary administration of gene therapy is feasible. Current vector systems are not optimal for systemic delivery. Limitations of the current approaches include intratumor hydrostatic pressure, host-vector interactions, host immune responses, and limited transgene effect. In head and neck cancer, RPR/INGN trials of p53 gene transfection with Ad5CMV-p53 showed an objective response rate of 6% in recurrent tumors, with little toxicity (77). ONXY-015, an E1B-deleted oncolytic adenovirus designed to replicate only in p53-deficient cells, has been tested as a single agent and in combination with cisplatin and 5-fluorouracil in patients with head and neck cancer, with an improved response rate and 6 month disease-free interval compared with historical controls (78, 79). Randomized Phase III trials are planned for both Ad5CMV and ONXY-015. In summary, combined treatment with gene therapy and chemotherapy or radiation may be more effective than gene therapy alone, the response rate is higher for smaller lesions, antiadenoviral antibodies do not appear to interfere with therapeutic effect, and the agents are well tolerated.

Dr. James Pluda explored antiangiogenesis agents as possible therapy for head and neck cancer. Cytotoxic therapies have been potentiated with angiogenesis inhibitors in preclinical studies, without increased toxicity (80). In squamous head and neck cancer, the probability of metastatic disease correlates with microvessel density (a measure of angiogenesis), and aggressive disease correlates with tumor VEGF levels, making this tumor an appropriate clinical target for antiangiogenesis agents (81).

Such agents are cytostatic and may be useful in combination with more conventional therapy as a maintenance treatment or in the adjuvant setting. The role of such agents in reducing second primary tumors remains unexplored. Currently, the National Cancer Institute supports Phase II trials with thalidomide and with SU 5416 in head and neck cancer.

Dr. Barbara Conley explored the role of signal transduction inhibitors. The loss of p16 function appears to be an early event in head and neck cancer; this loss causes an override of the Rb checkpoint and increased cell proliferation (82). The epidermal growth factor receptor is overexpressed in 90% of head and neck cancer patients (83), and Her2neu is overexpressed in 25–30% of head and neck cancer patients (84). Drugs that affect the p16-cyclin D1-Rb pathway (flavopiridol, UCN-01, and rapamycin analogue CCI-779) and tyrosine kinase inhibitors (drugs that inhibit signaling from Her2neu and epidermal growth factor receptor) as well as antibodies to epidermal growth factor receptor and Her2neu (Herceptin) should be studied in head and neck cancer, alone and in combination with cytotoxics and radiation. Agents affecting the ras signaling pathway, such as farnesyltransferase inhibitors, may have efficacy even in cells without mutant ras (85). New clinical trial study designs to discern the appropriate dose and likely efficacy are needed because end points such as toxicity and response may not be appropriate for these cytostatic, relatively nontoxic agents. Databases of time to progression and disease-free survival with various treatments will be helpful in this regard.

Dr. Carter Van Waes discussed cytokines and immune system modulation. Different cytokines can promote or inhibit growth and metastasis of squamous head and neck cancer. Squamous cancer cells produce cytokines, IL-1α, IL-6, IL-8, granulocyte macrophage colony-stimulating factor, GRO-α, and VEGF; and measurable levels of IL-6, IL-8, VEGF, and GRO-α are present in sera from patients with head and neck cancer (86). Among these cytokines, the homologue of human IL-8 and GRO-α in the mouse, called KC, has recently been shown to promote angiogenesis, inflammation, growth, and metastasis (87). These findings make IL-8 and GRO-α and the C-X-C receptor 2 to which they bind possible therapeutic targets (87). Cytokines that inhibit squamous head and neck cancers have also been described. IL-12, IL-2, and IFN-γ have recently been shown to induce regression of oral squamous cancers in preclinical murine models (88). Additionally, antigenic signals and major histocompatibility and costimulatory (B7-1) molecules are needed (88). IL-12-treated mice had increased CD4 lymphocytes at the tumor site and were resistant to tumor rechallenge. Preclinical and clinical research is needed to exploit such data for therapeutic benefit.

**Summary of Conference**

A summary of the conference was give by Dr. Arlene Forastiere. The major impetus for the symposium is the goal to improve survival and achieve organ function preservation with good quality of life. Functional assessments are now available, and functional end points should be included in clinical trials. Organ preservation should be studied at sites other than the larynx and hypopharynx in a site-specific manner. Ideally, therapies should be tailored for the individual patient, but we need further criteria by which to assign patients to optimal therapies. Molecular markers should be helpful in this regard. Because no clear prioritization among the markers studied exists, tissue from as many patients as possible should be banked, with available linked clinical data. Mechanism-based drug discovery has yielded several potentially efficacious therapies. We need to study these agents creatively and efficiently in head and neck cancer patients.

**Appendix**

**List of Panel Participants**

**Panel Discussion 1.** The moderator was Dr. Gregory Wolf (Department of Surgery, University of Michigan, Ann Arbor, MI). Participants were: (a) Dr. Helmut Goepfert (Department of Surgery, University of Texas M. D. Anderson Cancer Center, Houston, TX); (b) Dr. C. Rene Leemans (Department of Surgery, University Hospital Vrije Universiteit, Amsterdam, the Netherlands); (c) Dr. Jean-Louis Lefebvre (Department of Surgery, Center Oscar Lambret (Lille, France) and European Organization for Research and Treatment of Cancer, Brussels, Belgium); (d) Dr. Everett Vokes (Department of Medical Oncology, University of Chicago, Chicago, IL); (e) Dr. John Ensign (Department of Medical Oncology, Wayne State University, Karmanos Cancer Center, Detroit, MI); (f) Dr. Kian Ang (Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX), and (g) Dr. William Mendenhall (Department of Radiation Oncology, University of Florida, Gainesville, FL).

**Panel Discussion 2.** The moderator was Dr. Everett Vokes (Department of Medical Oncology, University of Chicago, Chicago, IL). The participants were: (a) Dr. David Brizel (Department of Radiation Oncology, Duke University Medical Center, Durham, NC); (b) Dr. Philip Fox (Amarillo Biosciences, Inc., Cabin John, MD); (c) Dr. Ralph Weichselbaum (Department of Radiation Oncology, University of Chicago, Chicago, IL); (d) Dr. Jeri Logemann (Department of Speech Language Rehabilitation, Northwestern University, Chicago, IL); (e) Dr. Gregory Wolf (Department of Surgery, University of Michigan, Ann Arbor, MI); (f) Dr. Helmut Goepfert (Department of Surgery, University of Texas M. D. Anderson Cancer Center, Houston, TX); (g) Dr. Susan Urba (Department of Medical Oncology, University of Michigan, Ann Arbor, MI); (h) Dr. David Pfister (Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY); (i) Beth Solomon (Speech Language Pathology, NIH, Bethesda, MD); (j) Dr. Jonathan Ship (Dentistry, University of Michigan, Ann Arbor, MI); (k) Dr. Andy Trotti, III (Department of Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, FL); and (l) Dr. Stephen Sonis (Dentistry, Brigham and Womens Hospital, Boston, MA).

**Panel Discussion 3.** The moderator was Dr. Kian Ang (Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX). The participants were: (a) Dr. George Adams (Department of Surgery, University of Minnesota, Minneapolis, MN); (b) Dr. Ramon Esclamado (Department of Surgery, The Cleveland Clinic Foundation, Cleveland, OH); (c) Dr. Ashok Shaha (Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY); (d) Dr. William Mendenhall (Department of Radiation Oncology, University of Florida, Gainesville, FL).
William Mendenhall (Department of Radiation Oncology, University of Florida, Gainesville, FL); (c) Dr. Susan Urba (Department of Medical Oncology, University of Michigan, Ann Arbor, MI); (f) Dr. Lynn Gerber (Rehabilitation, NIH, Bethesda, MD); and (g) Beth Solomon (Speech Language Pathology, NIH, Bethesda, MD).

**Panel Discussion 4.** The moderators were Dr. Elizabeth Hammond (Department of Pathology, LDS Hospital, Salt Lake City, UT) and Dr. Theresa Whiteside (Department of Immunology, University of Pittsburgh, Pittsburgh, PA). The participants were: 
(a) Dr. Carter van Waes (Department of Surgery, National Institutes of Deafness and Other Communications Disorders, Bethesda, MD); (b) Dr. Carol Bradford (Department of Surgery, University of Michigan, Ann Arbor, MI); (c) Dr. Ralph Weichselbaum (Department of Radiation Oncology, University of Chicago, Chicago, IL); (d) Dr. C. Norman Coleman (Department of Radiation Oncology, National Cancer Institute, Bethesda, MD); (e) Dr. William McBride (Department of Radiation Biology, University of California, Los Angeles, CA); (f) Dr. John Enslay (Department of Medical Oncology, Wayne State University, Karmanos Cancer Center, Detroit, MI); (g) Reuben Lotan (Department of Cancer Biology, University of Texas M. D. Anderson Cancer Center, Houston, TX); and (h) Dr. Thomas Pajak (Department of Statistics, American College of Radiology, and Radiation Therapy Oncology Group, Philadelphia, PA).

**Panel Discussion 5.** The moderator was Dr. Arlene Forastiere (Department of Medical Oncology, Johns Hopkins Oncology Center, Baltimore, MD). The participants were: (a) Dr. Jean-Louis Lefebvre (Department of Surgery, Center Oscar Lambret, Lille, France and European Organization for Research and Treatment of Cancer, Brussels, Belgium); (b) Dr. K. Thomas Robbins (Department of Surgery, University of Tennessee, Memphis, TN); (c) Dr. Carter van Waes (Department of Surgery, National Institutes of Deafness and Other Communications Disorders, Bethesda, MD); (d) Dr. James Pluda (Department of Medical Oncology, National Cancer Institute, Bethesda, MD); (e) Dr. James Zwiebel (Department of Medical Oncology, National Cancer Institute, Bethesda, MD); (f) Dr. Barbara Conley (Department of Medical Oncology, National Cancer Institute, Bethesda, MD); (g) Dr. Andy Trotti, III (Department of Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, FL); and (h) Dr. James Mitchell (Radiation Biology Branch, National Cancer Institute, Bethesda, MD).

**References**


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