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O V E R V I E W

Head and Neck Cancer: Recent Advances and New Standards of Care

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The management of head and neck cancer in recent years has involved increasingly complex, combined-modality programs, as well as the integration of new diagnostic and therapeutic technologies. That head and neck cancer is the most complex "organ site" for treatment decision making is not an overstatement, and supports a best practices model of multidisciplinary team involvement. Head and neck cancer has long served as a model for other solid tumors with regard to the integration of chemotherapy into initial curative treatment, consistent with the remarkable sensitivity to chemotherapy of this disease, particularly in the previously untreated setting. Unlike with many solid tumors, combination chemotherapy will yield major responses in 70% to 90% of patients with untreated squamous cell cancers of the head and neck, with the response being clinically complete up to 50% of the time. Furthermore, the most active cytotoxics also enhance radiation effects.

The first prospective, multicenter randomized trial of combined-modality therapy for the treatment of newly diagnosed, resectable cancers evaluated one cycle of cisplatin plus infusional bleomycin before surgery.[1] This landmark study, initiated in 1978, was followed by numerous controlled trials conducted worldwide that tested various sequences of chemotherapy, surgery, and radiotherapy in nearly 20,000 patients during the ensuing decades. This research has culminated in new standards of care that employ cisplatin-based chemotherapy concurrent with radiation therapy in the treatment of locally advanced unresectable cancer, nasopharyngeal cancer, and larynx and oropharynx cancers with the intent of preserving speech and swallowing, and in the postoperative setting for patients at high risk of recurrence.[2-7] These recommendations come at a time when there are also advances in radiotherapy treatment planning and delivery, advances in reconstructive surgical techniques, and the introduction of molecularly targeted therapeutics into clinical practice. Thus, the landscape of treatment options is more complex than ever and based on not only tumor stage, primary subsite, and histology, but also physician expertise and patient preferences.

At this juncture, we felt it was particularly appropriate to dedicate a special issue of the *Journal of Clinical Oncology* to review current therapies for all stages of head and neck cancer, to highlight areas of new knowledge and controversy, as well as future directions. We begin this issue with a review by Fakhry and Gillison[8] focusing on a recently recognized change in epidemiology, specifically the role of human papillomavirus (HPV) infection in the pathogenesis of squamous cell cancer of the head and neck. The rising incidence of oropharyngeal cancer in younger individuals who do not have a typical history of alcohol and tobacco use is now clearly associated with infection by high-risk oncogenic HPV types 16, 18, 31, 33, and 35. Although HPV genomic DNA is detected in approximately 25% of all head and neck squamous cancers, more than 50% of oropharyngeal cancers show integration of the viral genomic DNA and localization to tumor cell nuclei. The virus has a predilection for the lingual and palatine tonsils, accounting for the rise in tonsil and tongue-base cancers that is occurring in the United States. Fakhry and Gillison discuss risk factors related to sexual behavior history, the clinical presentation, prognostic, and therapeutic implications, and how to make the diagnosis.

One of the most complex areas of management is determining when nonsurgical treatment of resectable disease is appropriate and should be recommended. In this context, Brizel and Esclamado[9] review a number of important issues in the use of concurrent chemoradiotherapy, including the choice of a chemotherapy regimen and the controversy over optimal radiation fractionation. They also discuss the controversy of performing a planned neck dissection versus observation in patients with initial regional node involvement and complete response to chemoradiotherapy. They point out that the subsite of head and neck disease, patient tolerance, and preservation of function should guide the choices of therapy. They further describe the developing role of agents that target hypoxia or specific receptors, such as those for the epidermal growth factor and vascular growth factors.

Intensity-modulated radiotherapy (IMRT) has been widely adopted as a standard technology for head and neck cancer. As current leader of one of the longest running head and neck practices in the United States, Mendenhall, Amdur, and Palta[10] discuss the promises and pitfalls of using IMRT in routine practice. They review the available data and note that not only does the application of IMRT to head and neck cases involve a learning curve, but the technology and standards also continue to evolve. They recommend regular continuing education efforts and monitoring of outcomes from individual practices to ensure high-quality care and patient safety.

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Although the natural history of head and neck cancer is one typically characterized by early locoregional recurrence and late manifestation of distant disease, it is known from autopsy series that up to 60% of patients have distant disease, varying with primary site.[11] The significant improvement in locoregional control achieved with administering chemotherapy concurrent with radiotherapy in a number of head and neck disease settings has now focused attention on therapeutic strategies that affect micrometastatic disease. This has led to renewed interest in the evaluation of induction chemotherapy, this time added to chemoradiotherapy. Adelstein and LeBlanc[12] discuss the rationale for this "sequential" treatment approach, the importance of testing this hypothesis in patients at high risk of developing distant disease based on stage-related prognostic indicators, and statistical issues to consider for trial designs. They review the three prospective randomized trials currently in progress in the United States and emphasize the investigational nature of this therapeutic approach.

Until recently, the medical oncologist typically played little or no role in the postoperative adjuvant setting. Two influential randomized trials with similar design published in 2004, one from each side of the Atlantic, have changed the management paradigm in patients with resected disease demonstrating poor risk features.[2,3] Bernier, Vermorken, and Koch[13] review the historical underpinnings for, and results of, the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) poor-risk adjuvant studies, as well as the insights learned from a recent analysis combining data from both trials. In addition, they highlight key treatment considerations geared to improve present outcomes in this setting, and important directions for future research.

It is clear from randomized trials comparing chemoradiotherapy with radiotherapy alone that chemotherapy substantially increases toxicity. There is a natural tendency to increase the intensity of treatment modalities under the belief that more will achieve better results. Head and neck cancer has not been an exception to this practice and thus, the adverse effects of current chemoradiotherapy regimens have generally reached the limits of toxicity. A result is that a number of centers have noted higher rates of acute and chronic swallowing disorders with the use of aggressive radiation and chemotherapy schedules. Rosenthal, Lewin, and Eisbruch[14] propose specific management techniques to prevent and reduce dysphagia and aspiration. Their approach involves early intervention and close monitoring of symptoms and swallowing progress during and after therapy to maximize long-term function.

Despite advances on a number of fronts, disease recurrence that is not amenable to salvage surgery is still a frequent cause of death for patients with squamous cancers of the head and neck. We therefore devote three reviews to different aspects of this topic. Colevas[15] reviews the evolution of cytotoxic therapies for palliation from methotrexate and bleomycin, the subsequent development and wide use of cisplatin, and through the excitement created by the availability of the taxanes. He summarizes the results of two and a half decades of phase II and III trials, and, on the basis of this literature, notes that the goals of a consistent and clinically significant improvement in survival have proved elusive. He provides practical guidelines on when to treat, and which treatment regimens, doses, and schedules to consider, along with factors predictive of response outcome. In patients with local or regional recurrence only, an alternative to the traditional management with palliative chemotherapy is now under investigation. Recent trials of reirradiation combined with concurrent chemotherapy suggest improved cancer control and survival in selected patients. Wong, Machtay, and Li[16] review the available data on reirradiation and emphasize the potential risks and uncertainties. They are currently conducting a large Intergroup randomized trial to carefully compare both the safety and efficacy of chemo-reirradiation versus chemotherapy alone in this challenging population.

Therapies targeting the epidermal growth factor receptor (EGFR) and related downstream events have a compelling rationale in squamous cell head and neck cancer: EGFR is expressed in the vast majority of these tumors; there is an inverse relationship between expression and prognosis; preclinical data demonstrate activity including synergy with other therapy; and clinical trials have demonstrated activity in the disease. The third review of therapies for recurrent and metastatic disease, by Cohen,[17] covers the rationale and available clinical trial data for these agents, and outlines one possible paradigm for their integration into current clinical practice in this setting. There is, of course, great interest in these agents, particularly for patients with recurrent disease, because existing standard therapies yield median survivals consistently less than 1 year, and new therapeutic approaches are desperately needed. However, the precise role of these newer targeted treatments in standard practice is controversial. There are at present limited data regarding their efficacy compared to more established chemotherapies, and available data suggesting that on average, any incremental benefit will be modest. Not surprisingly, reimbursement policies for these costly agents vary frequently.

Because of the importance and complexity of the EGFR pathway and the ErbB/HER family of receptor tyrosine kinases to the development of targeted therapeutics, we felt that the biology of this pathway as it pertains to head and neck cancer should be covered. Kalyankrishna and Grandis[18] review the biology of EGFR in head and neck squamous cell cancer–receptor expression, activation, and function. They discuss molecular predictors of sensitivity to EGFR tyrosine kinase inhibitors. Drawing on the experience in head and neck, lung, and colon cancers, they present potential reasons for the relative limited efficacy of EGFR-targeting agents in the clinic and possible ways to circumvent resistance.

Cancers of the salivary glands are relatively uncommon tumors. Surgery and radiation therapy are the cornerstones of treatment. Historically, chemotherapy has most commonly been used in the recurrent or metastatic disease setting with palliative intent. However, the optimal strategy with regard to the use of chemotherapy and other systemic therapy in this setting is not well defined. Salivary cancer encompasses a broad spectrum of histologic subtypes, with potential variability in clinical behavior and responsiveness to treatment. Disease-specific, prospective clinical trials evaluating the role of drug therapies are limited. Laurie and Licitra[19] review the available literature regarding the use of systemic therapy in the palliative management of advanced salivary gland cancers. They also discuss the molecular profiles of these tumors and provide insights regarding the potential role of targeted agents.

In summary, this collection of reviews highlights recent changes in the standards of care. These advances have resulted from decades of well-designed clinical trials and new insights into the biology of head and neck cancer. We expect an acceleration of

the pace of change as investigators strive to optimize combined-modality programs and systematically integrate molecularly and physically targeted therapies. All this is occurring within the backdrop of shifts in epidemiology, increasing development of and access to new agents, and rapid advances in diagnostic and therapeutic technologies. Thus, head and neck cancer will continue to be a model for multidisciplinary care and research. In the near future, we are optimistic regarding the development of new interventions and modifications of existing ones that will reduce toxicity and improve efficacy, as well as improvement in our ability to better select patients for more individualized treatment approaches and rehabilitation strategies.

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