The Evolving Role of Combined Modality Therapy in Head and Neck Cancer

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It is a privilege and an honor to address the members of the American Head and Neck Society and our guests. To my knowledge, this organization represents the largest group of individuals in the world whose primary mission is dedicated to promoting education and research on head and neck cancer. This past year, an inaugural year, has been a major step forward for head and neck surgeons in this country. We have restructured; we have accommodated important goals from each of the 2 merging societies; and, most importantly, we have been able to work together to build an infrastructure that will serve us well for the future. I am indebted to my copresident, Ashok Shaha, with whom it has been an absolute pleasure to interact. He is a man who is sensitive to those around him, as well as a great team player. I would also like to acknowledge the council, especially cosecretaries Jonas Johnson and Bill Farrar, cotreasurers Ernie Weymuller and John O'Brien, and President-Elect Jesus Medina, who have performed their responsibilities diligently, have provided wisdom and guidance, and, most importantly, have shown respect for each other and our new system of governance. Robin Wagner, who does all the work behind the scenes, deserves a special thanks. Finally, I would like to acknowledge Gayle Woodson, my wife, colleague, and best friend, for her support, encouragement, and confidence.

The theme I have chosen for my address today is motivated by a personal interest I have held for many years: the treatment of advanced head and neck cancer with targeted chemoradiation therapy. Also, we must recognize an evolution of treatment options for our patients, including a trend toward a greater role for nonsurgical modalities. Was it coincidental that we chose not to include the word *surgery* in the name of our new society? I personally believe that it signifies a growing change in attitude toward the nonsurgeons who have become involved in the treatment of patients with head and neck cancer. Although the treatment of this disease has primarily been the responsibility of surgeons, the past century is indicative of a pattern of increasing involvement by physicians from other specialties. The trend has been heralded by certain events and discoveries, initially within the field of radiation oncology and subsequently within the field of medical oncology. I will attempt to highlight these events; to review the reasons why combined modality therapy has come to the forefront, as well as its progress and refinements; and, in a prophetic way, to project a vision for future progress using this strategy.

Although the first pioneers for treating head and neck cancer were surgeons during the early part of the 20th century, the stage was subsequently shared with the radiation oncologists. Roentgen discovered x-rays in 1896, and within months, patients with a variety of malignant neoplasms, including several with advanced carcinomas of the head and neck, were receiving radiation therapy. Rapid progress followed: There were Regaud's experiments with multiple fractions and Coutard's application of fractionated radiation to mucosal cancers of the upper aerodigestive tract. Baclese modified treatment parameters, such as fraction size, overall dose, and treatment fields, to such an extent that radiation therapy began to take on the regimens recognized today.

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The development of high-energy machines using cobalt and linear accelerators made it possible to avoid severe skin reactions and long treatment breaks. Other technical refinements included radiation therapy simulators, higher energy linear accelerators, electron beam therapy, individualized field blocks, and patient immobilization techniques. Further concepts involved an understanding of the relationship of tumor control with tumor size, a decrease in treatment volumes, and elective irradiation of clinically occult disease. Improvements continue to be made in the optimization of radiation dose delivery through the use of charged particles, brachytherapy, computerized 3-dimensional conformal treatment planning, stereotactic radiosurgery, and intensity modulated radiation therapy.

THE TERM *combined therapy* initially referred to the use of surgery and radiotherapy to treat a tumor in the same location. Initial studies using combined therapy were performed in the 1920s for rectal and breast cancer and showed promising results.[1-3] Among these early studies was a trial from Sweden in which a large series of patients were treated for squamous cell carcinoma of the head and neck.[4] Although this study showed improved survival with the use of combined therapy compared with radiation therapy alone, the results of subsequent investigations were nonconfirmatory. The concept was also tempered by the poor wound healing that was observed after preoperative irradiation. Thus, the trend in the 1930s and 1940s was to use combined therapy, with radiation administered postoperatively.[5] However, studies failed to consistently demonstrate benefit from this type of sequencing, and enthusiasm again was dampened by the frequent skin reactions often encountered with the use of kilovoltage irradiation. However, the introduction of megavoltage radiotherapy, with its skin-sparing effects, in the 1950s prompted a renewed interest in the combined use of the 2 modalities.[6,7] With subsequent advances in radiation techniques, as mentioned previously, this option became an even more viable approach.

The rationale for combined therapy is that surgery best addresses gross disease, whereas radiotherapy eradicates microscopic disease, for which surgery is less effective. Recent studies using molecular techniques have provided further evidence that surgical margins are frequently involved by tumor, even though such involvement is not always obvious on microscopic examination.[8]

The advantage of preoperative radiation therapy is based on the observation that poorly oxygenated cells are much less susceptible to the effects of irradiation than are similar cells that are oxygenated.[9] The advantages of using postoperative radiation is that the identification of tumor extent is more accurate and the technical performance is easier in tissue planes that have not been altered by fibrosis, fusion of planes, and the increased vascularity that characterizes recently irradiated tissue. The issue of the relative efficacy of preoperative vs postoperative radiotherapy was addressed in a prospective randomized trial that was begun in 1973 by the Radiation Therapy Oncology Group.[10] This trial showed a significant superiority of postoperative irradiation in terms of local regional control and was instrumental in shifting the practice to postoperative radiation therapy.

The dose of irradiation administered in a postoperative setting was studied by Peters et al in 1993.[11] They showed in a randomized setting that a minimum tumor dose of 57.6 Gy, in daily fractions of 1.8 Gy, should be administered to the whole operative bed, with a boost of 63 Gy being delivered to sites of increased risk.

Although the data indicate that local recurrence rates are decreased when radiotherapy is added to the surgical treatment of advanced stage head and neck cancer, there are inherent limitations in demonstrating whether improved locoregional control results in better survival. Peters et al[11] noted that despite an overall 2-year 74% rate of freedom from recurrence above the clavicles, the survival rate in their series of patients undergoing postoperative radiotherapy was only 31% at 5 years. This poor survival rate is the result of additional mortality from metastases, second primary cancers, and intercurrent illness. Nonetheless, any improvement in disease control above the clavicle is of major significance for quality of life.

Chemotherapy has been used for head and neck cancer for several decades. In fact, one of the first experimental agents ever used to treat solid tumors was for a recurrent cancer of the head and neck afflicting the baseball legend Babe Ruth. After undergoing radiation therapy for nasopharyngeal cancer and showing evidence of persistent disease, he received daily injections of teropterin, a precursor of the folic acid antagonists.[12] The results were dramatic, with dissolution of his facial pain, a 9-kg weight gain, and an improvement in his spirit. Teropterin also markedly decreased his need for narcotics; the mass in the neck completely disappeared; and there was improvement in his voice and in his ability to swallow. Unfortunately, this response was temporary and his symptoms gradually returned a few months later, shortly before his death in August 1948.

Following the failure to use chemotherapy effectively for recurrent disease, oncologists turned to neoadjuvant approaches. The findings of several randomized, controlled trials in which chemotherapy was given before surgery[13-17] and before irradiation[18,19] have been reported, none of which showed any survival advantage for the chemotherapy arm. Perhaps the most successful trial of neoadjuvant therapy was reported by the Department of Veterans Affairs Laryngeal Cancer Study Group.[18] Survival was not compromised in the group receiving chemotherapy, yet two thirds of the patients who survived retained a functioning larynx.

The success of the Department of Veterans Affairs Laryngeal Cancer Study has established induction chemotherapy and definitive radiotherapy as a standard treatment option in laryngeal cancer. A large randomized trial by the European Organization for Research and Treatment of Cancer applied the Veterans Affairs protocol to patients with piriform sinus cancer. As with the laryngeal experience, survival was not compromised by a trial

of induction chemotherapy, and 42% of patients in the experimental arm had a functioning larynx at 3 years.[20]

Two recent meta-analyses of randomized trials of chemotherapy for head and neck cancer have shown that the modest improvement in overall survival that can be demonstrated is confined to regimens in which the chemotherapy is given simultaneously with the definitive therapy.[21,22] Recently, an intergroup study showed a clear survival benefit with the use of concomitant chemoradiation in the treatment of nasopharyngeal carcinoma.[23] This study randomized patients to receive radiotherapy alone or radiotherapy and synchronous intravenous cisplatin and fluorouracil followed by adjuvant chemotherapy after the completion of radiotherapy. Despite relatively poor compliance with the adjuvant portion of the therapy, there were such significant differences in relapse-free survival (24% vs 69%) and overall survival (46% vs 76%) rates at 3 years that the trial was closed early after an interim analysis.

Other studies have demonstrated the efficacy of concomitant radiotherapy and cisplatin-based chemotherapy. For example, investigators from the Cleveland Clinic demonstrated improved relapse-free survival with primary site preservation but not overall survival in a randomized study comparing treatment with concurrent cisplatin and fluorouracil and continuous-course radiotherapy with radiotherapy alone in patients with resectable laryngeal and pharyngeal tumors.[24] A study from Duke University compared hyperfractionated radiotherapy with and without concurrent chemotherapy and demonstrated improved local control and a trend toward improved survival at 3 years.[25] The French Group of Radiation Oncology for Head and Neck Cancer recently presented preliminary results of a randomized study comparing radiation with and without concomitant carboplatin and fluorouracil in patients with advanced oropharyngeal carcinoma. They reported a significant improvement in locoregional control and in disease-free and overall survival rates, although two thirds of patients receiving chemotherapy had significant mucositis.[26]

At the University of California, San Diego, and subsequently at the University of Tennessee, Memphis, we have studied the effects of a targeted chemoradiation protocol referred to as *RADPLAT*. The treatment program incorporates a novel technique for infusing cisplatin directly into the tumor bed, while minimizing the effects of the drug systemically. This is achieved by using microcatheters placed angiographically to permit superselective rapid infusions, while sodium thiosulfate, a neutralizing agent for cisplatin, is simultaneously infused systemically. Because of the systemic neutralization, it is feasible to increase the dose intensity of cisplatin by a magnitude that is at least 5 times higher than standard chemotherapy protocols, thereby enabling the delivery of an enormous amount of drug over a relative short period.

In a phase 1 study, it was determined that the maximum tolerated dose of cisplatin that could be administered is 150 mg/m^2 per week for 4 weeks.[27] After the initial studies in which targeted cisplatin was used as a single treatment modality, investigations focused on the use of concomitant therapy in which cisplatin is given simultaneously with radiation therapy (RADPLAT).[28,29] Two hundred thirteen patients with stage III-IV squamous cell carcinoma of the upper aerodigestive tract completed the treatment protocol between June 1993 and March 1998 at the University of Tennessee Health Science Center.[30] There were 22 tumors (10.3%) arising in the oral cavity, 89 (41.8%) in the oropharynx, 44 (20.7%) in the hypopharynx, 44 (20.7%) in the larynx, 7 (3.3%) in the nasopharynx, and 7 (3.3%) in other sites. Ninety-four patients (44%) had T4 lesions, and 106 patients (50%) had bulky (N2-3) nodal disease. Thus, 152 patients (71.4%) had stage IV disease.

Of the 189 patients who were evaluable for response to treatment in the primary site, 171 (90.5%) had a complete response, 17 (9%) had a partial response, and 1 (0.5%) had no response. Of the 130 patients who were evaluable for response to treatment in the regional nodes, 92 (70.7%) had a complete response, 37 (28.5%) had a partial response, and 1 (0.8%) had no response. There were 49 grade III-IV chemotoxic reactions among the 213 patients undergoing a cumulative total of 717 infusions. There were 6 patients with grade V toxic reactions (treatment-related deaths), 3 of whom had evidence of severe neuropenia. The total number of central nervous system events was 7: 5 were cerebral strokes and 2 were transient ischemic attacks. With a median follow-up interval of 30 months, the Kaplan-Meier plot projects the survival rate at 5 years among patients dying of their malignancy to be 53.6% (SD, 3.9%), and the overall survival rate, including all causes of death, to be 38.8% (SD, 3.7%). Comparison of survival rates between patients with T3 vs T4 lesions did not show any significant difference between the 2 subsets. However, there was a significant difference between patients with N0-1 and patients with N2-3 disease.

The Kaplan-Meier plot for the rate of disease control above the clavicle for all patients was 74.3% at 5 years. Eighteen patients (8%), most of whom did not complete the protocol, had persistent disease after treatment. Of the remaining 195 patients who were disease free after treatment, 51 (26%) developed recurrent disease: 11 (6%) within the primary site, 5 (3%) within the regional lymphatics, and 35 (18%) in distant sites.

The data from this study[30] indicate that the treatment program incorporating high-dose intensity intra-arterial cisplatin infusions combined with radiation therapy administered to patients with advanced head and neck cancer eradicates clinical and pathologic evidence of tumor in the majority of patients. The analysis indicates that few patients have had recurrent disease.

A major goal of this research was to identify a new strategy that could offer patients an improved survival outcome, while avoiding major loss of organ function. As to improving survival, the data suggest that subjects are remaining alive at a rate that is higher than expected. The fact that locoregional control was maintained in 74.3% of all patients included in the study demonstrates that the loss of major organs can be avoided. Subsets of patients with piriform sinus and laryngeal cancer treated with RADPLAT have also been found to have a very high rate of laryngeal preservation.[31,32]

Although organ preservation treatment has highly significant advantages over standard surgical treatment protocols, we must realize that preservation of organs does not necessarily imply preservation of function. For example, one would not expect to see return of normal laryngeal function in a patient whose advanced tumor had effaced a large part of the organ. Instead, one might expect to see some degree of dysphonia and possibly compromised respiration and/or aspiration with associated dysphagia. Detailed analyses of functional impairment are currently being carried out on our patients to better assess this problem. The analyses include the development and validation of objective measures of phonation[33] and the application of swallowing assessment and quality-of-life questionnaires that pertain to patients with head and neck cancer.[34,35] The latter also reflects the patient's ability to tolerate the therapy, which is particularly important to monitor among patients undergoing aggressive treatment with chemotherapy and irradiation.

It is likely that distant metastatic disease among patients with head and neck cancer is usually masked by locoregional disease. With improved methods to control disease above the clavicle, one can expect an unmasking of distant disease among patients who had occult metastatic disease prior to therapy. The emerging problem of death from distant disease will require designing subsequent studies to include a systemic treatment component, particularly for patients who are at greatest risk. We have also extended our targeted chemoradiation studies to include paranasal sinus disease,[36] other advanced malignancies of the skull base,[37] and intermediate mucosal lesions[38] of the oral cavity and oropharynx using a reduced total dose of radiation.

Currently, the major thrust in the development of cancer therapeutics is gene therapy. Buoyed by the explosion of new knowledge of tumor biology through the application of recently discovered molecular techniques, the strategy has turned toward manipulating tumors or the host to favor conditions for disease eradication. Approaches such as replacement of defective genes,[39,40] suicide gene therapy,[41] and immunologic gene therapy[42] have been applied to patients with head and neck cancer.[43,44] Although the initial reports from human clinical trials to date indicate disease response in only a small proportion of patients treated, these findings are significant and encouraging, considering that most of the patients had lesions that were recurrent and previously heavily treated. Researchers are continuing to perfect their techniques, particularly with respect to (1) developing more effective vectors to carry the gene to its proper target, (2) minimizing adverse effects, and (3) selecting patients who would benefit the most. Evidence is also emerging that the best gene therapy strategies may be those aimed at enhancing standard therapeutic modalities. For example, Chang et al[45] have demonstrated an ability to reverse the in vivo radiation resistance of squamous cell carcinoma cell lines through transfecting wild-type *p53* into tumors containing mutated *p53*.

Thus, looking to the horizon, one sees not only new concepts and modalities for treating head and neck cancer, but also continued strategies that involve multiple treatments. As we move into a new century, the lessons learned from the past century will serve as an important foundation for future management of head and neck cancer. Just as we have witnessed a change from single-modality therapy to bimodality therapy and ultimately to trimodality therapy, the new century will likely reflect treatment strategies that will continue to be complex and multifaceted. Chemobiological or radiobiological therapy will become as common as combined surgery and radiation therapy and chemoradiation therapy. With respect to the future, there is also no doubt as to the diminishing role of surgery as the single most important modality for this disease. A diminished role will initially apply to advanced disease, but ultimately, the use of nonsurgical modalities will challenge the surgical treatment of early disease. The survival of the head and neck surgeon as the captain of the team will hinge on his/her ability to adapt to new treatment strategies, to continue to serve the patient as the pivotal team leader, and to serve as the judge among the other therapists. This role should come naturally, since the head and neck surgeon often makes the diagnosis, has the training to accurately assess the cancer and the patient, and usually establishes a strong rapport with the patient. Within this context, the treatment planning conference serves us well as the ideal forum in which to develop the best treatment plan.

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