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PRESIDENTIAL ADDRESS

Tradition, Teamwork, and Tailored Treatment

Surgical Oncology in the Genomic Era

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The next decade will be one of the most exciting, challenging, and, perhaps, unsettling eras in head and neck surgical oncology. We can expect surgical dogma and traditional oncologic principles to be challenged in every aspect. These challenges will be raised by experienced colleagues who have observed the evolution of our understanding of tumor behavior and the limitations of conventional surgery, radiotherapy, and chemotherapy. New questions will be raised because of increasing knowledge of the basic biological characteristics of carcinogenesis, cellular proliferation, and immune homeostasis. How should we prepare ourselves and the next generation of surgical oncologists for these challenges? I believe that we are at a critical crossroads in head and neck oncology between a well-worn highway of surgical technique and a newer roadway of tumor biology and molecular medicine. The obvious main roadway will lead to superb technical advancements in areas such as free tissue transfer, robotics, minimal-access surgery, and application of new laser and optical technologies. Advances on this road will expand our capabilities to repair, restore, and preserve function. The other path that is currently being paved and is less traveled by surgeons is that of bio-oncology, tissue engineering, molecular risk profiling, tailored and personalized treatment, metabolic and molecular intervention, biochemical surveillance, and cancer prevention. Are these separate paths or do they diverge and then cross at future points? How can surgeons in training follow more than one road? What are the special requirements necessary to sustain surgical oncology during the development of these future paths? Importantly, as practicing surgeons, how do we best execute our responsibility to our patients during such rapidly evolving times?

HYPOTHESIS

I hypothesize that the future success and growth of head and neck surgical oncology, and the achievement of maximal benefit for our patients, will require taking the road less traveled. The following treatise describes the sequential development of three paradigm shifts in head and neck oncology that support this hypothesis and illustrates the ways these shifts will demand a new approach to surgical oncologic training.

Head and neck surgical oncology has a proud heritage that stands on the broad shoulders of technical giants such as Billroth, Crile, Hayes Martin, Ogura, and Conley. These giants were creative and thoughtful surgeons who were, in their time, pioneers. They formulated their theories of oncology by the study of tumor spread, metastatic behavior, anatomical barriers and pathways to cancer growth, and the natural presentation and evolution of head and neck squamous cell carcinoma. They were innovators ~~that~~ who used all the information available to them at the time to improve surgical management and to create treatment regimens that would be increasingly successful. Each also appreciated that patients benefited from multidisciplinary care: they organized and encouraged the development of ancillary services in nutrition,

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prosthodontics, nursing care, and, eventually, the cytotoxic therapies of radiation and chemotherapy. Head and neck oncology was one of the first organ-specific oncologic fields to embrace and promote multidisciplinary care by defining and integrating a variety of treatment team members to improve the quantity and quality of care for its patients. Ours was one of the first oncologic teams to incorporate multiple therapeutic modalities, and although there were differences and competition along the way, all team members persevered and thrived in their own areas. Our patients have been the direct beneficiaries of this competitiveness.

It is increasingly apparent that the genomic era has added an entirely new complexity to the burden that surgical oncology previously shouldered in leading this multidisciplinary team approach. This reality demands new levels of cooperation rather than competition. It is time to recognize that as team leaders, we have to expand the repertoire of the surgical oncologist to engage and recruit the new members to the team ~~that~~ who will help us travel that newly cleared and less-traveled path of surgical oncology that promises to become the superhighway of the future. To shirk this responsibility would be a failure of leadership in head and neck oncology at a time when leadership and historical perspective are needed more than ever. It will take steady hands at the wheel to navigate the challenging seas of biodiscovery. And we will need new hands to help steer through these uncharted waters if we are to be successful captains of the oncology team of the future. So, what are the data supporting this hypothesis?

THE CHALLENGE TO SURGEONS

To many investigators and physicians, the basic changes are obvious. Every year, our knowledge of the genetic basis of cancer, the pathways of cell proliferation, apoptosis, and immune regulation and our understanding of the tumor microenvironment are expanding. Surgical oncology, in general, is being challenged to translate these discoveries into improved treatment. This translation may seem simple: add a drug or add a molecular inhibitor and see what happens using trial and error and proof of principle clinical experiments. But for surgeons, it is difficult to shed our anatomical approach to cancer therapy because it has been such a successful mainstay of treatment for most of our patients. We have difficulty envisioning ways to to integrate newer biological concepts into our standard approaches, to test these concepts, and to collaborate more effectively. I propose to my colleagues that we must learn to do this. I do not believe we have a choice: it is our pressing responsibility to our patients. No one will do it for us. During the past 100 years, we have accepted and embraced the responsibility to provide the highest level of initial diagnosis, patient education, monitoring of therapy, follow-up care, coordination of care, provision of surveillance, diagnosis of recurrence, and emotional support during both successes and failures for our patients. If we are to incorporate new knowledge into this matrix of care, we will need to prepare ourselves through better basic science education during residency and fellowship. The prepared mind will then be able to evaluate, design, and integrate the innovations that will result in progress. One might imagine whole new fields in the surgical management of metastases, surgery for dormant stem cells, image-guided surgery for cell populations resistant to cytotoxic therapy, surgery for implantation of devices for biological gene monitoring or drug delivery, and even transplantation of entirely new or genetically altered tissue for reconstruction of cancer-ablated structures. But having a prepared mind is not enough. We must encourage the scientists driving these discoveries to join our team. We must value them, integrate them into our treatment decision making, and educate them to the pressing issues that challenge our patients. Perhaps these predictions are still too obscure to help us envision the ways our current training must evolve to prepare us for leadership in these areas. But, like it or not, we are actively engaged in this evolution, as demonstrated by 3 dramatic paradigm shifts that are currently occurring and that will significantly affect the future of our specialty in the next decade.

PARADIGM 1: TREATMENT SELECTION

The first change in the surgical oncology paradigm involves selection of alternative treatments based on patient morbidity. The concept of comparison and selection of treatment options by the balance of risks and benefits is not new; however, a major shift began with the introduction of highly effective chemotherapy drugs into our treatment armamentarium in the mid-1970s. The introduction of new combinations of chemotherapy and, particularly, the addition of cisplatin achieved high rates of histologically complete tumor regressions that have traditionally been the hallmark of progress in the chemotherapy of any malignancy. Surgeons rapidly adopted new intensive combined modality treatments under the premise that more cytotoxic therapy or more radical operations or more intense radiotherapy would logically increase patient cure rates. In the case of adjuvant chemotherapy, it has taken more than 20 years to determine that more was not necessarily better. In fact, new and intense long-term toxic effects in terms of swallowing function, tissue fibrosis, and necrosis were encountered. Patterns of failure were often altered, but overall survival improvements were minimal. The introduction of these effective cytotoxic regimens in the neoadjuvant setting raised the possibility that we might be able to reduce the morbidity of our other subsequent conventional modalities.[1] As surgical oncologists, we took the challenge to ask whether the morbidity of a radical resection could be avoided by the integration of chemotherapy.[2,3] Thus, the organ preservation approach, which incorporates combinations of intensive chemotherapy and intensive radiotherapy, became widely adopted as an alternative to radical tissue resections, particularly for advanced laryngeal or oropharyngeal cancers in which patients were facing laryngectomy or major tongue base resections.[4,5] We now must ask whether the biological characteristics of the tumor as reflected by clinical chemosensitivity might allow further reductions in the radiation dose or field and thereby reduce or avoid the toxic effects of the combined chemoradiation regimens. Also, surgeons will need to be the leaders in answering these questions because major improvements in cure rates have not been achieved with this paradigm shift. In the devel-

opment of these new treatments, we will need to carefully monitor patients for failure if timely surgical salvage is to be successful, and we must carefully assess whether the risk of increasingly morbid and challenging secondary surgery is low enough to offset longer-term chemotoxicity and any potential reductions in cure.[6,7]

PARADIGM 2: BIOLOGICAL STAGING

The second changing paradigm is biological tumor staging. The new era of tumor biology is replacing the anatomical concepts of clinical tumor staging as a basis for treatment selection rather than the traditional tumor site or extent. The evidence for this paradigm arose initially out of the first paradigm shift that occurred with the introduction of cytotoxic drugs and organ preservation approaches. It became readily apparent and was repeatedly demonstrated that some tumors are susceptible to drug treatment and some are resistant. The same was true for radiotherapy. Although the biological basis for these differences remains poorly understood, it was consistently demonstrated that response to drugs, particularly the achievement of a histologically complete tumor regression, defined a favorable overall prognosis for the patient regardless of subsequent conventional therapy. Using this biological fact should permit more rational selection of less morbid treatment for individual patients and, hopefully, achieve improved results. We have tested this concept in advanced laryngeal cancer and found it to be true. When we classified tumors based on an initial test dose of chemotherapy and selected either radiotherapy or surgical management based on this classification of responsiveness, we achieved dramatically improved survival rates for both groups of patients.[8] But even this classification is not precise enough because clinical chemoresponsiveness is not the whole story. We have turned to the laboratory to try to understand the biological basis that supports successful treatment selection based on tumor response by initially studying the genes that regulate chemotherapy-induced apoptosis. Initial investigations based on gene expression are just now beginning to allow characterization of molecular profiles that correlate with successful outcome. We started with *p53*, which is the most commonly mutated gene in head and neck cancer. Initially, it looked like overexpression of the p53 protein defined a group of patients with more aggressive cancers that benefited from chemotherapy and radiotherapy approaches.[9] However, follow-up prospective phase 2 biomarker testing did not confirm the same statistical correlation without the consideration of additional gene markers.[10]

We had found that more infiltrative tumors, as characterized by aggressive microscopic growth patterns, had a better prognosis when treated with chemoradiation but not when treated with surgery, which indicates that the prognostic significance of some markers depended on the therapeutic regimen used and that a homogeneous treatment group must be used to calibrate molecular markers.[11,12] Thus, when we looked at actual *p53* mutations, the usefulness of the *p53* mutation and overexpression was lost. By adding a second family of genes (*Bcl2, Bax,* and *Bclx*) that are important in regulating apoptosis, we found that the combination of low *p53* expression and low BclxL protein expression that blocks apoptosis resulted in better identification of patients with a better prognosis when treated with combination chemotherapy and radiation.[13] Newer investigations with additional gene markers that regulate the p53 pathway, such as MDM2, are also showing promise as combination markers[14]

Other groups have studied growth regulation and expression of the epidermal growth factor receptor and have found that tumors that overexpress epidermal growth factor receptor have a poor prognosis when treated with radiation.[15] In oropharyngeal cancers, we and others have also seen this and, together with basic laboratory investigations,[16] have used this information to lead us to pioneering clinical investigations. An example would be targeted therapies aimed at blocking the function of the epidermal growth factor receptor pathway with antibodies such as cetuximab or tryrosine kinase inhibitors such as erlotinib.[17] It is also likely that certain molecular profiles will define patients who are better treated with surgery. It is possible that such molecular classifications may differ significantly for tumors at varying sites, such as oral cavity or oropharyngeal cancers, and, thus, such studies and correlations will need to be evaluated in much more homogenous populations of patients than we have previously undertaken. This reinforces the necessity of increased multidisciplinary interinstitutional cooperation.

That this paradigm of tumor reclassification and molecular staging is of critical importance to future therapeutic advances is even more apparent in the human papilloma virus (HPV). Landmark molecular epidemiology studies[18,19] have now demonstrated an increasingly frequent incidence of HPV-16–positive tumors in the oropharynx and the fact that an HPV-16–positive immunohistologic profile defines a subset of patients with a favorable prognosis. This favorable prognosis is demonstrated in surgically treated patients and in patients treated with radiation alone.[20,21] Whether these discoveries can be used to define less radical therapy for subsets of patients remains a current oncologic challenge. However, the recognizition of these differences in the categorization of cancers of similar anatomical site and stage, and the use of these characteristics to guide therapy development, is a major paradigm shift for head and neck surgical oncologists. It is likely that this shift will improve survival and quality of life for many of our patients.

PARADIGM 3: MOLECULAR RISK ASSESSMENT

Finally, there is a third paradigm shift that will challenge surgical oncologists. It is just now evolving and incorporates studies of prevention and survivorship. One may argue that these are not new developments in oncology; however, the science of genetics and molecular biology has opened new possibilities and concepts for the primary and secondary prevention of cancer. Cancer is being viewed more and more as a chronic illness in which host factors in the tumor microenvironment and within innate immune function, together with dysregulation of normal processes, such as angiogenesis, play a role in tumor cell dormancy. The demonstration of head and neck cancer stem cells,[22] the effects of epigenetics on normal and cancer tissue,[23] and the role of chronic inflammation in cancer con-

trol[24] are just being explored. We recently started long-term population-based outcome studies combined with molecular genetics studies that should provide new insight into cancer prevention and lead to the development of molecular risk profiles that could guide new strategies for treatment and surveillance. When we looked at long-term outcomes and considered traditional prognostic factors, such as tumor stage, site, and treatment modality, we found a significant impact of social behaviors, such as smoking and nutrition, on overall survival.[25,26] Levels of nonspecific proinflammatory serum cytokines, such as interleukin 6, were also directly related to survival.[27] When these social and behavioral factors, combined with molecular prognostic factors, are investigated, one begins to uncover important interrelationships that could be of potential benefit in designing prevention strategies. For example, in a homogenous subset of patients with advanced oropharyngeal cancers treated with chemoradiation, we saw that the highly beneficial effect of having an HPV-16–positive tumor was almost always negated by the previous smoking behavior of a patient.[28] Clearly, such findings are provocative and preliminary, and much larger studies, combined with epigenetics and pharmacogenetics, are needed to explore and understand the significance of these observations. To conduct such studies requires complex multidisciplinary and multi-institutional efforts that have never before been necessary. Head and neck cancerous tumors are not of a common enough type for single institutions to mount such studies. We will need large databases, large tissue repositories, and unified treatment approaches that can accommodate and account for the molecular variability in tumors and host. This will require a change in the level of cooperation among physicians and researchers that has never before been achieved. The National Cancer Institute has recognized this need by organizing one of the first organ site–specific national clinical trial steering committees focused on better organization of multi-institutional clinical trials.[29] Although still in its infancy, this effort includes task force groups focused on tumor biology and tumor imaging and clinical trials for patients with advanced disease, recurrent or metastatic cancers, or rare tumors. All National Cancer Institute–supported clinical cooperative groups, Specialized Programs of Research Excellence, and large program project grantees, along with patient advocates, are represented on this committee, with additional experts serving on the various advisory task forces. The steering committee has been granted the authority to approve or disapprove national trials. The committee has already reviewed several clinical trial concepts, approved the development of a new phase 3 national trial of postoperative radiotherapy and cetuximab in patients undergoing potentially curative surgical resection, and organized a "state-of-the-science" conference on head and neck cancer and HPV (November 9-10, 2008, in Washington, DC).

A NEW TRADITION AND TEAM

How do we as surgical oncologists manage these challenging issues? We must be more collaborative if we are to remain leaders in providing the best care for our patients. Our model of multidisciplinary care, developed during the past 30 years, must adapt to changing times and research knowledge. We will see renewed dependency on more sophisticated immunohistopathologic and molecular pathologic methods. With these new tools, we will increasingly need the cellular and molecular biologist to help us understand the basics of genomic biology and the application of this knowledge. We will need new biostatistical approaches to the design and analysis of complex clinical trials with new end points that may incorporate quality-of-life and survivorship measures. Who is best prepared to incorporate these new players and lead this expanded team during sequential paradigm shifts? Based on tradition, aptitude, and training, I believe that the surgical oncologist must accept these expanded responsibilities. It is incumbent on residents, fellows-in-training, and their mentors to develop and pursue the prerequisite experiences and knowledge base in genetics, statistics, informatics, clinical trial methods, and multispecialty care coordination. For each of us actively involved in this education and in the evolution of cancer treatment, I offer the following recommendations for the head and neck oncology team of the future.

1. Identify an interested biologist or biopathologist and integrate him or her as a head and neck oncology team member.
2. Identify an interested biostatistician and integrate him or her into your team.
3. Provide the necessary surgical technical excellence and comprehensive surgical oncologic care and follow-up for patients.
4. Embrace regular and critical review and reevaluation of newer concepts and the implementation of quality-of-life and quality-of-care assessments.
5. Design and implement survivorship protocols that include and analyze the success of secondary (salvage) treatment regimens.
6. Participate as a team in collaborative clinical trials, including diagnostic, treatment, and epidemiologic trials.

As the American Head and Neck Society, we face 3 challenges to the future of surgical oncology. The first is to promote the development of leadership in the innovation and critical evaluation of evolving treatment paradigms. The second is to recognize a new responsibility to help define the role of surgical care with respect to timing, integration, new techniques, collaboration, and team science. Finally, we must expand the role of the American Head and Neck Society in training and education by including the new members of the treatment team through improved communication with the other specialty societies interested in the integration of new technologies and therapies. We should take the lead in initiating forums for treatment guideline development and encourage participation by our members on committees sponsored by the National Cancer Institute steering committee, the National Cancer Center Network, and other oncologic societies interested in head and neck cancer. In doing so, we must promote the highest levels of respect and recognition for what each team member brings to the effort. To address these challenges is our highest priority. Doing so may feel like taking the road less traveled, but will likely ensure the future success and growth of head and neck surgical oncology well into the 21st century.

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