ORAL CANCER BACKGROUND PAPERS

Chapter VI: Treatment

Working Draft

A. State of the Science

Multidisciplinary Tumor Board Concept

Patients with head and neck cancer should be evaluated before initiation of therapy by representatives of each discipline responsible for administering cancer care. Having a multidisciplinary tumor board composed of otolaryngologists, plastic surgeons, oral and maxillofacial surgeons, radiation oncologists, medical oncologists, dental oncologists, pathologists, radiologists, and allied health professionals facilitates this approach. Patients and their family members should attend this tumor board or conference.

After they review the case histories, microscopic slides, and pertinent studies from diagnostic imaging (e.g., computed tomography, magnetic resonance imaging, plain X-ray films), representatives of each discipline should examine the patient. The tumor board process is useful in establishing a correct pathologic diagnosis, determining the extent of disease, detecting other simultaneous head and neck primary cancers that might have escaped detection, and facilitating dental evaluation, which is particularly important in patients whose treatment will include irradiation, chemotherapy, or resection of oral or oropharyngeal tissues.

After examination of the patient, the board should reconvene to discuss therapeutic alternatives and to formulate a recommendation for treatment based on expected outcome (function, cosmesis, impact of treatment on lifestyle and career) and the expertise available at the treating institution. If the board believes that either the necessary expertise or technology is not available at its institution, or if the patient and family so desire, the board may recommend referral to another institution or physician. If no curative option exists, the board may recommend treatment with palliative intent. If further workup is indicated, there may be a recommendation to obtain other tests and re-present the patient's case to the board once additional information becomes available. Members of the board discuss these alternatives and recommendations with the patient and family, and in many instances, the patient and family are active participants in the decision-making process about the case. Patients are routinely advised to discontinue use of all tobacco products and alcohol.

Secondary benefits that accrue to patients and physicians from a multidisciplinary tumor board include the efficiency of: having multiple consultations by a number of specialists in a short period of time without having the patient travel from one office to the next; avoiding delays in obtaining consultative appointments; providing patient, family, and physician education; and assuring that the most appropriate therapy is applied first (as opposed to the commonplace situation in which the first practitioner to evaluate the patient provides the treatment as well).

Treatment Selection for the Primary Site: General Principles

Surgery or radiotherapy is curative for most early carcinomas of the oral cavity and oropharynx; cure rates for the two modalities are similar. Chemotherapy is not curative and is used only as an adjunct. Selection of the treatment modality must be based on factors such as functional outcome, cost, length of treatment, risk of complications, the patient's general medical condition, and patient preference. Choices are also influenced by clinicians' skills, experience and philosophies, and by available facilities.

More advanced lesions typically require combined radiotherapy and surgery to obtain optimal cure rates. In the past, preoperative radiotherapy of the primary site was common, but in recent years most centers have preferred to use postoperative radiotherapy, primarily because surgical complication rates are lower if irradiation is withheld until then. Postoperative radiotherapy is also used when the primary surgical specimen is found to have vascular or perineural invasion or close surgical margins.

Management of the Neck: General Principles

The incidence of cervical nodal metastases for each oral primary site increases with increasing local stage of disease. The patient with no neck disease or very early stage positive neck disease (N1) may be treated electively by radiotherapy or neck dissection. Because cure rates are the same, the neck is generally treated with the same modality selected for the primary site. If the risk of lymph node metastases is believed to be less than 15%, the clinician may simply observe the neck for the occurrence of metastases.

More advanced neck disease generally requires combined treatment for optimal regional disease control. Combined therapy is essential if there is extranodal spread of cancer or multiple positive nodes are identified. If surgery was used to treat the primary site, postoperative radiotherapy is appropriate. The only exceptions are when the nodal mass is fixed to the carotid artery or the cervical fascia; then preoperative radiotherapy is given. When radiotherapy is selected for the primary tumor, the neck dissection is generally performed 4-6 weeks after radiotherapy has been completed.

Oral Cavity

Most centers advocate surgical excision for early-stage primary disease (T1-T2) of the lip, floor of mouth, oral tongue, alveolar ridge, retromolar trigone, hard palate, or buccal mucosa. The CO_2 laser may also be used as a cutting tool in removing oral cavity cancers.[1] In addition, this laser may be useful in removing dysplastic lesions without scarring the area significantly. However, clinicians must still observe the patient closely after the lesions are removed, as there is a significant likelihood of recurrence.

Although radiotherapy may work as well as surgery for early malignant lesions in several of these

subsites, such as the floor of mouth, concern about complication rates has made surgery the choice for most of these lesions. However, more advanced primary tumors in any of these sites typically require a combination of surgery and radiotherapy. Advanced primary tumors adjacent to the mandible may require a rim mandibulectomy, and those tumors that frankly invade the mandible are treated with a segmental mandibulectomy. The plan for surgical resection must also include reconstructive options; reconstructive teams composed of head and neck surgeons, oral surgeons, and prosthodontists are most successful at achieving the best functional and cosmetic result. (Chapter VIII contains a full discussion of reconstruction and rehabilitation.)

Most radiotherapy for carcinoma of the oral cavity uses an interstitial implant either alone or combined with external beam. For carcinoma of the oral tongue and buccal mucosa, the results of an interstitial implant alone or combined with external beam radiotherapy are generally better than those achieved with external beam radiotherapy alone.

Recurrence rates vary by primary site and increase with increasing primary stage. For lesions on the floor of the mouth, 5-year cause-specific survival rates by stage are as follows: I: 90%, II: 80%, III: 70%, favorable IV: 40-50%, and unfavorable IV: 20%. Five-year cause-specific survival rates for oral tongue cancers by stage approximate the following: I and II: 70-80%, III: 40%, and IV: 15-20%.[2]

Oropharynx

The main goals in treating patients with oropharyngeal cancer are achieving a cure and preserving both speech and swallowing functions. Although some institutions favor surgery[3] alone or in combination with radiotherapy, a review of the literature showed no definite advantage for surgery over radiotherapy in either tumor control or survival;[4] surgery has the added disadvantage of causing losses (e.g., of velopharyngeal competency, of tongue musculature or tongue mobility, of all or part of the mandible, or of the larynx) that are not always fully compensated by reconstructive procedures. Thus, in a great many institutions, treatment consists of radiotherapy to the primary site, with or without subsequent neck dissection.

Base of Tongue

Because it responds strongly to irradiation, frequently metastasizes to the lymph nodes, and has poorly differentiated histology, carcinoma of the base of the tongue is usually treated by radiotherapy. Surgery for more advanced lesions usually results in a loss of major organ function. However, there remains disagreement about the optimal radiotherapy technique; similar results have been obtained by external beam irradiation followed by an interstitial implant boost and by external beam irradiation alone.[5] Local control rates are 90% for stage T1, 78% for T2, 79% for T3, and 47% for T4 lesions treated by external beam alone; and 88%, 70%, 74%, and 70%, respectively, for external beam plus interstitial implant.[3,6]

Extended supraglottic laryngectomy may be used for limited, lateralized vallecular lesions only if one lingual artery can be preserved and the patient is in good medical condition. If the glossectomy is extensive or a total glossectomy is required, a total laryngectomy is also usually necessary to prevent aspiration. Because of the risk of bilateral neck node metastasis, consideration should be given to bilateral neck dissections or postoperative radiotherapy if there are no clinically positive lymph node metastases.

Tonsillar Region

Occasional, discrete, superficial lesions of the anterior tonsillar pillar can be managed by wide local excision. More advanced tumors usually require resection of the tonsillar region (which includes the fossa and pillars), part of the soft palate, and frequently part of the tongue; a segmental mandibular resection; and a neck dissection.

Radiotherapy for tonsillar region cancers is highly successful for early and moderately advanced disease. Treatment is given by parallel-opposed portals or, in patients with well-lateralized tumors, by either a wedged-pair technique or a mixture of high-energy electrons and photons so that the contralateral salivary tissue is spared. An interstitial (cesium or iridium) boost dose is sometimes administered when the primary cancer invades the tongue. For tonsillar pillar primaries, treatment can be initiated with an intraoral cone using orthovoltage x-rays or electrons as a "reverse boost" to the primary. External beam radiotherapy is then directed to a more generous field encompassing the primary tumor and the regional lymph nodes. The intraoral cone technique allows administration of a high radiation dose confined to a limited volume of tissue—a technique that not only improves the control rate but also reduces the risk of serious late radiation injury.

The overall rate of tumor control at the primary site for early (T1-T2) tonsillar fossa primaries is 95%, compared with 70% for T1-T2 tonsillar pillar primaries. T3 tumors at either site are controlled approximately 70% of the time, and T4 lesions have a 40-50% chance of local control.[7] Treatment of tonsillar pillar cancers should be intensified with intraoral cone or implant therapy or other suitable approach.

Conventional standard fractionated radiotherapy consists of 1.8-2.0 Gy per fraction, once a day, 5 days per week, for a total weekly dose of 70-75 Gy. However, hyperfractionated and accelerated fractionated radiotherapy employing using smaller doses per fraction, twice a day, 5 days per week, has recently been used in the treatment of head and neck cancer. A randomized trial by the European Organization of Research on Treatment of Cancer (EORTC) showed improved local control using hyperfractionated radiotherapy compared with conventional fractionated radiotherapy for stage II and III oropharyngeal carcinoma. The survival was also better for the hyperfractionation arm, although the difference was not statistically different.[8]

Hyperfractionation has been used at the University of Florida,[7,9] split-course accelerated fractionation at the Massachusetts General Hospital,[10] and accelerated fractionation with a concomitant boost

technique at the M.D. Anderson Cancer Center.[11] In contrast to the EORTC trial, University of Florida results showed no significant improvement in local control of carcinoma of the oropharynx by hyperfractionated radiotherapy compared with that achieved for historical controls treated by conventional fractionated radiotherapy.[9] However, Massachusetts General Hospital and M.D. Anderson Cancer Center results suggest improved local control with the regimens used at those institutions compared with historical controls treated with conventional fractionation.[10,11] The results of hyperfractionated or accelerated fractionated radiotherapy may depend on primary site and stage. The Radiation Therapy Oncology Group (RTOG) is investigating through a Phase III randomized trial the relative efficacy of standard fractionation, hyperfractionation, and the two variants of accelerated fractionation in the radiotherapy of stage III and IV carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx.

Five-year survival is achieved in 50-55% of patients with early or moderately advanced (stages I, II, III) cancer of the tonsillar region and in approximately one-third of patients with stage IV disease.[7]

Soft Palate

Small, well-defined lesions of the soft palate may be excised, but because these lesions are multifocal, recurrence of soft palate tissues at the margin will likely occur unless patients are carefully selected. Radiotherapy is commonly used because it leaves the patient functionally intact with no need for a prosthesis or elaborate reconstruction.

Morbidity associated with surgery is minimal if the full thickness of the palate is not removed. Moderate-sized through-and-through defects are usually closed with local flaps, although velopharyngeal incompetence is a potential hazard with this approach. If a major resection is required, a prosthesis is necessary.

The basic radiotherapy technique for soft palate cancer involves parallel-opposed portals to the primary site and neck. If the lesion is located very much to one side of the mouth, it can sometimes be treated with a single ipsilateral portal arrangement or other field arrangements using 3-D treatment planning, so that contralateral salivary tissue is spared. Often the initial 15-20 Gy is administered via an intraoral cone as a reverse boost to limit the volume of tissues receiving high-dose radiotherapy.

Local control with radiotherapy is achieved in approximately 85% of T1, 75% of T2, 60% of T3, and 20% of T4 tumors.[9] Five-year survival rates of about 80% are achieved for stage I-II cancers; stage III-IV patients have 5-year survival rates of about 30-40%.

Chemotherapy

Although improvements in radiation therapy and surgery have led to modest improvements in survival and relapse-free survival rates, there is still considerable room for improvement, particularly for

patients with advanced-stage disease. Chemotherapy has been used in attempts to improve survival or to reduce the incidence of distant metastases, to serve as an adjunct to radiotherapy for organ preservation, and to select patients for subsequent therapy based on their response to chemotherapy. However, how much chemotherapy actually contributes to achieving these goals remains controversial.

Chemotherapy has been applied as induction (so-called neoadjuvant therapy), concurrently with radiotherapy and as post-treatment adjuvant therapy. Neoadjuvant therapy has been widely studied in recent years; a number of drug regimens have been used. The combination of cisplatin and fluorouracil (5-FU) has achieved considerable popularity because of high rates of response with acceptable rates of toxicity. In previously untreated patients, response rates of 60-90% have been reported—with a complete clinical response in 20-40% of patients.[12] (Patients who experience a complete clinical response have a favorable prognosis compared with patients having partial or no response.) Unfortunately, randomized studies have shown no significant impact on survival rates.[12,13]

Concomitant chemotherapy and radiotherapy has been used to try to increase the rate of local-regional control, on the theory that these might be either an additive or synergistic interaction between the two treatments. Both single and multiagent chemotherapy have been used. Several randomized trials have shown an improvement in local-regional control and disease-free survival with concurrent single-agent chemotherapy and radiotherapy compared with radiotherapy alone.[12] Unfortunately, the toxicity of concurrent multiagent chemotherapy and radiotherapy is significant.

Adjuvant chemotherapy, given after radiation or surgery, has received less attention, mostly because patients are reluctant to continue prolonged treatment after extensive, sometimes debilitating local-regional therapy. Results have generally been discouraging.

B. Emerging Trends

Immunologic response modifiers such as alpha interferon and interleukin have been used in combination with other therapies to boost the patient's own immune response against oral carcinoma. In addition, monoclonal antibodies to an individual tumor are being used in an attempt to image the lesion better and to deliver specific toxic substances, including radiolabeled substances, directly to the tumor. Efforts continue to develop antibodies capable of reaching the entire tumor cell population while avoiding systemic toxicity.

Twice-a-day radiotherapy is being used increasingly in a variety of head and neck sites to improve

outcomes. However, the relative efficacy of twice-a-day hyperfractionated or accelerated fractionated radiotherapy compared with conventional fractionated radiotherapy for the various head and neck primary sites other than stage II and III oral carcinoma (excluding base of tongue) remains to be established by ongoing randomized clinical trials. Another new technique, stereotactic radiosurgery, is being considered in patients for whom radiotherapy or surgery (or both) has failed.

Tumor markers, such as oncogene and tumor suppressor mutations and specific allelic losses in the genome of a carcinoma, are being investigated to determine the relationship of such molecular alterations to clinical outcome. The development of such markers would allow treatment to be more properly tailored to the individual tumor. To date, however, no specific marker has been identified that correlates for all sites with tumor response to treatment.

Gene therapy has been used to treat other tumors, particularly hematologic tumors. In this approach, investigators or clinicians try to introduce new molecular material into human cells. They may be trying to alter the tumor's immunogenicity, activate the host response, modulate the tumor's sensitivity to chemotherapy or radiotherapy, insert tumor suppressor genes, inhibit oncogenes, prevent malignant transformation, or introduce lethal genes. Despite a number of potential obstacles, there may be a future for gene therapy in the treatment of squamous cell carcinoma of the head and neck.

In surgical therapy, the use of microvascular free flaps permits resection of larger areas because of the ease of reconstructing such defects; suitable soft tissue or bone can be moved from a variety of different sites to fill the defect. For example, fibular reconstruction at the time of mandibular resection has improved rehabilitation in some patients. Neural reanastomoses are attempted to try to improve swallowing after free flap reconstruction. The advent of osseointegrated dental implants as part of the reconstructive technique has allowed for more aggressive tumor removal, since oral rehabilitation is now more feasible.

C. Opportunities and Barriers to Progress

Initial Diagnostic Steps

One frequent misunderstanding about the treatment of patients with carcinomas of the oral cavity concerns the first diagnostic steps. Initially, only an incisional biopsy of the primary lesion should be performed, not an excisional biopsy. Inadequate excisional biopsies only cause confusion about the initial extent of the tumor and add an unnecessary procedure. Of greater concern is that excisional neck node biopsies are frequently used to establish a diagnosis of head and neck carcinoma. A physical examination combined with imaging of the mucosa of the upper aerodigestive tract will

usually reveal the source of suspicious adenopathy. If the relationship of lymphadenopathy to primary oral cavity tumors remains uncertain, a fine needle aspiration biopsy will almost always provide a tissue diagnosis from the lymph node. Removing a lymph node during diagnosis complicates management, as radiotherapy then must be the next treatment step to have the usual chance of a successful outcome.

Imaging

Successful treatment depends on precise delineation of tumor extent. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful. Unfortunately, these technologies require strict physician monitoring if optimal images are to be obtained. All too often, the techniques used for CT, the manner in which intravenous contrast was utilized for this modality, or poor patient positioning limits the clinician's ability to obtain useful diagnostic information. In many cases, carelessly performed studies have to be repeated at additional cost, inconvenience, and sometimes additional risk to the patient.

New imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT) scanning, and imaging with fluorodeoxyglucose (FDG) may help to diagnose new cancers and detect tumor recurrences.[14] Both the scarcity and expense of the equipment are problems, but early results look promising. However, confirmatory data are needed.

Radiation Therapy

Not all cancers need the same type of fractionation schedule; already the groundwork has been laid for new fractionation methods. Hyperfractionated radiotherapy[8] and accelerated fractionated radiotherapy[10,11] may offer better local-regional control for some primary sites and stages of head and neck cancer; their relative efficacy is currently being investigated in randomized clinical trials. Cell kinetic parameters may help determine the best means of fractionating treatment in the individual patient.[15] Improved tumor control and reduced long-term morbidity are the goals.

New treatment planning and delivery systems in radiation therapy using 3-dimensional computer treatment planning programs and computer-driven multi-leaf collimator systems can provide better confirmation of the high-dose radiation volume to the tumor while sparing normal structures. More widespread availability of these technologies can be anticipated in the very near future. Major barriers to their widespread use are that they are very time- and labor-intensive, require sophisticated computer programming capabilities, and are expensive.

Chemotherapy

Chemotherapy has been shown to have positive effect in squamous cell carcinomas of the head and

neck. There appears to be an opportunity to integrate chemotherapy into therapeutic strategies, although there is an issue of how it should be timed in relation to other therapies (surgery or radiation therapy). However, the benefits of chemotherapy should not be measured only by survival, but also by organ preservation and quality of life. Continued support for randomized trials and new drug discovery and development is essential.

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