Current management of oral cancer

A multidisciplinary approach

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ABSTRACT

Background. Recent basic science discoveries have contributed to our understanding of the etiology of oral cancer and allowed us to consider innovative approaches to therapy.

Methods. The authors evaluated and summarized current approaches to the management of oral cancer, emphasizing the multidisciplinary team approach to coordinate surgery, radiation therapy and chemotherapy. Current concepts in management, including complications of therapy, are described.

Results. State-of-the-art surgical techniques can spare patients with oral cancer from much of the morbidity and complications common in the past. The refinement of treatment strategies reduces complications and improves efficacy. Many exciting new clinical trials in the areas of gene therapy and immunomodulation are showing promise.

Conclusions. Management of oral cancer has undergone radical change in the past 10 years and continues to evolve rapidly. Discoveries in molecular biology, diagnosis, surgery, radiation therapy and medical oncology have altered many traditional concepts and practices.

Clinical Implications. General dental practitioners need to understand current treatment modalities for oral and pharyngeal cancers to determine to whom they should refer patients for the most appropriate treatment, and to make recommendations regarding complications associated with these cancers.

The management of oral cancer has undergone radical change in the last 10 years and continues to evolve rapidly. Discoveries in molecular biology, diagnostic techniques, surgery, radiation therapy and medical oncology have altered many traditional concepts. In this article, we discuss current concepts in the management of oral cancers and review emerging ideas and therapies. In addition, we describe complications of current therapy.

General dental practitioners need to understand current treatment modalities for oral and pharyngeal cancers.

THE MULTIDISCIPLINARY APPROACH

Oral cancer is best managed by a team of health care professionals who have a sufficient number of patients to develop the experience necessary to provide excellent care. All cases should be reviewed by a tumor board, consisting of pathologists, radiologists, surgeons, radiation oncologists and medical oncologists. The participants discuss each case in depth to optimize treatment planning. Other team members include general dentists, dental hygienists, nurses, speech pathologists, prosthodontists and nutritionists. The most common oral cancer is squamous cell carcinoma; thus, we will focus on this neoplasm.

Early-stage (I and II) oral squamous cell carcinoma can be treated with surgery or radiation. Five-year survival rates are similar for both modalities, and a decision is made on the basis of the tumor's site and size, histologic findings, the patient's wishes and the advice of the multidisciplinary team. Unfortunately, the majority of oral cancers present at an advanced stage (III and IV), when therapy is more complex and the prognosis is worse. In advanced-stage (III and IV) oral squamous cell carcinoma, a combination of surgery and radiation therapy provides the best survival rate, although this increases the complications and morbidity. The role of chemotherapy has not been clearly defined in oral squamous cell carcinoma.

This approach has brought about an increase in locoregional control (that is, at the primary site and cervical nodes). However, patients with advanced disease now live long enough to develop distant metastases, and patients with early disease survive to develop second primary cancers. Thus, the battleground in treating this disease has begun to shift. The traditional concept of oral cancer as a disease of the head and neck region has evolved into the concept of oral cancer as a systemic disease. As such, initial therapy and follow-up are more comprehensive.

SURGERY

Imaging using computerized tomography, or CT, and magnetic resonance imaging has increased visualization of the extent of the primary tumor and has improved assessment of the cervical lymph nodes. To resect a primary tumor with adequate margins, surgeons use craniofacial approaches involving osteotomies of the mandible or maxilla, which can be "swung" out of the surgical field to provide access to any area of the mouth. Rigid fixation plates applied before osteotomy cuts are made enable the surgeon to replace the jaw to its preoperative position, maintaining contour, occlusion and function. When squamous cell carcinoma invades the mandible, the results of a study by McGregor and MacDonald[1] help the surgeon decide whether the entire mandibular segment must be removed or whether continuity of the mandible can be maintained. The technique of marginal mandibular resection provides less morbidity, allows earlier function and requires less-extensive reconstruction.[2]

Management of the node-negative (that is, stage N0) neck using elective selective neck dissection now is the standard when the estimated possibility of metastasis approaches 20 percent. The supraomohyoid neck dissection, which involves removal of lymph nodes from levels I through III while preserving the internal jugular vein, spinal accessory nerve and sternocleidomastoid muscle, is the operation of choice. However, in cases of tongue cancer, level IV nodes often are removed as well. Using the tumor size (T2-4), site, depth (> 4 millimeters) and other criteria (such as perineural invasion), surgeons can predict which patients with clinical and radiologic N0 neck are at increased risk of developing occult micrometastases.[3]

In the field of reconstruction, the development of microvascular surgery and the use of osseointegrated implants have allowed great improvements in function and esthetics. Microvascular free-tissue flaps allow the transfer of skin, fat, muscle, bone or any combination of these to primarily reconstruct the postablative defect. The radial forearm flap has become the workhorse flap for soft-tissue defects, with the fibula or iliac osseomyocutaneous flaps used for mandibular reconstruction.

The success of osseointegrated implants, in both nonvascularized and vascularized bone grafts in patients with cancer, is well-substantiated.[4,5] Implants have been placed successfully even in irradiated tissues (whether or not hyperbaric oxygen is essential in these cases is controversial).[6,7] Certainly, however, the goal of providing patients who have oral cancer with teeth and the ability to manage a normal diet now is achievable.

Recent reports have shown that the ability to reduce parotid gland exposure to radiation significantly reduces subsequent xerostomia.

RADIATION THERAPY

Sophisticated planning using three-dimensional CT images of the tumor permits conformal radiation therapy (that is, it conforms to the tumor). This has allowed directed irrradiation and the development of intensity-modulated radiation therapy, or IMRT. IMRT is a technique that delivers a homogenous dose of radiation focused at the target site, but consists of a spatially nonuniform radiation exposure from various points of reference that minimizes radiation exposure to healthy tissue. The concept of a more conformal radiation dose with less tissue damage and subsequently less morbidity is attractive in the head and neck.

Recent reports have shown that the ability to reduce parotid gland exposure significantly reduces subsequent xerostomia and improves quality-of-life scores.[8] An ongoing Radiation Therapy Oncology Group, or RTOG, study is examining whether the use of pilocarpine during radiation treatment, as well as in the postradiation period, will prevent xerostomia. In addition, amifostine (a radioprotectant) has reduced the severity of xerostomia after radiation[9] and chemoradiation therapy.[10] Other attempts to improve tumor kill via radiation therapy have

included the use of hyperfractionation and accelerated fractionation regimens (that is, higher doses or more frequent doses than conventional radiation therapy). Although these methods have shown increased local control, they have increased acute toxicity.

CHEMOTHERAPY

In a comprehensive review of all prospective randomized trials of chemotherapy for head and neck cancer, Fu[11] found no evidence of increased survival when chemotherapy alone was used. Therefore, chemotherapy usually is combined with radiation therapy. Currently used agents include cisplatin, carboplatin, 5-fluorouracil and the taxanes (paclitaxel and docetaxel). 5-fluorouracil and the taxanes also are radiation sensitizers. Recent interest has been shown in intra-arterial delivery of chemotherapy, which increases the drug dose to the tumor and decreases systemic toxicity.[12]

Combination chemoradiation therapy is used after surgery for patients with poor-prognosis stage IV cancer, for patients with unresectable stage IV disease and in protocols for organ preservation. Despite its popularity, neoadjuvant chemotherapy has not been shown to improve survival rates,[11,13] and few data exist for adjuvant chemotherapy after radiation therapy. However, the use of concurrent chemotherapy and radiation therapy has been shown to increase survival rates in patients with head and neck cancer.[14] Unfortunately, most series have combined all head and neck sites, and it is difficult to interpret data for the oral cavity alone when sites such as the larynx, oropharynx and nasopharynx (which are very sensitive to chemoradiation therapy) are included. Our own institution's report showed excellent results for concurrent chemoradiation treatment; however, only 17 (15 percent) of 111 cases involved the oral cavity.[15]

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Regarding organ preservation protocols, excellent data exist for the larynx[16,17] and protocols exist for the base of the tongue, but no trials have been conducted for the oral cavity. The improvements seen in locoregional control with combined chemoradiation therapy are associated with higher morbidity.

EMERGING THERAPIES

New horizons in conventional therapy. Position emission tomography scanning appears to be most useful for identifying recurrent cancer after radiation therapy or chemotherapy.[18,19] Sentinel node biopsy has been used to diagnose melanoma and breast cancer, and, if successful in the head and neck, could prevent patients' having negative neck dissections.[20] Re-evaluation of the role of surgery for distant metastatic oral cancer has shown a possible role for excision of pulmonary metastases.[21] Finally, reirradiation in the head and neck is being investigated, mostly in the nasopharynx and larynx. However, although locoregional control has been improved, complication rates have increased with reirradiation.[22, 23]

New directions in experimental therapy. Sophisticated staining techniques have shown the presence of distant metastatic cells in the bone marrow in patients with early oral cancer. Thus, oral cancer may be a systemic disease from its onset—a revolutionary theory. Enormous strides in the study of molecular biology of cancer have revealed the genetic changes that occur when a benign cell transforms to oral cancer.[24] The accumulated molecular abnormalities (that is, molecular markers) that occur in oral cancer may provide prognostic data, allow selection of the most useful therapeutic modalities and provide targets for specific therapy (for example, gene therapy).[25]

Trials have been conducted of adenovirus transfected p53 gene injected into head and neck carcinomas containing mutant p53 to induce tumor cell apoptosis.[26] The entire field of apoptosis (that is, programmed cell death) provides an area for new anticancer therapies.[27] Research in the field of molecular biology has allowed a deeper understanding of carcinogenesis and opened up areas for experimental therapies. Another area of experimental interest is immunotherapy. Interleukin-2 has been used with some success in treating melanoma and renal carcinoma, but few trials in head and neck cancer have been conducted.[28]

COMPLICATIONS OF THERAPY

Mucositis is a common acute accompaniment of radiation therapy, chemotherapy and combined therapy. Extensive ulceration of the oral mucosa may cause difficulty in swallowing and pain and lead to interruption of treatment. Traditional symptomatic treatments involving viscous lido-

caine and coating agents provide some relief. A recent meta-analysis of prophylactic treatment for postradiation mucositis showed that narrow-spectrum antibacterial and antifungal agents appear to be efficacious.[29] In chemotherapy-induced mucositis, the stimulation of neutrophil recovery by granulocyte colony–stimulating factor may reduce the duration and extent of mucositis.[30]

Xerostomia remains a major quality-of-life problem for patients who have undergone radiation therapy or chemoradiation therapy, which usually causes difficulties in talking, swallowing and performing oral hygiene, as well as increased dental caries and ulceration. Clinicians may order publications and other materials to help patients with oral complications of cancer treatment from the National Oral Health Information Clearinghouse ("www.nohic.nidcr.nih.gov/cgi-bin/ohpubgen_new"). Virtually all of the artificial saliva products on the market provide only temporary relief. Most patients routinely carry a bottle of water to provide lubrication. The use of fluorides is critical for these patients.

Attempts at prophylaxis using parotid-sparing radiation fields, amifostine and pilocarpine during radiation therapy have been discussed. Unfortunately, a novel surgical approach of transposing the submandibular gland outside the field of radiation therapy does not seem appropriate for cancer of the oral cavity.[31]

COMPREHENSIVE DENTAL TREATMENT

The importance of receiving a comprehensive dental evaluation and treatment before cancer treatment is illustrated by osteoradionecrosis. All patients who are to receive chemoradiation therapy should have unsalvageable teeth removed, periodontal health maximized and fluoride therapy instituted. Osteoradionecrosis is a feared complication for patients, requiring tooth extraction after radiation therapy, and the risk does not appear to diminish with time. Concepts of reversing radiation-induced tissue damage by the use of hyperbaric oxygen, or HBO, therapy are based largely on the work of Marx.[32,33] Although nonsurgical therapy with HBO will help many patients who have osteoradionecrosis, mandibular resection and reconstruction frequently are required. All patients who require extraction of teeth in an irradiated field should be considered at risk of developing osteoradionecrosis. Prophylactic HBO therapy must be considered when appropriate.[34]

CONCLUSIONS

The mainstay of current therapy for oral cancer is surgery and radiation treatment. Advances in molecular biology have explained the genetic alterations that lead to development of carcinomas. This provides hope that targeted therapy will be possible in the future. Exciting challenges include improving success rates of current therapy, reducing the morbidity of treatment, and using molecular markers to predict tumor behavior and select the most appropriate treatment. The use of molecular markers in premalignant lesions will allow us to develop more specific diagnostic and preventive strategies. Today, our patients have a better quality of life and improved locoregional control. Tomorrow, our focus will be on using the continuing scientific and technological innovations to ultimately defeat this disease. ■

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