
ORAL CANCER BACKGROUND PAPERS

Chapter VII: Sequelae of Treatment

Working Draft

Introduction

Administration of cancer therapy is designed to eliminate or reduce tumor burden. A number of variables, including tumor cell kinetics, site of the tumor, and extent of tissue involvement affect outcome of such treatment. Depending on these and related variables, single or multi-modality therapy may be indicated. Principal forms of therapy include ionizing radiation, surgery, and chemotherapy.

Depending on the extent of the tumor, treatments may not be specific to the tumor; if they are not, normal tissue included within the surgical wound or rapidly replicating normal tissues can be profoundly affected. Injury can be either reversible or irreversible. Because oral epithelium is highly active tissue with replacement times estimated at 9-16 days, chemotherapy and radiation may be directly toxic to the oral mucosa, resulting in dysgeusia, extensive ulceration, pain, bleeding, and compromised normal function.^{1,2} The dental/periapical, periodontal, or salivary gland tissues may suffer acute injury. Radiotherapy can cause both serious destruction to bone and permanent salivary gland disturbances.³⁻⁵ Because the sequelae associated with cancer therapy may have a profound psychosocial impact on the patient, a multidisciplinary team approach that reviews all aspects of patient care is necessary.

A. State of the Science

Complications of therapy depend on the cancer treatment protocol of choice. Table 1 offers a selected list of oral sequelae associated with therapy.

Surgical Risks and Complications

Surgical management of intraoral lesions typically includes both the primary lesion and the cervical lymph nodes. Ideally, surgery is selected when permanent control of the tumor is likely. Staging of the patient is essential to determine whether surgery alone is indicated or whether radiation or chemotherapy is also needed.

The risks and sequelae of surgery develop directly from and are primarily based on the extent of the tumor and its relationship to contiguous oral structures. Sequelae may include disfigurement and compromise of vascularity and nerve tissue as well as gustatory, masticatory, speech, and swallowing functions (see Chapter VIII).

Table 1:
Selected List of Oral Sequelae Related to Treatment

<p>Surgery: Acute Sequelae functional disturbances speaking mastication swallowing vascular compromise</p>	<p>Ionizing Radiation: Chronic Sequelae salivary gland pathoses acute parotitis irreversible changes (flow rates, compositional alterations) dental alterations rampant caries demineralization osteoradionecrosis dysgeusia trismus laryngeal alterations</p>
<p>Surgery: Chronic Sequelae cosmetic alterations functional disturbances speaking mastication swallowing vascular compromise nerve damage muscular atrophy</p>	<p>Chemotherapy oral mucositis dysgeusia immune dysfunction dentition infections mucosa periodontium hemorrhage salivary dysfunction (variable)</p>
<p>Ionizing Radiation: Acute Sequelae salivary gland pathoses acute parotitis irreversible changes (flow rates, compositional alterations) oral mucositis infections mucosa periodontium dysgeusia</p>	

Risks and Sequelae of Radiation or Chemotherapy

Mucositis and Infection

Mucositis can be caused by either radiation or chemotherapy; the severity and extent of lesions are correlated with the treatment protocol being administered. Radiation-induced mucositis depends on absorbed radiation dose, fractionation, delivery modality, and soft tissue status. The patient may feel a mucosal “burning” sensation 1-2 weeks after initiation of therapy; the mucosa may be edematous and leukoplakic or erythematous on clinical examination. Depending on the intensity of the therapy and patient variables, extensive ulcerations may develop following initial clinical signs and symptoms. With chemotherapy, outcomes are specifically related to the pharmacologic class of drug selected as well as its dose concentration and the extent of neutrophil depletion or leukopenia.

Strategies for preventing mucositis are limited, but the problem can be partially minimized by fractionation techniques, shielding, and modifying modes of delivery. Supportive care for the acute

components of mucositis (bleeding, pain, and infection) is the mainstay of treatment. Although not directed principally at preventing mucositis, comprehensive oral care, including mechanical plaque removal supplemented by an antimicrobial rinse if indicated and frequent rinsing with saline bicarbonate solutions, can reduce the severity of secondary complications. Topical anesthetics or systemic analgesics are administered frequently for palliation of pain. Smoking can exacerbate mucositis; patients should be assisted with cessation using nicotine replacement therapy if indicated.⁶

Candidiasis is the most common oral infection during treatment for oral cancer, although other mycotic, bacterial, or viral infections are possible. Prophylactic or therapeutic topical and/or systemic antifungal agents are necessary to control candidiasis. Selection of an antifungal agent must consider the patient's degree of xerostomia and possible inability to dissolve a troche. Also of concern is the patient's level of oral hygiene and the risk associated with high levels of sucrose in topical preparations. The addition of chemotherapy to the treatment protocol may increase the severity of mucositis, xerostomia, and infection; it also increases the risk of bacterial and herpetic infections.

Because of the high probability of mucositis and infection, their potential severity, and their nutritional consequences, the radiation or chemotherapy patient needs comprehensive management protocols, particularly during periods of highest infection risk. Some cancer centers prescribe a "cocktail" preparation of antimicrobials, a steroid, a coating agent, and a topical anesthetic. However, the effectiveness of such preparations is empirically based and needs to be examined in a well-controlled clinical study.

Salivary Gland Dysfunction

Directing radiation therapy to the salivary glands or administering chemotherapeutic, antiemetic, or psychotropic drugs may alter salivary gland function. Chemotherapy does not typically cause chronic salivary gland changes; in contrast, high-dose ionizing radiation delivered to major glandular sites can cause permanent salivary gland dysfunction. The degree of oral dryness (xerostomia) will vary by the extent of salivary gland injury. These changes can exacerbate oral infection risk at various sites, including the mucosa and periodontium. Xerostomia may also affect mastication, speech, and the patient's overall quality of life.

Unfortunately, there are few effective preventive or palliative interventions for xerostomia. Frequent oral rinses with water or saline and commercial saliva substitutes may be minimally helpful, as may salivary stimulants such as sugarless candies and gum. Currently, no saliva substitute exists that can adequately replace the organic and biologic constituents of saliva. However, two studies⁷⁻⁹ that examined the effectiveness of oral pilocarpine as a sialogogue in irradiated patients with residual functional salivary gland tissue demonstrated its efficacy and safety; pilocarpine is now approved by the FDA for treating hyposalivation. However, the practitioner must be aware of its potential side effects and contraindications.

Symptoms of dry mouth do not necessarily correlate with quantitative or qualitative changes in saliva.

Some patients receiving high-dose radiotherapy to major salivary glands may experience reduced saliva production but perceive an improvement in function over time after cessation of therapy. Despite improvement in symptoms, however, saliva production in these patients may continue to be impaired, with reduced levels of antimicrobial proteins secreted.^{10,11} Thus, these patients will be at high risk for aggressive caries formation, demineralization, and periodontal disease for the balance of their lives. In addition, because mucous secretions from minor salivary glands are often unaffected, patients frequently complain of thick, ropery saliva. Comprehensive long-term preventive oral hygiene and dental follow-up are needed.^{12,13}

Dysgeusia

Both chemotherapy and radiation therapy patients can experience disturbances in taste. Mechanisms for this sensory disturbance are often complex and range from direct molecular effects on acinar cell function to conditioned aversions to selected foods. Compositional and/or flow rate changes in saliva may also contribute to the symptom, although underlying mechanisms are not clearly established.

Direct chemotherapy or radiotherapy injury to taste buds may produce partial (hypogeusia) or absolute (ageusia) taste loss. Taste buds may regenerate about 4 months after cessation of therapy, and normal taste function may resume. Given the complex interplay between physico-chemical and psychologic alterations, however, this recovery may not occur. Patients should be counseled as to realistic outcomes and give ongoing dietary consultation as well as programs to resolve food aversions that may have emerged during cancer therapy.¹⁴ High-dose zinc supplementation has helped some patients.

Nutritional Complications

Radiation, chemotherapy, or surgery can impair nutrition through a variety of mechanisms.¹⁵ Maintenance of appropriate levels of nutritional support is essential; indeed, many cancer patients are underweight at diagnosis and lose weight during therapy.

Nutritional complications stem from altered taste sensations, ageusia, anorexia, food aversion, pain, xerostomia, and dysphagia. Inadequate intake of calories leads to weight loss, weakness, and malaise.¹⁶ Tumor factors responsible for anorexia include direct tumor utilization of metabolites. Release by the tumor of chemical moieties that produce protein loss and negative nitrogen balance has also been hypothesized to contribute to cachexia.

Finally, nutritional complications may be caused by lack of access to appropriate reconstructive techniques and rehabilitation, leaving the patient without complete masticatory restoration.

Dental Caries and Periodontal Disease

Patients receiving adjuvant chemotherapy for management of disseminated oral cancer are not typically at high risk for chemotherapy-induced progressive compromise of the dentition and periodontium. However, the compliance of such patients with oral hygiene protocols and nutrition

guidelines may be deficient. Such limitations can produce extensive oral disease patterns.

Patients whose major and minor salivary glands have been exposed to therapeutic doses of ionizing radiation are at significant risk for progression of oral infections and demineralization, even if routine oral management strategies are utilized. Several covariates, including salivary function, nutrition, medications, parafunctional habits, tobacco habits, and compliance with comprehensive oral care protocols that include remineralizing solutions and fluoride use, collectively interact and produce either a stable or regressive oral disease profile. These diseases are caused by infecting pathogens, with consequences that include hard or soft oral tissue destruction, pain and bleeding, and systemic sequelae consistent with infection progression.

Osteoradionecrosis

Ionizing radiation can lead to osteoradionecrosis (ORN), a complication that results from compromised vascularity following surgery or from radiation-induced hypovascularity, as well as from cytotoxic effects on bone-forming cells and tissue, hypocellularity, and hypoxia of affected bone.¹⁷⁻²¹ The risk of ORN increases over time following completion of radiation dosing and is present through the lifespan. Complications associated with ORN include intractable pain, drug dependency, pathologic fractures, oral and cutaneous fistulas, and loss of large areas of bone and soft tissue.²²

The incidence of ORN is quite variable and depends mostly on the aggressiveness of radiation therapy; reported incidence ranges from 2% to 40%.¹⁷ Although trauma (e.g., dental extraction or scaling, denture irritation, periodontal disease) can initiate ORN, the etiologies of many cases are not identified. Managed unsuccessfully, ORN can have serious consequences, including progressive pain, trismus, and, eventually, loss of major segments of the jaw bone.

Ideal management of ORN calls for eliminating potentially riskful foci of oral disease prior to instituting radiation therapy. This approach requires a multidisciplinary team, which conducts comprehensive treatment planning well in advance of the cancer therapy. (See Table 2 for a list of evaluation and management issues.) Intact teeth can be preserved under certain conditions, such as when the patient is highly motivated toward maintaining ideal oral health and receiving comprehensive dental care. Conversely, compromised teeth in the poorly compliant patient should be extracted at least 10 days prior to radiation. However, the patient's disease state may change the timing of extraction.²³ Realistic clinical judgment combined with comprehensive management is the best tool for preventing osteoradionecrosis.

**Table 2: Evaluation and Management Issues
Prior to Surgery and Radiotherapy**

extraoral head and neck exam
complete intraoral exam
proposed surgical defects
radiographic evaluation
oral hygiene
previous dental or oral hygiene compliance
status of dentition and periodontium
temporomandibular dysfunction
parafunctional habits
baseline salivary flow
diet and medication analysis
tobacco and alcohol habits
psychosocial impact of treatment

Management of ORN with antibiotics and surgical debridement is not always successful. Courses of hyperbaric oxygen to facilitate healing of compromised bone may be helpful when combined with appropriate surgery and antibiotics. However, because this treatment is expensive and offered by only a limited number of facilities, many patients will not be able to take advantage of it.

Trismus Alterations

Ionizing radiation can also cause obliterative endoarteritis with associated tissue ischemia and fibrosis. This process can contribute to development of trismus if the masticatory muscles are within the portals of radiation. As treatment of trismus can be very difficult, preventive management with jaw exercises using tongue blades and other devices is recommended when signs of this disorder occur.

Psychosocial Impact

Functional and aesthetic changes may profoundly affect a patient's psychic and social status. The clinician should give these factors serious consideration in pre-treatment consultation and post-operative rehabilitation. Failure to do so may have critical consequences for the patient's later quality of life in socioeconomic areas as well as in personal relationships and lifestyles.²⁴

B. Emerging Trends

A number of emerging trends in the management of head and neck cancer may directly affect complications of therapy by altering treatment approaches in ways that will selectively protect normally functioning tissues. To assure effective use of new approaches, organizations such as the American Cancer Society (ACS) have for years promulgated the principle of multidisciplinary care for the cancer patient, including those with head and neck malignancies (see the discussion of

treatment and the multidisciplinary tumor board concept in Chapter VI).

C. Opportunities and Barriers to Progress

There are several approaches to improving the management of patients with oral cancer, including professional and public education, increased multidisciplinary management, and applied and laboratory-based research. However, the current situation is not promising because of:

- limited attention in medical, dental, dental hygiene, and nursing curricula to the oral complications of cancer therapy
- limited patient education about the need to comply with preventive or therapeutic oral interventions
- declining availability of both public and private research funding
- lack of trained basic and applied research directed specifically at management of oral complications.

Currently, there is a great need to develop tools to assess and prevent oral mucositis. Over the past 5 years, the standard for oral mucosa assessment tools has changed from a simplified, global scale to a more complex scale that assesses changes in multiple qualities of oral status that collectively contribute to mucositis severity. Future research must be directed to developing instruments that: (1) eliminate subjectivity in assessing and classifying oral complications; (2) measure oral toxicities with high degrees of specificity and sensitivity relative to the pathologic process under investigation; (3) take little time and are cost-effective to administer; and (4) can be tolerated by the patient with severe mucositis. Such instruments are essential to assess whether new technologies can reduce the severity of radiation- or chemotherapy-induced mucositis.

At present, clinical studies are needed to develop mechanisms for increasing patient compliance with recommended long-term care and preventive measures. The effect that cultural, sociologic, and psychologic factors have on compliance also needs investigation (see Chapter IX).

Current deficits in professional knowledge frequently stem from a failure to understand that communication between the medical and dental teams is essential. Although some cancer centers have integrated medical, nursing, dental, and dental hygiene management of the patient, a number of university-based and most community-based oncology programs have not done so. Yet, the complex management of the oral cancer patient mandates multidisciplinary care; unless the relevant professional groups communicate successfully, patient care may suffer.

More research on managing the patient with mucositis and xerostomia is also needed. Protocols to manage mucositis should be tested in clinical studies. Additional research is also needed on slow-release techniques for the drug oral pilocarpine that might minimize its side effects while maximizing its therapeutic effect.

Long-term studies are also needed to evaluate reconstructive techniques, including their effect on dental function, to prevent nutritional complications and ensure full rehabilitation (see Chapter VIII).

Finally, outcome assessments are necessary to evaluate the impact of treatment and non-treatment on long-term results and quality of life. Information from these assessments will be useful in allocating research dollars and establishing protocols for care.

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