Stereotactic Body Radiotherapy Treatment for Head and Neck Cancer

I. Introduction

This white paper will focus on the definition, epidemiology, diagnosis, staging and treatment of head and neck cancers with sections I – VIII comprising a general view of head and neck cancer from the National Cancer Institute (more information can be found at www.cancer.gov). Sections IX and X (available to society members only) will provide a literature review on stereotactic body radiotherapy (SBRT) for head and neck cancer.

II. Definition of Head and Neck Cancer

Head and neck cancer encompasses several forms of the disease including cancers of the mouth, nasal cavity, sinuses, salivary gland, throat, pharynx, larynx, and lymph nodes of the neck. Most head and neck cancers begin in the cells that line the mucosal surfaces in the head and neck area. Mucosal surfaces are moist tissues lining hollow organs and cavities of the body open to the environment. Most head and neck cancers are squamous cell carcinomas. Some head and neck cancers begin in other types of cells which are further defined below.

Cancers of the head and neck are identified by the area in which the tumors originate:

- **Oral cavity.** The oral cavity includes the lips, the front two-thirds of the tongue, the gingiva (gums), the buccal mucosa (lining inside the cheeks and lips), the floor (bottom) of the mouth under the tongue, the hard palate (bony top of the mouth), and the small area behind the wisdom teeth.

- **Salivary glands.** The salivary glands produce saliva, the fluid that keeps mucosal surfaces in the mouth and throat moist.

- **Paranasal sinuses and nasal cavity.** The paranasal sinuses are small hollow spaces in the bones of the head surrounding the nose. The nasal cavity is the hollow space inside the nose.

- **Pharynx.** The pharynx is a hollow tube about five inches long that starts behind the nose and leads to the esophagus (the tube that goes to the stomach) and the trachea (the tube that goes to the lungs). The pharynx has three parts:
  - Nasopharynx. Involves the upper part of the pharynx and is located behind the nose.
o Oropharynx. The oropharynx is the middle part of the pharynx. The oropharynx includes the soft palate, the base of the tongue, and the tonsils. These structures play an essential role in swallowing and speech.

o Hypopharynx. The hypopharynx is the lower part of the pharynx. It extends from the hyoid bone superiorly to the cricoids inferiorly. It is divided into three components: the pharyngeal walls, pyriform sinus, and postcricoid pharynx.

- Larynx. The larynx, also called the voicebox, is a short passageway formed by cartilage just below the pharynx in the neck. The larynx contains the vocal cords. It also has a small piece of tissue, called the epiglottis, which moves to cover the larynx to prevent food from entering the air passages.

- Lymph nodes in the upper part of the neck.

Cancers of the brain, eye, and thyroid as well as those of the scalp, skin, muscles, and bones of the head and neck are not usually grouped with cancers of the head and neck.

### III. Epidemiology and Etiology

Head and neck cancer is the eighth most common cancer worldwide, with 481,000 new cases estimated in 2008, and the sixth most common cause of death from cancer with 406,000 deaths worldwide. [1] More than 80% of the cases and of the deaths occur in developing countries, with South Africa and Eastern Asia having the highest incidence and mortality rates for both sexes worldwide. Head and neck cancer is two to four times more common among men than women.

In the United States, head and neck cancers account for approximately 3 to 5 percent of all cancers. [2, 3] These cancers are more common in men and in people over age 50. It is estimated that 36,540 men and women (25,420 men and 11,120 women) will be diagnosed with cancers of the oral cavity and pharynx and 7,880 men and women will die of the disease in 2010. Oral cavity cancer is the most common form of head and neck cancer with approximately 5,490 males and 4,790 females diagnosed in the United States. Cancers originating in the salivary gland, nasal cavity, and pharynx are less common and incidence rates vary geographically. For example, cancers in the nasopharynx are uncommon in the United States, occurring at a rate of 0.2 to 0.5 cases/100,000 people, while the incidence of nasopharyngeal carcinoma is considerably greater in southern China and Hong Kong (25 to 50 cases/100,000 people) and southeast Asia, Philippines, and Malaysia. [4] Hypopharyngeal carcinoma is also uncommon in the United States with approximately 2,500 new cases in the each year. [2, 3] The peak incidence of this cancer occurs in males and females aged 50 to 60 years. Laryngeal cancer accounts for approximately one quarter to one third of all head and neck cases [2, 3]. In the United States, approximately 12,720 men and
women (10,110 men and 2,610 women) will be diagnosed with cancer of the larynx and 3,600 men and women will die of this disease each year. Larynx cancer remains predominantly a disease affecting older men and persons using tobacco and alcohol. [5] With the increase of tobacco use in women, the incidence of cancer of larynx in women is also increasing. [6]

Significant risk factors for head and neck cancer include tobacco (including smokeless tobacco) and alcohol, particularly for cancers of the oral cavity, oropharynx, hypopharynx, and larynx. Eighty-five percent of head and neck cancers are linked to tobacco use. [3] People who use both tobacco and alcohol are at greater risk for developing these cancers than people who use either tobacco or alcohol alone. [7]

Other risk factors for cancers of the head and neck include the following:

- Oral cavity. Sun exposure (lip); possibly human papillomavirus (HPV) infection, poor dental and oral hygiene.
- Salivary glands. Radiation to the head and neck. This exposure can come from diagnostic x-rays or from radiation therapy for noncancerous conditions or cancer.
- Paranasal sinuses and nasal cavity. Certain industrial exposures, such as wood or nickel dust inhalation. Tobacco and alcohol use may play less of a role in this type of cancer.
- Nasopharynx. Epstein-Barr virus (EBV) infection; occupational exposure to wood dust; and consumption of certain preservatives or salted foods.
- Oropharynx. HPV-16 infection, poor oral hygiene, and use of mouthwash that has a high alcohol content are possible, but not proven, risk factors.
- Hypopharynx. Plummer-Vinson (also called Paterson-Kelly) syndrome, a rare disorder that results from iron and other nutritional deficiencies. This syndrome is characterized by severe anemia and leads to difficulty swallowing due to webs of tissue that grow across the upper part of the esophagus.
- Larynx. Exposure to airborne particles of asbestos, especially in the workplace.

Immigrants from Southeast Asia who use paan (betel quid) in the mouth should be aware that this habit has been strongly associated with an increased risk for oral cancer. [8] Also, consumption of mate, a tea-like beverage habitually consumed by South Americans, has been associated with an increased risk of cancers of the mouth, throat, esophagus, and larynx. [9]
IV. Clinical Symptoms and Patient Evaluations

Oral cavity lesions commonly present with leukoplakia (white patches) in the mouth or lip. Other symptoms may include ulcers in the mouth or lip, difficulty in swallowing, neck mass, local pain, or pain that radiates to the ear. Intermittent bleeding may occur when the lesions are irritated by chewing. Patients with tongue carcinoma usually present with a sense of tongue irritation or of a mass in the tongue. Deep infiltration may affect speech or swallowing and advanced ulcerative lesions are often associated with odor and pain. Carcinoma of the lip usually presents as a slow enlarging exophytic lesion with an elevated border. Occasionally, there may be minor bleeding. Numbness of the skin may indicate perineural invasion.

Tumors in the nasal cavity often present as asymptomatic plaques or nodules. Chronic lesions may be associated with pain, obstruction, unilateral nasal discharge, bleeding, headaches, tenderness, and swelling. Advanced lesions extending into deep muscle and bone and nerve involvement may be accompanied by pain and bleeding. Maxillary cancers are usually diagnosed at advanced stages and signs and symptoms related to disease extension to the premaxillary area can include facial swelling, pain or numbness of the check.

Oropharyngeal tumors are relatively asymptomatic in the early stages, but patients may present with localized pain or pain that radiates to the ear. An asymptomatic neck mass is also an initial sign of disease. Tongue based cancers generally cannot be visualized directly which can lead to a delay in diagnosis. Patients with advanced stage disease can present with trismus, odor, dysphagia and dysarthria.

Patients with nasopharyngeal cancer typically present with multiple symptoms. In a series of 378 patients from the MD Anderson Cancer Center (MDACC), the presenting symptoms included neck mass, hearing loss, ear drainage, nasal bleeding and obstruction, cranial nerve deficits, and enlarged lymph nodes. [10] Nasopharyngeal cancer can frequently spread to the base of the skull and extension of tumors superior to the nasopharynx. Tumor invasion of critical structures were cranial nerves exit the base of the skull can lead to clinical symptoms. In the MDACC study, the most frequently involved cranial nerves were cranial nerve VI, V (trigeminal), VIII, X, and XII. Lateral extension of nasopharyngeal tumors can lead to erosion of the opening of the auditory canal, carotid artery, and internal jugular vein. Lymph node involvement is also common in nasopharyngeal carcinoma with 65% to 80% of patients presenting with clinically involved cervical neck lymph nodes. [10-12]

Patients with hypopharyngeal cancer typically present with throat pain with or without otalgia. Other symptoms can include dysphagia, weight loss, and/or hoarseness. If there is presence of lymph node involvement, patients with hypopharyngeal carcinoma can occasionally present with asymptomatic neck masses.
Hoarseness is the main presenting symptom in patients with laryngeal carcinoma. Patients with neglected advanced disease can also present with airway obstruction, pain or dysphagia. Recurrent laryngeal nerve involvement may cause local pain or otalgia.

The initial evaluation of patients with head and neck tumors generally includes a history and physical examination. Lab studies, including complete blood counts, chemistry panel and urinalysis are typically performed. Patients may undergo an endoscope to assess the tumor size, morphology and infiltration of adjacent structures. Examination of the neck is important to detect neck lymphadenopathy or direct tumor extension.

Biopsy of the primary lesion is typically done to determine the exact pathology classification. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck are useful in evaluation of both erosion of the tumor into the bony structures of the base of the skull, invasion into soft tissue, and lymph node involvement. Positron emission tomography (PET) can be useful, particularly in the evaluation of possible recurrence after radiotherapy and can be useful for radiotherapy planning. Further evaluation of possible metastasis is done on the basis of the clinical presentation.

V. Cellular Classification

Cellular classification of head and neck cancers is defined by the tumor origin. Most head and neck cancers are of the squamous cell type, but tumors can form from other cell types. Description of the various tumor types for each head and neck cancer are discussed below.

- Oral cavity. Most oral cancers are of the squamous cell type and may be preceded by precursor lesions.
- Salivary gland. More than 50% of salivary gland lesions are benign, and approximately 70% to 80% of all salivary gland neoplasms originate in the parotid gland. [13, 14] The palate is the most common site of minor salivary gland tumors. The frequency of malignant lesions varies by site, which consists of approximately 20% to 25% of parotid tumors, 35% to 40% of submandibular tumors, 50% of palate tumors, and more than 90% of sublingual gland tumors. Histologically, salivary gland tumors represent the most heterogeneous group of tumors of any tissue in the body. [15] Although almost 40 histologic types of epithelial tumors of the salivary glands exist, some are exceedingly rare and may be the subject of only a few case reports. [16] The most common benign salivary gland tumor is the pleomorphic adenoma, which comprises about 50% of all salivary gland tumors and 65% of parotid gland tumors. The most common malignant salivary gland tumor is the mucoepidermoid carcinoma. [17]
- Paranasal sinus and nasal cavity. Cancers of the maxillary sinus are the most common of the paranasal sinus cancers. [18, 19] Tumors of the ethmoid sinuses, nasal vestibule,
and nasal cavity are less common, and tumors of the sphenoid and frontal sinuses are rare. Squamous cell carcinoma (SCC) is the most frequent cell type of malignant tumor in the nose and paranasal sinuses (70%–80%). Malignant melanoma presents in <1% of neoplasms in this region. Some 5% of cases are malignant lymphomas. [20]

- Nasopharynx. Squamous cell carcinoma is the most common cell type of nasopharyngeal neoplasms. [21] Subdivisions of squamous cell carcinoma in this site include lymphoepithelioma (Schminke tumor), transitional cell tumors, and well to poorly differentiated grade keratinizing or nonkeratinizing varieties. The presence of keratin has been associated with reduced local control and survival.

- Oropharynx. Most oropharyngeal tumors are the squamous cell type. Other forms include minor salivary gland, lymphoma, and lymphoepitheliomas (e.g., tonsillar fossa).

- Hypopharynx. Almost all hypopharyngeal cancers are mucosal squamous cell carcinomas. Multiple primary tumors are not uncommon.

- Larynx. The majority of cancers of the larynx are of squamous cell histology. Squamous cell subtypes include keratinizing and nonkeratinizing and well-differentiated to poorly differentiated grade. A variety of nonsquamous cell laryngeal cancers also occur.

VI. Staging

The staging systems for head and neck cancer are all clinical staging and are based on the best possible estimate of the extent of disease before treatment. The initial assessment of the primary tumor is based on inspection and palpation. Biopsy of the tumor is required for histological confirmation and appropriate lymph node areas are examined by careful palpation. Information from diagnostic imaging studies may be used in staging. Magnetic resonance imaging offers an advantage over computed tomographic scans in the detection and localization of head and neck tumors and in the distinction of lymph nodes from blood vessels. If a patient relapses, complete restaging must be done to select the appropriate additional therapy. The American Joint Commission on Cancer (AJCC) has defined specific TNM staging criteria for head and neck tumors based on location of the tumor origin. These include staging criteria specific for lip and oral cavity, salivary gland, maxillary sinus, nasal sinus, oropharynx, nasopharynx, hypopharynx, and larynx. Lymph node (N) and metastasis (M) staging use common definitions for each type of head and neck cancer. The definitions for T stage for the various types of head and neck cancers differ and may involve tumor size, tumor characteristics, and disease extension. A brief summary of T staging for lesions of the oral cavity, paranasal sinuses and nasal cavity, oropharynx, nasopharynx, hypopharynx and larynx is listed below:
• **Oral Cavity.** T staging for oral cavity primary tumors is based primarily on tumor size. T1 lesions are ≤ 2 cm, T2 lesions are less than 2 cm but not greater than 4 cm, and T3 lesions are > 4 cm. T4 lesions of the lip are defined as tumors that invade through the cortical bone, inferior alveolar nerve, floor of mouth, or skin of the face. T4 lesions of the oral cavity are defined as tumors that invade through the cortical bone into deep muscle of the tongue, maxillary sinus, or skin of the face. T4b lesions involve the masticator space, pterygoid plate, or skull base and/or encase the internal carotid artery.

• **Paranasal Sinuses and Nasal Cavity.** T staging for paranasal sinuses and nasal cavity is defined by extension of the disease, with specific attention to invasion to bone, but not tumor size. For maxillary sinus lesions, T1 disease is limited to the mucosa with no erosion or bone disease. T2 maxillary sinus lesions involve bone erosion or destruction including extension into the hard palate/or middle of the nasal meatus. For nasal cavity and ethmoid sinus, T1 lesions are restricted to one site and may involve bony invasion. T2 lesions invade two subsites with or without bony invasion. T3 disease extends into any of the following structures: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of the orbit, pterygoid fossa, or ethmoid sinuses. T4 maxillary sinus tumors are divided into T4a (resectable) and T4b (unresectable) lesions. Generally the incidence of lymph node involvement is relatively uncommon at diagnosis.

• **Nasopharynx.** Staging and prognostic significance of the staging of nasopharyngeal cancer are complex. For most nasopharyngeal cancers, there is a high incidence of lymph node involvement and clinically involved neck disease. Several staging systems have been implemented and revised to improve risk stratification and to better predict prognosis. The AJCC staging system is widely used for nasopharyngeal cancer and has revised both T and N stage definitions. To summarize, T1 lesions are confined to the nasopharynx, T2 lesions involve soft tissue invasion, T3 lesions extend into bony or paranasal sinus, and T4 lesions include intracranial extension or cranial nerve or infratemporal fossa, hypopharynx, or orbital involvement. For lymph node staging, N1 is defined as unilateral involvement ≤ 6 cm, N2 is bilateral ≤ 6 cm, N3a is > 6 cm, and N3b includes supravacular involvement. Further refinement of the AJCC staging may occur to improve risk stratification and in the future biological assays may be incorporated to assess risk.

• **Oropharynx.** T staging for oropharyngeal tumors is based on primary tumor size. T1 lesions are ≤ 2 cm, T2 lesions are greater than 2 cm but not greater than 4 cm, and T3 lesions are > 4 cm. Lesions classified as T4a include invasion into the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible. Lesions
classified as T4b include invasion into lateral pterygoid muscle or plates, lateral nasopharynx, or skull base or encase the carotid artery.

- **Hypopharynx.** T staging for hypopharyngeal tumors is based on tumor size, sites of involvement, and larynx motion, an indirect measurement of disease extension. T staging of hypopharyngeal cancer does not reflect tumor morphology, although tumor morphology is frequently used for basis of treatment decision for organ vs. non-organ preserving therapies. For advanced T4 lesions, two subcategories are included to describe tumor invasion beyond the hypopharynx. T4a disease can invade the thyroid or cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue. T4b disease invades prevertebral fascia, encases the carotid artery, or involves mediastinal structures.

- **Larynx.** The AJCC system stages larynx cancer primary tumors by the sites of extension and vocal cord mobility, but not size. For glottic tumors, stage T1 is disease limited to the vocal cords. T1 staging is further defined by presence of disease in one or two vocal cords. T2 glottic tumors have supraglottic or subglottic extension and/or impaired mobility. T3 lesions have disease limited to the larynx with vocal cord fixation or invasion of paraglottic or minor thyroid cartilage invasion. T4 disease is subdivided into T4a (resectable) with tumor invading through the thyroid cartilage and/or invading tissues beyond the larynx and T4b (unresectable) is tumor invading prevertebral space, encasing the carotid artery, or invading mediastinal structures.

**VII. Treatment Options for Primary Therapy for Head and Neck Cancer**

The treatment plan for an individual patient depends on a number of factors, including the exact location of the tumor, the stage of the cancer, and the person's age and general health. In general, single-modality treatment with surgery or radiotherapy is generally recommended for the approximately 30% to 40% of patients who present with early-stage disease (stage I or II). [22] The two modalities result in similar survival in these individuals. In contrast, combined modality therapy is generally recommended for the approximately 60% of patients with locally or regionally advanced disease at diagnosis.

**a. Surgery**

Surgery has been shown to be a single modality treatment option for selective patients with head and neck tumors. [22] For early stage oral cavity lesions (T1 and T2) surgical excision can achieve excellent local control and survival (85-90%). [23] Surgery must adequately encompass the gross tumor as well as the presumed microscopic extent of the disease. If regional nodes are positive, cervical node dissection is typically performed. With modern approaches, the surgeon can
successfully ablate large posterior oral cavity tumors and with reconstructive methods can achieve satisfactory functional results.

Early lesions (T1) of the anterior tongue may also be managed by surgery or by radiation therapy alone. Both modalities produce 70% to 85% cure rates in early lesions. [24] Moderate excisions of tongue can often result in little speech disability. More extensive surgical approaches may result in complications, including aspiration of liquids and solids and difficulty in swallowing in addition to speech difficulties. Large lesions generally require combined surgical and radiation treatment. The control rates for larger lesions are about 30% to 40%. More advanced lesions may require segmental bone resection, hemimandibulectomy, or maxillectomy, depending on the extent of the lesion and its location.

Early lesions of the upper gingiva or hard palate without bone involvement can be treated with equal effectiveness by surgery or by radiation therapy alone. [23] Advanced infiltrative and ulcerating lesions should be treated by a combination of radiation therapy and surgery. Most primary cancers of the hard palate are of minor salivary gland origin. Surgical treatment of cancer of the hard palate may require excision of underlying bone producing an opening into the antrum. This defect can be filled and covered with a dental prosthesis, and can result in satisfactory swallowing and speech.

Treatment of small T1 laryngeal tumors can also be effectively treated with laser excision, laryngo-fissure or partial laryngectomy. An important factor in selecting therapy for patients is the anticipated voice quality after therapy.

The accepted method of treatment for tumors of the nasal cavity is a combination of radiation therapy and surgery. For patients with operable tumors, radical surgery is generally performed first to remove the bulk of the tumor and to establish drainage of the affected sinus(es). This is followed by postoperative radiation therapy.

Cervical lymph node dissection may be incorporated in the surgical management of head and neck tumors. The National Comprehensive Cancer Network (NCCN) guidelines classify cervical lymph node dissection as either comprehensive (historically known as radical dissection) or selective (a less radical procedure preserving the sternocleidomastoid muscle, jugular vein, spinal accessory nerve, or selective lymph node levels). The chief role for selective cervical lymph node dissection is to select patients for possible adjuvant therapy, although it may be used as a treatment when tumor burden is low. Patients with cervical lymph node metastases who undergo surgical operations with therapeutic intent typically undergo comprehensive lymph node dissection.
It is particularly important for patients treated surgically to have careful and regular follow-up examinations by a head and neck surgical oncologist so that any local or regional recurrence is detected early and salvage surgery, radiation therapy, or chemoradiation can be performed.

b. Radiation Therapy

Radiation therapy is used as both a single modality treatment option for selective head and neck tumors, and in combination with surgery and chemotherapy for more locally advanced and regional disease. Selection of radiation total dose depends on the primary tumor and lymph node involvement, fractionation schedule, and clinical circumstances, including whether to use concurrent chemotherapy. In general, the primary tumor and gross adenopathy require a total of 66 to 74 Gy (2.0 Gy/fraction) and up to 81.6 Gy (1.2 Gy/fraction). [22, 23] External radiation doses exceeding 75 Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury. In contrast, elective irradiation to low- and intermediate-risk nodal regions in the neck requires 44 to 64 Gy, depending on the estimated level of tumor burden and fraction size. Postoperative radiation therapy is recommended based on stage, histology, and surgical/pathologic findings. In general, postoperative radiotherapy is recommended for selected risk factors, including advanced T stage, depth of invasion, multiple positive nodes, or perineural/lymphatic/vascular invasion. Higher doses of radiation alone (60–66 Gy) or radiation with chemotherapy are recommended for the high-risk disease, including extracapsular extension or positive surgical margins. The preferred interval between surgery and commencement of postoperative radiotherapy is typically six weeks or less.

Nasopharyngeal cancers traditionally have not been treated with surgery due to difficulty of exposing the area and resecting the tumor with adequate surgical margins. [25] Radiation therapy and chemoradiotherapy are generally the main treatment option for nasopharyngeal cancers. MD Anderson Cancer Center investigated the long-term outcome of patients with nasopharyngeal cancer treated with radiotherapy alone. Five-year local control rates for T1, T2, T3 and T4 stages were 93%, 79%, 68%, and 53% respectively.[10] Advanced stage, squamous histology, and cranial nerve deficits were predictive of poor prognosis for local control. Other studies have shown that the incidence of local failure for advanced nasopharyngeal carcinoma after conventional radiation ranges from 26 – 100%. [10, 26] Increased radiation doses and brachytherapy boost can improve local control rates, however concerns of normal tissue injury and the ability to effectively treat tumors involving the skull base are limitations.
The recent development of intensity modified radiation therapy (IMRT) devices make it possible to deliver highly conformal radiotherapy for head and neck cancers, as is the case in central nervous system tumors. IMRT is typically delivered with conventional fractionation (30 - 35 fractions) for a total dose of 60-70 Gy delivered over 6-7 weeks.[27] The most common acute side effects include dysphagia, xerostomia, dermatitis and pain. Significant late side effects may include xerostomia, dysphagia, hearing loss, skin fibrosis and radiation-induced necrosis. IMRT is becoming more widely used for the treatment of head and neck cancer. It is useful in reducing long-term toxicity in oropharyngeal and nasopharyngeal cancers, by reducing the dose to salivary glands, temporal lobes, mandible, auditory structures and optic structures.

There are very few randomized clinical trials comparing IMRT and conformal radiation therapy (CRT). In the PARSPORT study, 94 patients with oropharyngeal or hypopharyngeal carcinoma were randomized to either CRT or IMRT (60-65 Gy delivered in 30 fractions).[28] The primary endpoint was incidence of Grade 2 or higher xerostomia after one year. Eighty-three percent of patients treated with CRT had RTOG grade 2 or higher xerostomia compared to 29% of patients treated with CRT two years after treatment. One year after treatment, no differences were observed in local control or overall survival between the two arms.

In two other randomized studies comparing CRT vs. IMRT for nasopharyngeal carcinoma, IMRT patients had decreased late effects with parotid gland sparing and better quality of life compared to patients treated with CRT.[29, 30] As discussed in the review by J. Thariat et al. other advantages of IMRT for treating head and neck cancer may include the ability of IMRT to spare the pharyngeal constrictor muscles thus decreasing acute and late radiation-induced dysphagia, and sparing dose to the cochlea, resulting in decreased radiation-induced hearing loss.[27] In theory, IMRT should have an advantage over CRT because it is more conformal and therefore may have better tumor coverage and dose escalation.

Altered Fractionation Schemes

To improve clinical outcomes, while maintaining acceptable toxicities, several approaches to altered fractionated radiation therapy treatment schemes have been explored. Altered fractionated radiation aims to increase the dose intensity of radiation by delivering a total dose as high as possible in a shorter period of time. This increased dose intensity of radiation can be obtained either by increasing the total dose and/or decreasing the overall time compared with the dose and schedule for conventional radiation. Several studies have shown increased local control rates for head and neck tumors with altered fractionation schemes, but no single fractionation scheme has shown to be beneficial for all tumor types.
Two large, randomized clinical trials from Europe have reported improved loco-regional control using altered fractionation. The EORTC protocol 22791 compared hyperfractionation (1.15 Gy twice daily, or 80.5 Gy over 7 weeks) with conventional fractionation (2 Gy once daily, or 70 Gy over 7 weeks) in the treatment of T2-T3, N0–1 oropharyngeal carcinoma excluding base of tongue primaries.[31] At five years, a statistically significant increase was seen in local control in the hyperfractionation arm (38% vs. 56%) and no increase in late complications. A long-term follow-up analysis has also shown a small survival advantage for hyperfractionation. Another EORTC protocol (22851) compared accelerated fractionation (1.6 Gy 3 times daily, or 72 Gy over 5 weeks) with conventional fractionation (1.8–2.0 Gy once daily, or 70 Gy over 7–8 weeks) in intermediate to advanced head and neck cancer (excluding cancers of the hypopharynx).[32] Patients in the accelerated fractionation arm had significantly better loco-regional control (13% gain) at five years. Disease-specific survival showed a trend favoring the accelerated fractionation arm. Acute and late toxicities were increased with acceleration, with 14% of patients in the accelerated arm reporting late severe irradiation damage compared to 4% in the conventional arm, thus questioning the safety of the accelerated arm.

The GORTEC trial randomized 268 patients to either 70 Gy at 2 Gy per fraction over 49 days or 62-64 Gy in 31-32 fractions delivered at 2 Gy per fraction twice a day (accelerated fractionation).[33] The loco-regional control rate was more favorable in the accelerated arm, with a 24% improvement at two years that was maintained through five years. Progression-free survival and overall survival were not significantly different between the two arms. Acute mucositis was more severe and prolonged in the accelerated treatment arm and there were no differences in the late complications between the two arms.

The RTOG 90-03 study compared standard fractionation, hyperfractionation and accelerated fractionation schemes in head and neck cancers.[34] Over 1000 patients were randomized to either standard fractionation (70 Gy delivered at 2 Gy/fraction in 35 fractions), hyperfractionation (81.6 Gy delivered at 1.2 Gy/fraction in 68 fractions), accelerated fractionation with concomitant boost (72 Gy given as 54 Gy delivered at 1.8 Gy/fraction for 30 fractions plus 18 Gy delivered at 1.5 Gy/fraction for 12 fractions), and split accelerated fractionation regimens. This study demonstrated a local tumor control advantage of about 8% for both accelerated and hyperfractionated regimens compared to standard fractionation. Neither progression-free survival nor overall survival and disease-free survival were significantly improved. Acute side effects, primarily mucositis, were more prevalent in the altered fractionation schemes.
A group in Osaka, Japan, randomized 180 patients with T1 glottic tumors to either 60 – 66 Gy delivered at 2 Gy per fraction or 56.25 – 63 Gy delivered at 2.25 Gy per fraction.[35] The five-year local control rate was significantly higher in the 2.25 Gy per fraction arm (92%) vs the 2 Gy per fraction arm (77%). There was no difference in disease-specific survival between the two arms and no differences in minor late toxicities. No severe late toxicities were reported. Together these studies demonstrate that altered fractionation schemes can increase local control rates with acceptable toxicities; however overall and disease-specific survivals were not significantly impacted.

**External beam radiation with brachytherapy boost**

Several studies have shown increased local control of head and neck tumors when treating patients with conventional radiation plus a brachytherapy boost. Brachytherapy allows to safely boost regions of tumor involvement with higher doses of radiation while sparing normal tissues. Wang et al. compared external beam radiation with and without brachytherapy boost in patients with T1-T3 nasopharyngeal carcinoma treated at Massachusetts General Hospital.[36] The five-year local control rate was 91% for patients receiving the brachytherapy boost compared to 60% local control for patients treated with external beam radiation alone. Levendag et al. also showed increased 3-year local control in head and neck patients with locally advanced disease treated with combined external beam plus brachytherapy boost compared to radiation alone (86% vs. 60%, respectively).[37] These studies demonstrate that the addition of a brachytherapy boost can result in superior local control rates.

Advanced cancers (stage III and stage IV) of the head and neck represent a wide spectrum of challenges for the surgeon and radiation oncologist. Most patients with stage III or stage IV tumors are candidates for treatment by a combination of surgery and radiation therapy. Furthermore, because local recurrence and/or distant metastases are common in this group of patients (30-50%), they should be considered for clinical trials.[22, 25] Such trials evaluate the potential role of radiation modifiers or combination chemotherapy combined with surgery and/or radiation therapy.

c. **Chemotherapy**

Chemotherapy has been combined with radiation therapy in patients who have locally advanced, unresectable head and neck oral cancers. No consensus exists regarding the optimal radiation dose-fractionation scheme when administered with concurrent chemotherapy. Most published studies have used conventional fractionation at 2.0 Gy per fraction to 70 Gy or more in seven weeks with single-agent cisplatin. Other clinical trials have evaluated various dose and fractionation schedules, altered dosing...
schedules of cisplatin, other single agents, and multi-agent chemotherapy alone or in combination with radiation. A meta-analysis of 63 randomized prospective trials published between 1965 and 1993 showed an 8% absolute survival advantage in the subset of patients receiving concomitant chemotherapy and radiation therapy.[38] The best chemotherapy to use and the appropriate way to integrate the two modalities is still unresolved.[39] The NCCN recommends that clinical trials for advanced tumors evaluating the use of chemotherapy preoperatively, before radiation therapy, or as adjuvant therapy after surgery are appropriate.

VIII. Treatment for Recurrent Head and Neck Cancer

Salvage treatment for local failure of head and neck cancer is difficult due numerous factors including the deep-seated location of the tumor, proximity of the recurrence to critical structures and the high radiation dose used in the primary treatment. Surgery may not be an option because of the extent of the disease or involvement of the critical structure. Chemotherapy is widely used for palliation for patients with unresectable, recurrent disease, but response rates are < 50% with median survival time of 5-6 months.[40] Brachytherapy may be considered if surgery is not an option, however brachytherapy is an invasive procedure requiring anesthesia. Brachytherapy may be limited to patients with superficial and minor recurrence. It is generally not used for recurrences involving deep tissues and the skull base.

The retreatment of nasopharyngeal carcinoma with radiation after prior radiation is well documented. Wang et al. compared survival rates of 51 previously irradiated patients treated for recurrent disease who received a radiation dose of less than 60 Gy or greater than 60 Gy. The 5-year survival rate for patients treated with greater than 60 Gy was 45% compared to 0% in patients that were treated with < 60 Gy.[41] Lee et al. treated 105 patients with two-year overall survival and disease-free survival rates of 37% and 42%, respectively. Acute and late grade 3-4 toxicities were reported in 23% and 15% of patients, respectively.[42] Chang et al. reported on 186 patients who developed a local recurrence of the nasopharynx and retreated with radiation.[43] The one-, three- and five-year survival rate was 54.9%, 22.1% and 12.4%, respectively and a retreatment dose ≥ 50 Gy yielded better survival. Late complication rates were significantly decreased in patients treated with CRT (9%) compared to conventional radiation (22.9%). Dawson et al. delivered 60 Gy using three dimensional conformal radiation therapy (3DCRT) to previously irradiated patients with recurrent disease and achieved a 2-year overall survival rate of 32.6%, with 18% of patients experiencing severe radiation complications.[44] More recent data using IMRT techniques have shown improved local control rates. Lu et al. treated 49 patients with IMRT and reported a local control rate of 100% with a median follow up of 9 months. Although the follow up period was short, these results are encouraging.[45]
Koutcher et al. treated patients previously irradiated with recurrent nasopharyngeal carcinoma using IMRT with and without a brachytherapy boost and reported 5-year local control and overall survival rates of 52% and 60%, respectively.[46] They also demonstrated that late complication rates were significantly reduced in patients treated with IMRT plus brachytherapy (8%) compared to IMRT alone (73%), even though the dose was 14.4 Gy lower in the combined arm. This study demonstrates that high doses of radiation delivered as a boost is safe and results in improved local control and survival rates for patients with recurrent head and neck cancer.
References


