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 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 anterior 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.

- 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.

- 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] These cancers are more common in men and in people over age 50. It is estimated that 41380 men and women (29620 men and 11780women) will be diagnosed with cancers of the oral cavity and pharynx and 7,890 men and women will die of the disease in 2013.[3] Oral cavity cancer is the most common form of head and neck cancer with approximately 18,420 males and 9030 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] Laryngeal cancer accounts for approximately one quarter to one third of all head and neck cases. In the United States, approximately 12,260 men and women (9680 men and 2,580 women) will be diagnosed with cancer of the larynx and 3,630 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] While the incidence of Head and Neck cancer has risen in the last 5 years, mortality has remained stable.[3]

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. [2b] 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]

Human Pailloma Virus (HPV) has been recognized in the last decade as a significant etiological factor in oropharyngeal cancer.[10] [10b] This has implications in clinical presentation and workup[11] and in the prognosis of these patients.[12]

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. [13] 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. [13-14]

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. [15] 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. [16] 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. [17] 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. [18]

- Paranasal sinus and nasal cavity. Cancers of the maxillary sinus are the most common of the paranasal sinus cancers. [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 suprocalvicular 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 hyopharyngeal 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. This is followed by postoperative radiation therapy in Stage III and IV tumors or with positive margins.

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, selective 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.[13] 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%. [13, 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] 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.[30] 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).[31] 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).[32] 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.[33] 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.[34] 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.[35] 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).[36] 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.[37] The best chemotherapy to use and the appropriate way to integrate the two modalities is still unresolved.[38] 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.[39] 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.[40] 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.[41] Chang *et al.* reported on 186 patients who developed a local recurrence of the nasopharynx and retreated with radiation.[42] 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.[43] 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.[44]

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.[45] 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.

Based on initial an initial Phase II trial of hyperfractionation and systemic therapy, the RTOG has embarked on a randomized trial (0421) comparing this with systemic therapy. There has been several promising single institution and non-randomised experience with re-irradiation in recurrent head and neck cancer.[46] Unfortunately the results have not been very promising and frought with significant toxicity.

IX. The Role of SBRT For The Treatment of Primary Head and Neck Cancers

High doses of radiation to primary head and neck tumors have been shown to increase local control.[47] The challenge of treating head and neck tumors with high doses of radiation is limiting the dose to surrounding critical structures within the head and neck, including visual organs, cranial nerves, spinal cord and brainstem. The development of SBRT allows the physician to safely increase the dose to the tumor while limiting the dose to surrounding normal tissue. There are several single institution studies reporting the role of SBRT in the management of primary head and neck cancer treatment.

Stanford University first reported their experience treating newly diagnosed nasopharyngeal patients with conventional radiation followed by SBRT as a boost in 1999.[48] Twenty-three patients with nasopharyngeal carcinoma with disease extension into the skull base received a conventional dose of 64.8 – 70 Gy followed by a single boost dose of 7 – 15 Gy (mean dose 12 Gy) delivered by SBRT. With a mean follow up of 21 months, local control was 100%. No acute or late toxicities were reported. Regional or distant disease occurred in seven patients, suggesting that systemic therapy is needed to control disease progression outside of the radiation treatment fields. The authors concluded that high local control was achievable in advanced stage nasopharyngeal carcinoma by safely boosting regions of involvement with high doses of radiation while sparing normal tissues. In 2008, the Stanford group updated their report of 82 nasopharyngeal carcinoma patients who received an SBRT boost of one fraction of 7-15 Gy after conventional external beam radiation (median dose 66 Gy).[49] The majority of patients had Stage IV disease (16 patients had Stage II, 19 had Stage III and 47 had Stage IV) and 75 patients received either concurrent or adjuvant capsulation-based chemotherapy. At 5 years, freedom from local relapse was 98%, freedom from nodal relapse was 83%, and overall survival was 75%. Freedom from distant metastasis was 68%. Patients experienced anticipated side effects of external beam radiation, including skin erythema, nasopharyngitis, oropharyngitis, decreased taste, xerostomia, and Eustachian tube dysfunction. Late toxicities included three incidences of retinopathy, carotid aneurysm in one

patient and radiographic temporal lobe necrosis in 10 patients (9 of the 10 patients had T4 tumors). The authors concluded that an SBRT boost after conventional external beam radiation provides excellent local control in a group of homogenously treated nasopharyngeal carcinoma patients. Acceptable late toxicities were achieved, but improved target delineation and dose homogeneity in both external beam and SBRT is important to avoid long-term complications, especially in more advanced (T4) lesions. The predominant site of failure was distant indicating a need for more effective systemic treatments.

Chen *et al*. also reported excellent local control rates for nasopharyngeal carcinoma treated with conventional radiotherapy followed by an SBRT boost.[50] In this study, 58 patients with Stages I – IVB nasopharyngeal carcinoma were treated with 64.8 – 68.4 Gy followed by an SBRT boost dose of 12-15 Gy. Fifty-two patients also received cisplatinum-based chemotherapy and 14 of the 52 patients with T3-T4 disease received concurrent chemotherapy. A complete response was reported in all patients at three months post treatment with a 93% local control rate at three years. Fifteen patients developed recurrences: 3 in the nasopharynx, 4 in the neck, and 5 at distant sites. Overall survival was 85% and regional control was 92%. Three patients with large T3-T4 lesions developed severe nasal bleeding and died. The authors commented that tumor invasion into the great vessels occurred following radiation treatment and that tumor cell regression coupled with poor generation of supporting wall tissue caused vessel wall rupture. No other severe late radiation-induced complications were reported. These results support that SBRT can achieve excellent local control rates (93%) as a boost following external beam radiation for both early and more advanced nasopharyngeal cancers (T3 and T4 lesions). Distant disease progression was the biggest challenge, and the optimal dose of chemotherapy agents and radiation schemes need to be further investigated.

In a more recent study, a Japanese group conducted a retrospective review on 10 patients with primary head and neck cancer treated with conventional radiation followed by SBRT.[51] Tumors located in the nasopharynx, oropharynx, maxillary sinus, and nasal cavity were treated with 40-60 Gy delivered at 2 Gy per fraction followed by a boost dose of 9-16 Gy delivered in 3 or 4 fractions by SBRT. A complete response was reported in 60% of patients and a partial response in 40% of patients. Local progression occurred in three patients at 5, 12, and 13 months within the boost area. One patient developed distant metastases at six months. Of six patients who received cisplatinum-based chemotherapy concurrently with the preceding conventional radiotherapy, one patient experienced acute grade 2 esophagitis and three patients developed acute grade 3 oral cavity-pharyngeal mucositis. Two patients with external auditory canal cancer developed grade 2 acute otitis. There were no reported grade 3 or higher acute toxicities directly attributable to the SBRT boost. The results of the above studies conclude that excellent local control rates for primary nasopharyngeal cancers can be achieved with SBRT boost after conventional radiation therapy with acceptable acute and late toxicities. In these studies, controlling progression of distant disease was the biggest

challenge and further studies need to be conducted to determine the optimal chemotherapy dose and radiation schemes.

SBRT is also being explored as a treatment option for the management of squamous cell carcinoma of the vocal cord. Levendag *et al*. recently described a novel 4D conformal technique for treating a single vocal cord with SBRT.[52] Using this technique, it was feasible to irradiate one vocal cord within 1-2 mm accuracy, thus sparing the contra lateral vocal cord and contralateral normal tissues. They propose this technique may be a competitive alternative to laser surgery for early glottic cancer by preserving vocal cord function. A feasibility study using SBRT to deliver 8.5 Gy x 5 fractions to T1a vocal cord lesions is currently underway at the Erasmus Medical Center, Rotterdam, Netherlands. There has been other promising single institution experience using SBRT as part of primary treatment in head and neck cancer.[53] [54]

X. The Role of SBRT For The Treatment of Recurrent Head and Neck Cancer

For the treatment of head and neck cancers, SBRT is mostly used in the setting of re-irradiation of local recurrences. The therapeutic outcomes and toxicities reported in these studies vary considerably due to different patient characteristics, heterogeneity of tumor types and tumor histology, differences in initial therapies to the primary tumor, and different SBRT dose and fractionation schemes. Below is a summary of therapeutic outcomes of SBRT for the treatment of recurrent head and neck cancer. In the majority of studies, SBRT is used as a single treatment modality for recurrent head and neck cancer; however, more recently combinations of SBRT and systemic therapies are being investigated.

SBRT as a single treatment modality for recurrent head and neck cancer

The University of Pittsburgh Medical Center (UPMC) conducted a Phase I dose escalation study to determine the maximum tolerated dose (MTD) for SBRT for the treatment of recurrent, unresectable squamous cell carcinomas of the head and neck (SCCHN) in previously irradiated patients.[55] Thirty one patients were treated in a 5 tier dose escalation design with a maximum dose of 44 Gy. Primary tumors involved the oropharynx, oral cavity, larynx, nasopharynx, and one patient with an unknown primary site. All patients had received prior radiotherapy (median dose 64.7 Gy), 16 patients had surgery as a component of their initial therapy, and 56% of patients received chemotherapy during their primary treatment. Of the 31 patients, 25 were evaluated for toxicity. Two patients had grade 1 mucositis, one patient had grade 2 dysphagia, and 1 patient had grade 1 hyperpigmentation. There were no grade 3 or higher toxicities reported and the MTD was not reached. Two patients died before disease response assessment and, of the 23 patients for whom response was evaluated, one patient had a complete tumor regression response, three patients had a

partial response, 12 patients had stable disease, and four patients had disease progression. Although the MTD was not reached, the authors concluded that SBRT seems to be feasible, well tolerated, and a potential alternative to surgery or external beam radiation. SBRT may be a more convenient and effective form of re-irradiation given the relatively short time required for delivery of the scheduled treatment fractions.

In a subsequent report, the UPMC group published results of 85 patients with recurrent SCCHN re-treated with SBRT.[56] All patients were previously treated with full-dose irradiation to the primary tumor, 72% had prior surgery, and 65% had chemotherapy. Doses of 15 – 44 Gy (median dose of 35 Gy) were delivered with fraction sizes of 4-18 Gy. The median follow up for all patients was six months (1.3 – 39 months). One- and two-year local control rates were 51.2% and 30.7%, respectively; and one- and two-year overall survival rates were 48.5% and 16.1 %, respectively. Those patients who received SBRT < 35 Gy had significantly lower local control than those with ≥35 Gy at 6 months median follow-up time. There were only four patients who experienced severe acute toxicities (two patients with grade 3 xerostomia, one patient with grade 3 pain, and one patient with grade 3 dysgeusia). No grade 4 or 5 retreatment-related toxicities were reported. There were no differences in grade 1-3 toxicities in patients that received < 35 Gy vs. those that received ≥ 35 Gy. The authors concluded that SBRT is a feasible and safe treatment for recurrent SCCHN patients who were previously irradiated. They also concluded that dose escalation studies and studies combining SBRT with systemic therapy were needed to further improve regional and distant recurrence free survival and overall survival while maintaining minimal acute and late toxicities.

Other single institution studies have confirmed that SBRT achieves good local control and overall survival rates for recurrent head and neck cancer patients previously irradiated, however there are mixed morbidity and mortality rates. A group from Korea reported on 36 patients with recurrent, unresectable head and neck cancer (nasopharynx, maxillary sinus and lymph node) that was previously irradiated. Doses of 18 – 40 Gy (median 30 Gy) were delivered in 3-5 fractions. Local/regional free survival at one- and two-years was 61% and 52%, respectively, and two-year overall survival was 30.9%. Acute radiation toxicities occurred in 24 patients. Late grade 3 toxicities occurred in three patients, with one treatment-related death due to soft tissue necrosis and skull base necrosis.[57]

Seo *et al*. conducted a retrospective review of 35 patients with locally recurrent nasopharyngeal carcinoma treated with SBRT.[58] Doses of 24 – 45 Gy were delivered in 3-5 fractions. The median follow up time was 24 months (range 2 – 81 months). The 5-year local failure-free rate, disease progression-free survival and overall survival rates were 74%, 79% and 60%, respectively. Patients with T1-2 disease had significant increased local control rate compared to T3-T4 lesions (80% vs. 39%, respectively). Late serious grade 4

and 5 complication rates occurred in 16% of patients. Mucosal necrosis developed in two patients and nasopharyngeal hemorrhage developed in three patients. Two of the three hemorrhage patients developed massive hemorrhage of the carotid artery and died due to complications. The authors concluded that, in terms of local control and overall survival, the results for SBRT for the treatment of recurrent head and neck cancer were favorable but the incidence of late toxicities was high.

Kodani *et al*. conducted a retrospective review of SBRT treatment of advanced head and neck tumors that were predominantly recurrent SCCHN tumors.[59] Other tumor types included adenocarcinoma, melanoma, undifferentiated carcinoma, small cell carcinoma, and leiomyosarcoma. Twenty one of 34 patients had prior radiation therapy (50 – 70 Gy). Patients were treated with a median dose of 30 Gy (19.5 – 42 Gy) in 3 to 8 fractions (median 5 fractions). With a median of 16 months follow up, 32.4% had a complete tumor regression response and 38.6% had a partial response. One and two year overall survival rates were 70.6% and 58.3%, respectively and a median survival time of 28 months. Late severe complications occurred in six patients, all who had received prior radiation. Two patients suffered from severe mucositis and dysphagia requiring hospitalization, one patient had necrosis of the skin in the re-irradiation area, and two patients developed massive carotid hemorrhage and died. The destruction of the carotid artery has been reported in other studies using conformal techniques.[60] The authors concluded that SBRT is an effective treatment method for recurrent head and neck cancers and has the advantage of short treatment duration; however, careful attention is needed in cases where the tumor is closely situated to or invades the carotid artery in the prior irradiation area.

In another study, Cengiz *et al.* reported on the efficacy and toxicity of 46 patients with recurrent head and neck cancer (nasopharynx, oral cavity, paranasal sinus, larynx, and hypopharynx) treated with SBRT.[61] Re-irradiation doses ranged from 18 – 45 Gy (median 30 Gy) delivered in 1-5 fractions. Excellent one-year local control was achieved (84%) and overall survival at 1 year was 46%. Grade 2 and higher complications occurred in 13% of the patients. In addition, eight patients had carotid artery blowout (17.8%) and nine patients died. Eight of the deaths were due to carotid artery blowout and one patient died due to disease progression of an esophageal tumor. The authors noted that there was a significant relationship between the amount of dose the carotid artery received and bleeding. None of the patients with carotid artery dose < 100% exhibited carotid artery blowout. In addition, bleeding only occurred in patients where the carotid artery wall was circumscribed by the tumor with a degree of ≥ 180. The exact mechanism of carotid artery blowout is not known; however the authors stated that the high incidence of carotid artery blowout in this series might be attributed to the large number of patients with large tumor volumes that encompassed the carotid arteries. The authors conclude that SBRT is an effective treatment for recurrent head and neck patients previously irradiated, but for patients with tumors encompassing the carotid artery, SBRT hypofractionation should be considered cautiously

and, furthermore, IMRT or conventionally fractionated SBRT may be a better option for these cases. Longer term studies are needed to determine the proper SBRT dose and fractionation scheme to increase local control and minimize late toxicities.

St. John's Mercy Research Institute, St. Louis, MO has launched a single institution study investigating local control, overall survival and long-term complication rates of multiple SBRT dose regimens for the treatment of benign and malignant head and neck cancers (NCT01344356). Eligible patients include those with benign paraganglioma, chondromas, and unresectable head and neck tumors that have recurred after prior radiation treatment. SBRT dose regimens include the following:

Benign Tumors		Malignant Tumors	
Dose (Gy)	# of fractions	Dose (Gy)	# of fractions
14-16	1	8-12	1
18-21	3	12-18	3
25-45	5	34-45	5

Local control, overall survival and complication rates will be assessed up to 5 years to determine the optimal dose and fractionation schemes for benign and unresectable, recurrent head and neck tumors.

To date, there are no reported prospective studies comparing therapeutic outcomes of SBRT with other methods of radiation delivery for the management of head and neck cancer. There is one retrospective study reported by a group in Ankara, Turkey, comparing outcomes of SBRT treatment for locally recurrent nasopharyngeal carcinoma with 3DCRT with and without brachytherapy.[62] In this study, 51 patients with recurrent nasopharyngeal carcinoma previously irradiated were treated with either 30 Gy in 5 fractions by SBRT or 57 Gy in 2 Gy per fraction using 3DCRT. The median follow up was 24 months. The two-year local control rate for SBRT and 3DCRT was 82% and 80%, respectively. The two-year cancer specific survival rate was 64% for SBRT-treated patients compared to 47% for 3DCRT. Severe late complications (cranial neuropathy, carotid artery blowout, brain necrosis, and trismus) were significantly higher in the 3DCRT treated patients (48%) compared to SBRT treated patients (21%). Brachytherapy did not have an effect on the complication rate of 3DCRT. These results suggest that SBRT achieved longer overall survival in patients with locally recurrent nasopharyngeal carcinoma compared to 3DCRT with less toxicity. Prospective studies with larger number of patients and longer follow up are needed to validate the feasibility and efficacy of SBRT for recurrent head and neck cancers.

The Japanese group, Kawaguchi *et al*., investigated whether lymph node involvement in recurrent SCCHN was a predictor of tumor response to SBRT in previously irradiated patients.[63] In this study, 22 patients received a dose of 20 – 42 Gy delivered by SBRT. Complete tumor regression was achieved in 64.3% of patients that did not have lymph node involvement, in contrast to a 12.5% tumor response in patients with lymph node involvement. Disease progression occurred in 87.5 % of patients with lymph node involvement vs. 21.4% in patients with no lymph node involvement. The authors concluded that positive lymph node involvement significantly predicts tumor response and that patients with positive lymph nodes require multi-modality therapy.

SBRT with concurrent systemic therapy for the treatment of recurrent head and neck cancer

After reporting their initial experience of SBRT for the treatment of unresectable, recurrent SCCHN, the UPMC group investigated whether concurrent cetuximab with SBRT could enhance the clinical efficacy while minimizing toxicity.[64] Cetuximab is a monoclonal antibody targeted to inhibit epidermal growth factor receptor and was FDA approved in 2006 for use in combination with radiation therapy for treating SCCHN. In a retrospective matched-cohort study, Heron *et al*. compared SBRT alone (n = 35) vs. SBRT with cetuximab (n = 35) for recurrent SCCHN previously irradiated. The median duration of local control and overall survival was longer in patients treated with cetuximab and SBRT vs. SBRT alone. Cetuxamib conferred an overall survival advantage of 24.5 months vs. 14.8 months when compared to SBRT alone. In addition, patients previously treated with cetuximab benefited in local control and overall survival. There were no significant differences in toxicities between the two patient groups and no grade 4 or 5 treatment-related toxicities were reported for either group. The authors concluded that SBRT with concurrent cetuximab is feasible and safe for patients with recurrent previously irradiated head and neck tumors. Future randomized studies are needed to determine if these results are comparable to conventional radiation therapy. A matched pair analysis revealed improved outcomes with cituximab. [64] More importantly the same group showed improved patient reported quality-of-life outcomes after SBRT and cetuximab.[65]

The Centre Oscar Lambret, Lille, France, also assessed whether cetuximab combined with SBRT is an effective treatment for non-operable locally recurrent or new primary head and neck cancer in previously irradiated areas.[66] Patients received a total dose of 36 Gy delivered in 6 fractions of 6 Gy with concurrent cetuximab. With a median follow up of seven months, 11 of 37 patients had a complete response, 15 had a partial response, 10 had stable disease, and one had progression. Acceptable acute toxicities were reported which included mucositis, skin rash, and necrosis. Seven percent of patients receiving cetuximab had grade 3 mucositis and 28% of patients had late toxicity. The authors concluded that cetuximab combined with SBRT is an effective treatment for recurrent or new primary head and neck

cancer arising in previously irradiated areas in selected patients; however, longer follow up is needed to evaluate late effects and progression-free survival.

In a retrospective study, the Georgetown University group reported their experience treating 65 recurrent previously irradiated head and neck patients with SBRT with and without concomitant chemotherapy.[67] Thirty three patients received concomitant chemotherapy, the most common agent was cetuximab followed by carboplatin. Patients were treated with SBRT doses of 21 - 35 Gy delivered in 5 fractions. The maximum doses to the spinal cord, brainstem and optic nerve were 9 Gy, 16 Gy and 15 Gy, respectively. The median follow up period was 16 months. Of the 56 patients that were evaluated, 54% had complete tumor regression, 27% had a partial response, and 20% had no response. Patients receiving doses ≥ 30 Gy had a higher response rate (69%) than those receiving < 30 Gy (29%). The two-year local control and overall survival were 30% and 41%, respectively. Nineteen patients experienced grade 1 to 3 acute toxicity, including mucositis, dermatitis, and nausea. These complications were generally transient and resolved with conservative management. Seven patients experienced severe toxicities which resulted in one death. The use of chemotherapy did not result in improved outcomes on multivariable analysis, but the ability to detect a difference in outcomes was limited by the small patient cohort and variety of agents used. Similar rates of severe treatment-related toxicity were observed in patients who received concomitant chemotherapy (4/33) and in those who did not receive concomitant chemotherapy (3/32). This study demonstrates the feasibility of re-irradiation using SBRT with concurrent chemotherapy for treating recurrent, persistent, and second primary cancer of the head and neck. Prospective studies are warranted to further investigate fractionated re-irradiation SBRT with concurrent chemotherapy.

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