CHAPTER 4

Head and neck tumors

John Andrew Ridge, MD, PhD, Bonnie S. Glisson, MD, Eric M. Horwitz, MD, and Michael O. Meyers, MD

In 2003, it is estimated that head and neck cancers will comprise 2%-3% of all cancers in the United States and account for 1%-2% of all cancer deaths. This total includes 19,400 cases of oral cavity cancers, 9,500 cases of laryngeal cancer, and 8,300 cases of pharyngeal cancer. Most patients with head and neck cancer have metastatic disease at the time of diagnosis (regional nodal involvement in 43% and distant metastasis in 10%).

Head and neck cancers encompass a diverse group of uncommon tumors that frequently are aggressive in their biological behavior. Moreover, patients with a head and neck cancer often develop a second primary tumor. These tumors occur at an annual rate of 3%-7%, and 50%-75% of such new cancers occur in the upper aerodigestive tract or lungs.

The anatomy of the head and neck is complex and is divided into sites and subsites (Figure 1). Tumors of each site have a unique epidemiology, anatomy, natural history, and therapeutic approach. This chapter will review these lesions as a group and then individually by anatomic site.

Epidemiology

Gender Head and neck cancer is more common in men; 66%-95% of cases occur in men. The incidence by gender varies with anatomic location and has been changing as the number of female smokers has increased. The male-female ratio is currently 3:1 for oral cavity and pharynx cancers. In patients with Plummer-Vinson syndrome, the ratio is reversed, with 80% of head and neck cancers occurring in women.

Age The incidence of head and neck cancer increases with age, especially after 50 years of age. Although most patients are between 50 and 70 years old, head and neck cancer does occur in younger patients. There are more women and fewer smokers in the younger patient group.

It is controversial whether head and neck cancer is more aggressive in younger patients than in older individuals. This "aggressiveness" probably reflects the common delay in diagnosis in the younger population, since, in most studies, younger patients do not have a worse prognosis than their older counterparts.

Race Overall, there is no racial predominance of head and neck cancer in the United States. However, in recent years, the incidence appears to have declined among white and black males.

Among blacks, head and neck cancer is associated with lower survival for similar tumor stages. The overall 5-year survival rate is 56% in whites and 34% in blacks.

Geography There are wide variations in the incidence of head and neck cancer among different geographic regions. The risk of laryngeal cancer, for example, is two to six times higher in Bombay, India, than in Scandinavia. The higher incidence of the disease in Asia is thought to reflect the prevalence of risk factors, such as betel nut chewing and use of smokeless tobacco. In the United States, the high incidence among urban males is thought to reflect exposure to tobacco and alcohol. Among rural women, there is an increased risk of oral cancer related to the use of smokeless tobacco (snuff).

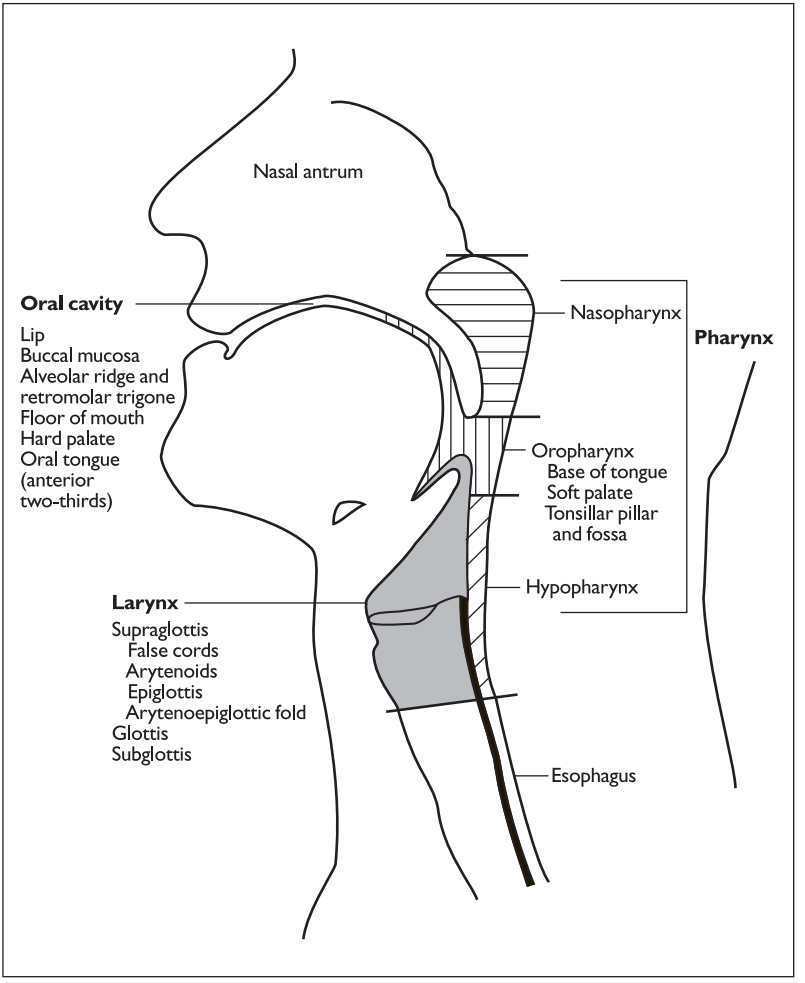

FIGURE 1: Anatomic sites and subsites of the head and neck.

Nasopharyngeal carcinoma is another head and neck tumor with a distinct ethnic predilection. Endemic areas include southern China, northern Africa, and regions of the far Northern Hemisphere—areas in which the diet of inhabitants includes large quantities of salted meat and fish. When people from these regions migrate to areas with a lower disease incidence, their risk falls but remains elevated. Cancer of the nasopharynx in these geographic areas also has been associated with Epstein-Barr virus (EBV) infection (see "Etiology and risk factors" section).

Disease site The approximate distribution of head and neck cancer follows: oral cavity, 44%; larynx, 31%; and pharynx, 25%.

Etiology and risk factors

Risk factors for head and neck cancer include tobacco and alcohol use, ultraviolet (UV) light exposure, viral infection, and environmental exposures.

Tobacco The incidence of head and neck tumors correlates most closely with the use of tobacco.

Cigarettes Head and neck tumors occur six times more often among cigarette smokers than nonsmokers. The age-standardized risk of mortality from laryngeal cancer appears to rise linearly with increasing cigarette consumption. For the heaviest smokers, death from laryngeal cancer is 20 times more likely than for nonsmokers. Furthermore, active smoking by head and neck cancer patients is associated with significant increases in the annual rate of second primary tumor development (compared with former smokers or those who have never smoked). Use of unfiltered cigarettes or dark, air-cured tobacco is associated with further increases in risk.

Cigars Total cigar consumption increased by nearly 50% in the United States in the 1990s. Often misperceived as posing a lower health risk than cigarette smoking, cigar smoking results in a change in the site distribution for aerodigestive tract cancer, according to epidemiologic data. Although the incidence of cancer at some sites traditionally associated with cigarette smoking (eg, larynx, lungs) is decreased in cigar smokers, the incidence of cancer is actually higher at other sites where pooling of saliva and associated carcinogens tends to occur (oropharynx, esophagus).

Smokeless tobacco Use of smokeless tobacco also is associated with an increased incidence of head and neck cancer, especially in the oral cavity. Smokeless tobacco users frequently develop premalignant lesions, such as oral leukoplakia, at the site where the tobacco quid rests against the mucosa. Over time, these lesions may progress to invasive carcinomas. The use of snuff has been associated with an increase in cancers of the gum and oral mucosa.

Alcohol Alcohol consumption, by itself, is a risk factor for the development of pharyngeal and laryngeal tumors, although it is a less potent carcinogen than tobacco. For individuals who use both tobacco and alcohol, these risk factors appear to be synergistic and result in a multiplicative increase in risk.

Head & Neck ch 4

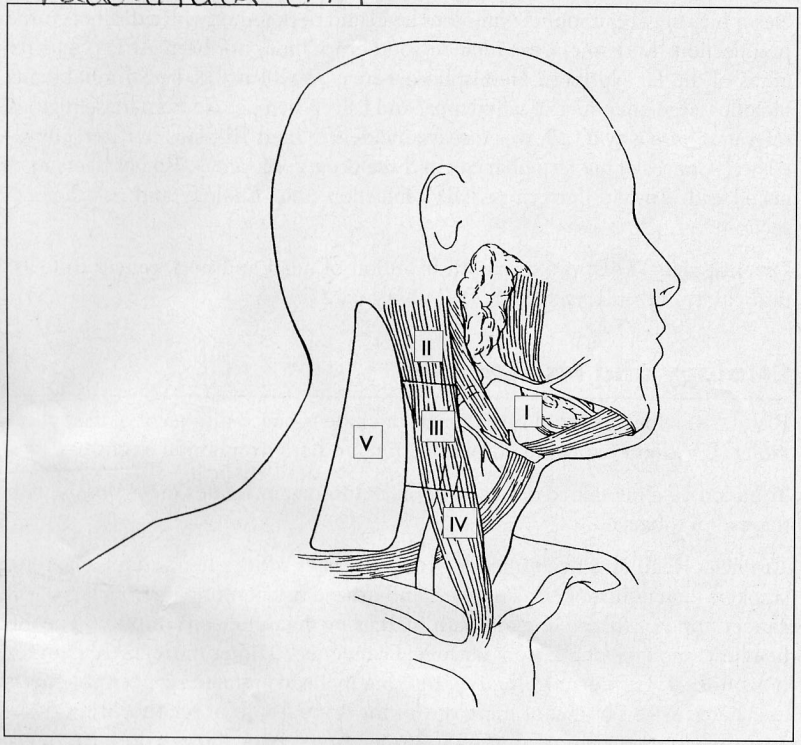

FIGURE 2: Levels of the neck as determined by lymphatic drainage patterns.

UV light exposure is a risk factor for the development of cancer of the lips. At least 33% of lip cancer patients have outdoor occupations.

Occupational exposures A small group of head and neck cancers may be attributable to occupational exposures. Nasal cancer has been associated with wood dust exposure, and squamous cell cancer of the maxillary sinus, with nickel exposure. Petroleum exposure may be associated with pharyngeal cancer, but the relationship has not been proven.

Radiation exposure Exposure to radiation is clearly an important risk factor for thyroid cancer and has been associated with cancer of the salivary glands.

Viruses There is a strong link between EBV exposure and the development of nasopharyngeal cancer. The relationship between other viruses, such as herpes simplex virus and human papillomavirus, and head and neck cancer is uncertain.

Diet Epidemiologic studies suggest that dietary intake of vitamin A, β-carotene, and α-tocopherol may reduce the risk of developing head and neck cancer.

Marijuana Smoking marijuana is associated with the development of head and neck cancer, but the degree of risk is unknown.

Anatomy

As mentioned above, the anatomy of the head and neck region is complex. The anatomic sites are illustrated in Figure 1. More detailed descriptions are included below in the discussions of specific sites and subsites.

Levels of the neck

The anatomy of the neck is relevant to the treatment of all head and neck cancers. The neck may be divided into levels (Figure 2). The lymphatic drainage of the unmanipulated neck is systematic and predictable; knowledge of these drainage patterns assists the clinician in locating the primary tumor that has given rise to a neck metastasis (Table 1).

Signs and symptoms

Head and neck cancer typically produces symptoms referable to the upper aerodigestive tract, including alterations in deglutition, phonation, hearing, and respiration. In particular, patients should be questioned about dysphagia, odynophagia, globus sensation, hoarseness, a change in the ability to form words, epistaxis, epiphora, otalgia, hemoptysis, stuffiness of the ears, and trismus. (Signs and symptoms of cancer at specific anatomic sites and subsites can be found in the respective discussions of these tumors.)

It is important to ascertain the duration and course (progression or improvement) of symptoms. Progression of disease is often noted during the evaluation and worsens prognosis.

Level I includes the submental and submandibular triangles.

Level II includes the superior jugular chain nodes extending from the mandible down to the carotid bifurcation and posteriorly to the posterior border of the sternocleidomastoid muscle.

Level III consists of the jugular nodes from the carotid bulb inferiorly to the omohyoid muscle.

Level IV continues from the omohyoid muscle inferiorly to the clavicle.

Level V represents the posterior triangle bounded by the sternocleidomastoid anteriorly, the trapezius posteriorly, and the omohyoid inferiorly. Few lesions metastasize to level V without involvement of more central nodes.

TABLE 1: Lymphatic drainage of the head and neck and associated sites of primary tumors

Lymphatic drainage	Likely primary sites
Level I	
Submental	Lower lip, chin, anterior oral cavity (including anterior one-third of the tongue and floor of the mouth)
Submandibular	Upper and lower lips, oral tongue, floor of the mouth, facial skin
Level II	Oral cavity and pharynx (including soft palate, base of the tongue, and piriform sinus)
Level III	Larynx, hypopharynx, and thyroid
Level IV	Larynx, hypopharynx, thyroid, cervical esophagus, and trachea
Level V	Nasopharynx, thyroid, paranasal sinuses, and posterior scalp
Supraclavicular	Infraclavicular sites (including lungs, esophagus, breasts, pancreas, GI tract, GU and gynecologic sources)

Screening and diagnosis

SCREENING

Because the cure rates for early-stage head and neck cancers are high, the concept of screening for the disease has intuitive appeal. Evaluation of asymptomatic individuals has not been shown to decrease mortality from head and neck cancer, however. The US Preventive Health Service Task Force does not recommend screening for oral cancer due to the lack of evidence supporting screening as a means of decreasing mortality. In countries with a high incidence of oral cavity cancer, such as India, screening may be helpful and is currently under evaluation.

DIAGNOSIS

The need for expeditious diagnosis of head and neck cancer and referral to a skilled head and neck specialist cannot be overemphasized, as early diagnosis can lead to a reduction in mortality. One study suggested that in the 24 months prior to the diagnosis of head and neck cancer, patients had a median of 10.5 health-care visits. These visits provide an opportunity to evaluate patients' symptoms and underscore the important role of dentists and primary care physicians in the early diagnosis of head and neck cancer.

History

Risk factors as outlined above, including a history of tobacco and alcohol use and environmental exposures, should be reviewed. Any adult patient with symptoms referable to the upper aerodigestive tract that have lasted longer than 2 weeks or with an asymptomatic neck mass should undergo a thorough examination with a high index of suspicion for carcinoma.

Physical examination

The physical examination is the best means for detecting lesions of the upper aerodigestive tract. Frequently, the initial assessment also will indicate the severity and chronicity of the disease. Due to the frequent occurrence of multiple primary tumors in patients with a head and neck tumor, careful evaluation of the entire upper aerodigestive tract is necessary at the time of diagnosis. The examination should always follow a systematic approach.

Skin/scalp A search should be made for ulcers, nodules, and pigmented or other suspicious lesions. This part of the evaluation is frequently overlooked.

Cranial nerves A cranial nerve evaluation is essential for any patient with a head and neck tumor or neck mass (which may be a manifestation of occult cancer). This evaluation should include assessing eye motion (cranial nerve [CN] III, IV, and VI); testing sensation of the face (CN V); examining the muscles of facial expression by having the patient grin, grimace, raise eyebrows, close eyes tightly, show teeth, and puff out the cheeks (CN VII); testing of hearing (CN VIII); assessing gag reflex (CN IX); evaluating vocal cord mobility (CN X); and having the patient fully abduct the shoulder (CN XI) and protrude the tongue (CN XII). Even the slightest abnormality may be helpful in identifying a primary tumor.

Eyes/ears/nose The eyes, ears, and nose should be evaluated for any sign of mass effect, abnormal drainage/discharge, bleeding, or effusion.

Oral cavity Halitosis may be the first indication of a lesion in the upper aerodigestive tract. The teeth, gingivae, and entire mucosal surface should be inspected. (Dentures should be removed.) The lymphoid tissue of the tonsillar pillars should be inspected and any asymmetry noted. Tongue mobility also should be evaluated.

The floor of the mouth, tongue, and cheeks should be palpated using a bimanual technique (one gloved finger inside the mouth and the second hand under the mandible). Palpation should be the last step of the examination due to stimulation of the gag reflex. Worrisome lesions should be biopsied.

Neck A systematic examination of the neck consistently documents the location of any mass. Palpation is the cornerstone of the examination. It is performed by grasping the tissue and feeling the nodes between the thumb and index and long fingers. The relationship of a mass to major structures, such as the salivary gland, thyroid, and carotid sheath, should be considered.

Important qualities of a mass include location, character, tenderness, size, mobility, and associated thrill or bruit. The thyroid should be palpated.

Indirect laryngoscopy The nasopharynx, hypopharynx, and larynx should all be examined with care. The vocal cords should be visualized and their mobility evaluated. Mirror examination provides an overall impression of mobility and asymmetry, which may point to a hidden tumor.

Direct laryngoscopy Nasopharyngoscopes permit a thorough inspection of the upper aerodigestive tract in the office setting. Attention should be focused individually on the piriform sinuses, tongue base, pharyngeal walls, epiglottis, arytenoids, and true and false vocal cords. Also, any pooling of secretions should be noted.

Endoscopy Approximately 5% of patients with head and neck cancer have a synchronous primary squamous cell cancer of the head and neck, esophagus, or lungs. "Triple" endoscopy includes direct laryngoscopy, esophagoscopy, and bronchoscopy with directed biopsy and should be performed in all patients with an occult primary squamous cell cancer and in many patients with a *known* head and neck primary. Triple endoscopy also can provide information regarding the extent of the tumor.

The most common sites of silent primary tumors are the tonsils, base of the tongue, and piriform sinuses. Tumors of the nasopharynx have become easier to identify with the increased use of flexible nasopharyngoscopy. Biopsies should be performed in common areas of silent primaries in addition to the primary anatomic sites associated with lymphatic drainage of any neck mass.

Laboratory evaluation

There are no specific screening laboratory tests other than preoperative studies performed in the diagnostic evaluation of most head and neck carcinomas. EBV, anticapsid antibodies, and serum IgG are tumor markers for nasopharyngeal carcinomas.

Diagnostic imaging

Plain x-rays PA and lateral chest x-rays should be obtained in all adult patients to eliminate the possibility of occult lung metastasis or a second primary. A Panorex film may be helpful in delineating bony involvement in some cases of oral cavity lesions.

Ultrasonography is of limited use in evaluating squamous cell cancer of the head and neck.

CT The CT scan is probably the single most informative test in the assessment of a head and neck tumor. It may delineate the extent of disease and the presence and extent of lymphatic involvement and will distinguish cystic from solid lesions. CT scans of the chest, abdomen, and pelvis sometimes may identify the site of an occult primary tumor presenting with a node low in the neck. CT

offers high spatial resolution and discriminates among fat, muscle, bone, and other soft tissues and surpasses MRI in the detection of bony erosion.

Dynamic contrast CT provides an increased ability to distinguish blood vessels from enlarged lymph nodes or masses and maintains image quality with the use of less contrast agent.

Spiral CT is a faster approach than dynamic contrast CT and has the capability for multiplanar reconstruction while maintaining the quality of the scan.

MRI may provide accurate information regarding the size, location, and extent of tumor. The advantages of MRI over CT include discrimination of tumor from normal tissue, multiplanar imaging without patient repositioning, and the ability to depict blood vessels clearly without iodinated contrast. The main disadvantage of MRI is movement artifact, which is a particular problem in the larynx and hypopharynx. Gadolinium-enhanced MRI is probably superior to CT for imaging tumors of the nasopharynx and oropharynx.

Angiography There are two indications for arteriography: a pulsatile neck mass and clinical evidence of a paraganglioma. High-resolution angiography is preferred over digital subtraction angiography because the former provides more information and permits embolization to be performed. Angiography is not used routinely in evaluating other primary tumors of the head and neck. In particular, angiography is not used routinely to assess arterial invasion or determine resectability of primary laryngeal tumors.

Nuclear scans are helpful in evaluating hyperthyroid patients but otherwise are of limited use.

PET has been evaluated in both primary and recurrent squamous cell carcinoma of the head and neck. Initial results are encouraging, but this tool should still be considered investigational.

Biopsy

Biopsies of the primary tumor often can be performed in an outpatient setting.

Punch or cup forceps biopsy is important in the diagnosis of mucosal lesions. The biopsy should be obtained at the border of the lesion away from areas of obvious necrosis.

Fine-needle aspiration (FNA) is a useful diagnostic modality. Multiple passes are made through the lesion with a fine-gauge (22-gauge) needle while suction is applied. Suction should be released before withdrawing the needle through surrounding soft tissue of the neck. FNA has an associated false-negative rate as low as 7%. The diagnostic accuracy depends on the physician's skill and the cytopathologist's experience.

Cytology is particularly useful in distinguishing a metastatic squamous cell carcinoma from other malignant histologies. However, a negative result should not be interpreted as "absence of malignancy."

Core biopsy should not be performed on a neck mass, with the rare exception of a proven lymphoma.

Open biopsy should be performed only when a diagnosis has not been made after extensive clinical evaluation and FNA is nondiagnostic. The operation should be performed only by a surgeon prepared to conduct immediate definitive surgical treatment at that time (which may entail radical neck dissection).

Pathology

Squamous cell carcinoma

More than 90% of all head and neck cancers are squamous cell carcinomas.

Histologic grade There are three histologic grades based on the amount of keratinization: A well-differentiated tumor is characterized by $> 75\%$ keratinization, a moderately differentiated tumor by 25%-50%, and a poorly differentiated tumor by $< 25\%$.

In general, the more poorly differentiated a lesion, the higher is the incidence of regional metastases and the poorer the prognosis. Histologic grade has not been a consistent predictor of clinical behavior, however. Features that predict aggressive behavior include perineural spread, lymphatic invasion, and tumor spread beyond the lymph node capsule.

Morphologic growth patterns Four morphologically distinct growth patterns have been recognized. The ulcerative type is the most common form and begins as a round or oval ulcer that is friable. Ulcerative lesions progress toward infiltration. Infiltrative lesions extend deeply into underlying tissues. The exophytic type tends to grow more superficially and metastasize later than the other types. It begins as an area of thickened epithelium.

Verrucous cancer is an uncommon variant that, in the United States, typically occurs in elderly patients with poor oral hygiene or ill-fitting dentures. It is characterized by a warty, bulky, elevated, fungating appearance. Verrucous cancers seldom metastasize.

Other tumor types

Other less common head and neck cancers include mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma, all of which may arise in the salivary glands. Head and neck cancers with neuroendocrine features include small-cell undifferentiated cancer and esthesioneuroblastoma (olfactory neuroblastoma). Both Hodgkin's disease and non-Hodgkin's lymphoma may also be diagnosed as head and neck tumors, often involving the lymph nodes of the neck or Waldeyer's ring.

Sequence of disease progression

There is a sequence of disease progression from atypia/dysplasia through carcinoma in situ to frankly invasive cancer. Leukoplakia and erythroplakia are terms applied to clinically identifiable lesions that may harbor invasive cancer or undergo malignant transformation.

Leukoplakia results from chronic irritation of mucous membranes by carcinogens; this irritation stimulates the proliferation of white epithelial and connective tissue. Histopathologic examination reveals hyperkeratosis variably associated with underlying epithelial hyperplasia. In the absence of underlying dysplasia, leukoplakia rarely ($< 5\%$) is associated with progression of disease to malignancy.

Erythroplakia is characterized by superficial, friable, red patches adjacent to normal mucosa. It is commonly associated with underlying epithelial dysplasia and has a much greater potential for malignancy than leukoplakia. Carcinoma is found in nearly 40% of erythroplakia.

Dysplasia is characterized by cellular atypia, loss of normal maturation, and loss of normal epithelial stratification. It is graded as mild, moderate, or severe, based on the degree of nuclear abnormality present. In the transition from mild to severe dysplasia, nuclear abnormalities become more marked, mitoses become more apparent, and these changes involve increasing depth of epithelium. The likelihood of developing a carcinoma relates to the degree of dysplasia. In the case of *severe dysplasia*, as many as 24% of patients may develop invasive squamous cell cancer.

Carcinoma in situ is characterized by the presence of atypical changes throughout the epithelium with complete loss of stratification. It is estimated that approximately 75% of invasive squamous cell carcinomas have an associated in situ component. Specific DNA mutations have also been identified in the sequence of disease progression from mild dysplasia to atypia to carcinoma in situ to invasive carcinoma.

Regional and distant metastases

The incidence of lymph node metastases is related to the size and thickness of the primary tumor. If the primary site is near the midline, contralateral or bilateral metastases should be anticipated. In the presence of lymph node metastases, extracapsular spread of tumor is an important prognostic factor.

Staging and prognosis

Staging system The TNM staging system of the American Joint Committee on Cancer (AJCC) maintains uniformity in the staging of head and neck tumors. The staging of primary mucosal tumors of the head and neck varies with the anatomic location and will be covered later by site. However, the staging system for metastases and stage groupings are nearly uniform for all mucosal sites.

Prognosis correlates strongly with stage at diagnosis. For many head and neck cancer sites, survival for patients with stage I disease exceeds 80%. For patients with locally advanced disease at the time of diagnosis, stages III and IV disease, survival drops below 40%. Development of nodal metastases reduces survival of a patient with a small primary tumor by ~50%. Involvement of even a single lymph node is associated with a marked decline in survival. Most patients with head and neck cancer have stage III or IV disease at diagnosis.

Pattern of relapse Despite aggressive primary treatment, the majority of relapses that occur following a head and neck cancer are within the head and neck. Locoregional relapse accounts for ~80% of primary treatment failures. Distant metastases increase as the disease progresses and most often involve the lungs, bones, and liver. By the time of death, 10%-30% of patients will have clinically detected distant metastases.

Field cancerization is an important concept related to the natural history of head and neck cancer. This term describes the diffuse epithelial injury throughout the head and neck, lungs, and esophagus that results from chronic exposure to carcinogens.

Clinically, field cancerization is manifested by the frequent occurrence of (1) mucosal abnormalities, such as leukoplakia and dysplasia, beyond the margins of a head and neck cancer and (2) second primary tumors within this exposed field. The lifetime risk of a head and neck cancer patient developing a new cancer is 20%-40%. Over time, as the risk of relapse of the initial cancer declines, the development of a new cancer represents the greatest risk for these patients.

Treatment approaches

Head and neck tumors may be treated with curative intent using surgery, radiation therapy, or a combination of the two modalities. Chemotherapy may be combined with irradiation (chemoradiation) in the management of advanced (stage III/IV) lesions of the oropharynx, hypopharynx, and larynx and for nasopharyngeal cancers more advanced than stage T2b.

Stages I and II disease at most sites may be treated with either resection or radiation therapy. The best therapeutic approach for the primary tumor depends on the anatomic site. The approach to treatment of the neck also varies with the site and treatment of the primary tumor. A neck dissection in a clinically negative neck might be considered optional for primary tumors of the oral cavity but would typically be performed in association with pharynx operations since resection would require incision/dissection in the neck. Neck dissections should remain standardized (ie, complete anatomic dissections, as opposed to "berry picking" or random biopsy) in these settings so as to avoid incomplete surgery.

Preoperative assessment Before surgical resection, preoperative assessment of the extent of disease is essential. Complete physical examination and appropriate radiologic evaluation are necessary. Triple endoscopy (laryngoscopy, bronchoscopy, and esophagoscopy) or "quad scopes" (adding nasopharyngoscopy) with an examination with the patient under anesthesia may be helpful to assess the full extent of disease and to search for concomitant primaries. Biopsy for histologic confirmation may also be performed in this setting.

Surgical principles Classic principles of surgical oncology apply to head and neck cancer. Complete resection is necessary. Securing sufficient margins may be challenging due to the many structures in this area. Reconstruction is complex after resection of head and neck tumors, as the surgery may have an impact on appearance, speech, and swallowing. Decisions regarding the extent of resection should be made by experienced surgeons.

Surgery plus radiation therapy

The combination of radical surgery and radiation therapy has been used for several decades to reduce the rate of locoregional recurrence in patients with advanced head and neck cancers.

Postoperative vs preoperative radiation therapy Postoperative radiation therapy (60-70 Gy in 6-7 weeks) reduces the rate of locoregional recurrence from ~50% to 15% for tumors with pathologic features predictive of locoregional recurrence (positive margins, extracapsular nodal disease, and multiple involved lymph nodes) that are resected using radical extirpative surgery.

Preoperative radiotherapy (45-50 Gy in 4-5 weeks) has been used for patients with advanced primary tumors, but rates of locoregional recurrence appear to be lower and complications fewer with postoperative radiation therapy. Preoperative radiotherapy is indicated for marginally resectable tumors, such as those with fixed cervical lymph nodes. In this setting, preoperative irradiation often permits resection of an otherwise unresectable tumor.

Postoperative chemotherapy/radiation therapy The indications for postoperative radiation therapy are well established and include a large primary tumor (T3/T4), close or positive margins, an involved lymph node >3 cm or multiple involved lymph nodes, extracapsular extension, tumor fixation, and connective tissue invasion. The addition of postoperative radiation therapy reduces the risk of locoregional failure but does not decrease the risk of developing distant metastases or change the overall survival rate.

The RTOG sponsored a phase III randomized prospective trial to determine whether the addition of postoperative chemotherapy would enhance locoregional control. The initial results and failure patterns of RTOG 95-01 were presented in 2002. This study randomized 459 patients who underwent primary surgery but who had high-risk disease (two or more involved lymph nodes, extracapsular extension, or positive margins) to receive 6,000-

6,600 cGy of postoperative irradiation with or without cisplatin (Platinol) (given days 1, 22, and 43). The median follow-up was 26.6 months and the locoregional control was 74% vs 79% for the radiotherapy and radiotherapy and chemotherapy arms respectively ($P = .16$). Two-year overall survival was 57% and 63% ($P = .51$) and disease-free survival was 43% and 54% ($P = .049$), respectively. The incidence of grade 3 and higher acute toxicity was 33% for the radiotherapy alone arm and 75% for the radiotherapy and cisplatin arm ($P < .0001$). The authors concluded that the addition of postoperative chemotherapy increased acute toxicity but did not significantly improve clinical end points compared with radiotherapy alone.

Curative radiation therapy

Radiation therapy with curative intent usually involves daily treatment for 6-7 weeks (total dose, 60-70 Gy). Although there is no tissue loss with radiation therapy, complications include dry mouth, tissue fibrosis, trismus, bone necrosis, and hypothyroidism. Some problems are common and sufficiently debilitating to warrant significant concern in treatment planning for head and neck cancer. Surgery often produces less morbidity.

Radiation fractionation

The RTOG 90-03 trial was conducted to determine the efficacy of various fractionation schemes in the treament of locally advanced head and neck cancer. Four schedules were tested: (1) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 70 Gy/35 fractions/7 weeks; (2) hyperfractionation at 1.2 Gy/fraction, twice daily, 5 days/week to 81.6 Gy/68 fractions/7 weeks; (3) accelerated fractionation with split at 1.6 Gy/fraction, twice daily, 5 days/week, to 67.2 Gy/42 fractions/6 weeks, including a 2-week rest after 38.4 Gy; or (4) accelerated fractionation with concomitant boost at 1.8 Gy/fraction/day, 5 days/week, and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days to 72 Gy/42 fractions/6 weeks. A total of 1,113 patients were entered in the study, with a median follow-up of 23 months. Patients treated with both hyperfractionation and accelerated fractionation with a concomitant boost had significantly increased locoregional control rates compared with patients on the other two arms. All three groups treated with the altered fractionation schemes had more acute, but not late, side effects. The study concluded that hyperfractionation and accelerated fractionation with a concomitant boost are the optimal treatment schemes.

Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) is a new approach to obtaining highly conformal radiation dose distributions needed to irradiate complex targets positioned near sensitive normal structures. In the case of head and neck cancer, these sensitive normal structures include the parotid glands, spinal cord, and eyes. Treatment planning for IMRT (also known as inverse planning) is different from that of conventional or three-dimensional cranial

radiation therapy. The starting point with IMRT is a description of the desired dose distribution rather than the application of traditional fields and beam modifiers to generate an acceptable plan. Conventional radiation treatment utilizes relatively uniform beams of radiation (typically between 2-4 beams), whereas IMRT, instead of using 4 beams of 50 cGy each, could use 50 beams of 4 cGy each. Each beam direction is divided into multiple segments to modulate the radiation dose. The use of IMRT in the treatment of head and neck cancer has focused primarily on sparing the parotid glands and preserving salivary function.

Various groups have examined dosimetric and quality-of-life differences between IMRT and conventional radiation techniques. The group at Memorial Sloan-Kettering Cancer Center compared its IMRT planned treatment for nasopharyngeal cancer with conventional treatment with a conformal boost. Locoregional control was 97% vs 78% at 2 years. The University of Michigan and Washington University have reported reductions in xerostomia.

A recent meta-analysis evaluating the role of chemotherapy in squamous cell carcinoma of the head and neck was reported. This study compared treatment of 10,741 patients in 63 trials with or without chemotherapy. The pooled data showed an absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy. This report also evaluated 861 patients in 6 trials comparing induction chemotherapy followed by irradiation with concomitant or alternating chemoradiotherapy. These data revealed a 3% absolute (but not statistically significant) survival benefit at 2 and 5 years favoring concomitant chemotherapy (*Pignon JP, Bourhis J, Domenge C, et al: Lancet 355[9208]:949-955, 2000).*

Chemotherapy

Induction (neoadjuvant) chemotherapy

The high response rates achieved with induction chemotherapy (clinical response rates of 70% with cisplatin-based regimens, including complete histologic responses) (Table 2) have not resulted in improved locoregional control or survival when compared with radiotherapy alone. However, several studies have documented a decreased rate of distant metastasis with induction chemotherapy.

Although response to chemotherapy is a strong predictor of response to radiation therapy, chemotherapy does not confer an additional survival benefit. Whether or not chemotherapy may allow a reduction in the type of surgery or radiation therapy that must be given to cure these patients is disputed and remains open to study.

Concomitant chemotherapy and radiation therapy The major goal of administering chemotherapy concurrently with irradiation is to "radiosensitize" the tissue in the radiation field and increase the likelihood of locoregional control. This approach has been associated with improvements in locoregional control and survival in several randomized trials, and its benefits have been confirmed in recent meta-analyses. The optimal way in which to combine these two modalities is the focus of much ongoing research in head and neck oncology.

Preliminary results from a Head and Neck Intergroup study confirm the superiority of concurrent chemoradiation therapy compared with irradiation alone for patients with unresectable squamous cell cancer. A total of 295 patients with stage III and IV head and neck were randomized to participate in one of three arms: (A) radiotherapy alone to 70 Gy in 35 fractions; (B) 70 Gy in 35 fractions plus concurrent cisplatin on days 1, 22, and 43; and (C) split-course radiotherapy and three cycles or concurrent cisplatin/5-FU chemotherapy with 30 Gy given with cycle 1 and 30-40 Gy given with cycle 3. Grade 3 or worse toxicity occurred in 53% of arm A patients; 86% in arm B patients, and 77% of arm C patients. The 2- and 3-year Kaplan-Meier projected survivals for arm A are 30% and 20%, compared with 43% and 37% for arm B ($P = .016$), and 40% and 27% for arm C ($P = .13$). Median survival is 12.6 months for arm A, 19.1 months for arm B, and 14.0 months for arm C. The addition of concurrent high-dose single-agent cisplatin to conventional radiotherapy significantly improves survival with acceptable toxicity. Additionally, concurrent multiagent chemotherapy did not offset the loss of efficacy resulting from split-course irradiation.

Induction chemotherapy followed by radiation therapy has been shown in a Veterans Affairs (VA) trial to produce survival comparable to that attained with primary surgery in patients with laryngeal cancer. The advantage of this approach is preservation of the larynx. Combinations of chemother-

TABLE 2: Chemotherapy regimens for head and neck tumors

Drug/combination	Dose and schedule
Cisplatin + fluorouracil	
Cisplatin	100 mg/m^2 IV on day 1
Fluorouracil	1 mg/m^2 IV infused continuously over 4 days
Repeat cycle every 3-4 weeks	
Jacobs C, Lyman G, Velez-Garcia E, et al: J Clin Oncol 10:257–263, 1992.	
Carboplatin + paclitaxel	
Carboplatin	Dose calculated by the Calvert formula to an area under the curve between 6 and 7.5 mg/mL/min infused over 1-2 hours on day 1 after paclitaxel
Paclitaxel	175 mg/m^2 IV infused continuously over 3 hours
Repeat cycle every 21 days	
PREMEDICATIONS: Dexamethasone, 20 mg PO 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, and ranitidine, 50 mg IV, both 30 to 60 minutes prior to paclitaxel	
Dang TP, Murphy BA, Cmelak A, et al: Proc Am Soc Clin Oncol 17:393a, 1998.	

Table prepared by Ishmael Jaiyesimi, DO

ECOG (Eastern Cooperative Oncology Group) 1393 randomized patients with recurrent squamous cell cancer of the head and neck to receive cisplatin (100 mg/m^2 day 1) and 5-FU (1 g/m^2 days 1-4; arm 1) or cisplatin (75 mg/m^2 day 1) and paclitaxel (75 mg/m^2 day 1; arm 2). Patients could have had no prior treatment for recurrent disease and were required to have ECOG performance status of 0 or 1. A total of 194 patients were studied, with 96 and 92 patients eligible on arms 1 and 2, respectively. Overall response and median survival rates were equivalent (arm 1: 22% and 8 months; arm 2: 28% and 9 months). The toxicity analysis favored arm 2, which was associated with fewer cases of stomatitis, diarrhea, myelosuppression, and infection. Quality of life did not favor either arm *(Murphy B, Li Y, Cella D, et al: Proc Am Soc Clin Oncol [abstract] 20:224a, 2001).*

apy and radiation therapy are being actively studied, and other approaches, such as concomitant treatment, appear to be effective.

Adjuvant chemotherapy following surgery or irradiation Adjuvant chemotherapy has been given following initial surgery or radiation therapy in an attempt to eliminate microscopic residual disease and distant metastases. Although this approach has resulted in a reduced rate of distant metastasis, it has not been associated with improved locoregional control or survival. As concomitant approaches evolve and locoregional control for advanced disease becomes the rule rather than the exception, the value of additional chemotherapy (as induction or adjuvant therapy) will need to be reexplored to address the problem of distant metastasis.

Locally advanced head and neck cancer Data from prospective trials continue to support the use of concurrent chemotherapy and irradiation as an alternative to surgery or irradiation alone for locally advanced cancers of the head and neck. RTOG 90-03 randomized 1,113 patients with stage III and IV squamous cell carcinoma of the oral cavity, oropharynx, or supraglottic larynx and stage II-IV squamous cell carcinoma of the base of the tongue or hypopharynx to receive one of four different schedules of irradiation alone. They included 7,200 cGy in 42 fractions (180 cGy/fraction initially, followed by 150 cGy/fraction to a boost field for the last 12 fractions bid). Locoregional control, disease-free survival, and overall survival rates were 54.5%, 39.3%, and 50.9%, respectively, which were superior to those obtained with single daily fractions of 2.0 Gy over 7 weeks.

RTOG 99-14 was a phase II study designed to integrate this altered fractionated irradiation regimen with chemotherapy. Cisplatin was given during weeks 1 and 3. When results on 77 evaluable patients were reported, 82% of patients were alive at the time of analysis. One-year overall survival was 81.3%; grade 3 and 4 chronic toxicity were 23% and 8%, respectively. The next RTOG phase III trial for advanced head and neck cancer will incorporate this regimen as the "experimental" arm.

Chemotherapy for recurrent or metastatic disease The combination of cisplatin/fluorouracil (5-FU) produces overall response rates of approximately 30% and survival rates of 6 months. In randomized trials comparing this combination with single-agent cisplatin, 5-FU, or methotrexate,

response rates with the single agents are lower but survival is equivalent. However, because many practitioners believe response is a surrogate for palliation, cisplatin/5-FU has been used widely in this setting.

The taxanes are the most active cytotoxins yet identified in head and neck cancer, with overall response rates of approximately 35% in patients with recurrent or incurable disease. In a recent randomized trial, the combination of paclitaxel (Taxol)/cisplatin has been compared with cisplatin/5-FU in patients with recurrent disease (see box on previous page). Although primary efficacy outcomes were equivalent for the two arms, paclitaxel/cisplatin was less toxic overall and can now be considered a safer, more convenient alternative to cisplatin and infusional 5-FU in recurrent disease. The evaluations of taxane-based neoadjuvant therapy and concurrent therapy with irradiation are ongoing.

Other drugs receiving recent attention are those targeting growth factors and their receptors. The epidermal growth factor receptor (EGFR) is particularly notable, since nearly 100% of head and neck tumors overexpress this receptor. A number of EGFR inhibitors are currently being evaluated alone and in combination with other drugs.

Photodynamic therapy

Photodynamic therapy may have some promise in the treatment of mucosal dysplasia and small head and neck tumors.

Small studies of photodynamic therapy, performed at several institutions, suggest that widespread areas of carcinoma in situ or severe dysplasia, as well as cancer, are often extirpated after photodynamic therapy. Although some patients have experienced durable remissions, the long-term efficacy of this modality remains uncertain.

Chemoprevention

The area of chemoprevention has received a great deal of attention in recent years, and the concept of "field cancerization" is important in this context. As mentioned previously, this concept refers to the diffuse epithelial injury incurred by upper aerodigestive tract mucosa due to chronic exposure to carcinogens (most commonly alcohol and tobacco). These mucosal changes increase the risk of developing premalignant lesions (leukoplakia and erythroplakia), as well as multiple primary lesions.

The retinoids (vitamin A analogs) have shown the greatest promise in achieving effective chemoprevention. The mechanism of action involves changes in gene expression mediated by nuclear retinoic acid receptors, which appear to function as transcription factors. In the mouse skin tumor and hamster buccal pouch models, retinoids have been shown to significantly prevent tumor growth and development. They have also been shown to significantly decrease the prevalence of premalignant lesions in humans in both randomized and nonrandomized clinical trials. Prospective trials have demonstrated

that serum levels of retinoids are lower in patients who subsequently develop upper aerodigestive tract tumors.

Ongoing clinical trials are investigating the possible role of retinoids in the prevention of second primary tumors in both the upper aerodigestive tract and lungs. However, a recent phase III ECOG (Eastern Cooperative Oncology Group) trial showed no benefit in prevention of recurrence with low-dose *cis*-retinoic acid (10 mg/d) in stage I/II patients. The ECOG trial used very low doses (7.5-10 mg/d). A study by Hong et al using high doses (1-2 mg/kg/d) produced positive results, but morbidity and compliance were problems. Results are pending from a trial employing intermediate dosing (30 mg/d).

Rehabilitation

Rehabilitation also is very important in the perioperative care of head and neck cancer patients. It includes physical and occupational therapy, speech and swallowing rehabilitation, and nutritional support. For example, resection of the spinal accessory nerve, which innervates the trapezius muscle, leads to scapular winging, inability to abduct the arm fully, and, eventually, to severe pain around the shoulder. These symptoms may be ameliorated with appropriate physical therapy.

Adapting to the loss of the larynx also requires intensive rehabilitation and patient motivation. Voice rehabilitation options include esophageal speech, artificial larynges (portable, battery-operated devices), and tracheoesophageal shunts.

Nutritional support is facilitated by temporary nasoduodenal tubes or gastrostomy tubes (which impose added morbidity but are more socially acceptable and ease the patient's transition to normal activities).

Management of symptoms and treatment side effects

Eating problems At the time of diagnosis, many head and neck cancer patients will have lost a significant amount of weight. Maintaining adequate nutrition is a major problem for these patients, as both the tumor and treatment side effects, such as mucositis from chemotherapy and radiation therapy, may be contributory. For patients who are unable to eat or who are being treated with aggressive concomitant chemotherapy and radiation therapy protocols, placement of a gastrostomy tube is often desirable in order to maintain caloric intake and adequate hydration.

Pain Clinicians must also be aware of the significant pain associated with these lesions and use narcotic analgesics appropriately to relieve discomfort.

Mucositis The use of chemotherapy concomitantly with radiation therapy increases the occurrence of mucositis.

Nephrotoxicity and ototoxicity For patients treated with cisplatin-containing regimens, renal insufficiency and ototoxicity are potential serious side effects.

Xerostomia Following radiation therapy of a head and neck cancer, xerostomia may be a significant long-term side effect. In some patients, pilocarpine hydrochloride (Salagen) has been useful in stimulating the production of saliva.

The use of organic thiophosphates, such as amifostine (Ethyol), in patients undergoing radiotherapy for head and neck cancer may reduce the severity of acute and late xerostomia without compromising the antitumor activity of the irradiation.

Gastroesophageal reflux Often asymptomatic or "silent" gastroesophageal reflux disease (GERD) is a common finding in patients treated for pharyngolaryngeal squamous cell carcinoma. In addition, cisplatin-containing chemotherapy may aggravate GERD.

Treatment of the neck

Either irradiation alone or radical neck dissection will control metastatic squamous cell cancer to a single small neck node more than 90% of the time if there is no extracapsular tumor spread. Hence, radiation treatment may easily provide prophylactic treatment of the neck if control of the primary tumor is un-

TABLE 3: Types of neck dissection and structures removed in the treatment of head and neck cancer

Type of neck dissection	Structures removed
Comprehensive neck dissection	
"Classic" radical neck dissection	All lymph-bearing tissue (levels I-V), spinal accessory nerve (cranial nerve [CN] XI), sternocleidomastoid muscle, and internal jugular vein
Modified radical neck dissection	Neck dissection with sparing of one or more of the above structures
Type I	CN XI spared
Type II	CN XI and internal jugular vein spared
Type III (functional neck dissection)	All three structures spared (CN XI, internal jugular vein, and sternocleidomastoid muscle)
Selective neck dissection	Removal of lymph-bearing tissue from:
Lateral	Levels II-IV
Posterolateral	Levels II-V
Supraomohyoid	Levels I-III

From Medina JE, Rebual NM: Neck dissection, in Cummings CW, Fredrickson J, Harker LE, et al (eds): Otolaryngology: Head and Neck Surgery, pp 1649–1672. St. Louis, Mosby Yearbook, 1993.

dertaken with irradiation. Traditionally, if the tumor in the neck was N2 or greater, or if there was tumor beyond the confines of a node, radical neck dissection and irradiation were combined for optimal control of the neck tumor. More recently, evidence suggests that N2-N3 disease that has a complete clinical and radiologic response to induction chemoradiotherapy may not require a complete neck dissection. This concept continues to evolve.

Types of dissection

There are several approaches to the surgical treatment of the neck nodes in patients with head and neck cancer (Table 3). This discussion will be limited to two types of neck dissection: comprehensive and selective dissection.

Comprehensive neck dissection entails complete removal of all lymphatic tissue from the neck (levels I-V). A radical neck dissection includes comprehensive node dissection with removal of the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. Modified radical neck dissection was developed to diminish the morbidity of the classic operation. The most important structure to preserve is the spinal accessory nerve.

Selective neck dissection consists of the removal of lymph node groups at highest risk of containing metastases from a primary cancer. In such procedures, the lymph nodes removed correspond to the most significant drainage basins of specific head and neck tumor sites. These are staging operations usually performed in patients with a clinically N0 neck cancer. If metastases are identified, further treatment to the neck will be required. A selective neck dissection should not be employed as the sole treatment of clinically palpable disease.

Sentinel lymph node biopsy for oral cavity lesions has been evaluated. Forty patients with clinically N0 necks underwent sentinel lymph node biopsy followed by complete neck dissection. A sentinal node was identified in 90% of necks, with a 97% accuracy rate in predicting the nodal status of the remainder of the neck. This finding corresponded to a sensitivity of 94% and a specificity of 100%. Although these results are encouraging, they need to be validated in a larger trial. An ongoing American College of Surgeons Oncology Group study (Z0360) is examining this technique in patients with T1 or T2, N0 oral cavity cancer. Sentinel lymph node biopsy may prove useful in small lesions without deep penetration, but it remains investigational.

Follow-up of long-term survivors

As mentioned, head and neck cancers are aggressive tumors. The majority (80%) of recurrences will develop within 2 years. Since many recurrences are treatable with curative intent, patients should be followed closely during the months following their treatment. This period coincides with the time of greatest need from the standpoint of rehabilitation.

TABLE 4: TNM staging system for cancers of the lips and oral cavity

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, ie, chin or nose[a]
T4a	(oral cavity) Tumor invades adjacent structures (eg, through cortical bone, into deep [extrinsic] muscle of the tongue, maxillary sinus, or skin of face)
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Regional lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

After 2 years, second primary tumors of the head and neck and lungs become important causes of death and morbidity. Late complications of treatment such as radionecrosis, radiation-induced fibrosis, and hypothyroidism, as well as sequelae of spinal accessory nerve sacrifice or injury, may develop even after years. Complications and second primary cancers are more common in patients who continue to smoke.

Timing of follow-up evaluations Follow-up evaluations at regular intervals should be complete and should include a focused history and examination, as outlined above. Physicians who are able to perform a head and neck examination (including laryngoscopy) should direct follow-up. After surgical treatment, this evaluation will usually require visits with the head and neck surgeon. Patients treated with irradiation should be followed by both their radiation oncologist and a head and neck surgeon or otolaryngologist.

Distant metastases (M)			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastases		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

[a] Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Evaluations should be scheduled every 1-2 months during the first year after treatment, every 2-4 months during the second year, every 3-6 months during the third year, and every 6 months thereafter for several more years.

Imaging and laboratory studies Any mucosal abnormality should be biopsied. There are no tumor markers or other useful laboratory studies to follow. Chest x-rays should be obtained yearly. There is little justification for performing CT scans or MRI in the follow-up of asymptomatic patients. Thyroid-stimulating hormone (TSH) should be measured yearly in patients who have received irradiation to the larynx or nasopharynx.

HEAD AND NECK TUMOR REGIONS

As mentioned above, tumors occurring at different anatomic sites and subsites of the head and neck vary considerably with regard to epidemiology, risk factors, anatomy, natural history, staging of the primary tumor, and therapy. The following sections highlight these differences.

ORAL CAVITY

Sites of the oral cavity include the lips, hard palate, floor of the mouth, buccal mucosa, and tongue. Cancers at these sites comprise < 5% of all malignancies in the United States.

Etiology and risk factors

Tobacco and alcohol As with other head and neck tumors, there is a correlation between the use of tobacco and development of oral cavity cancers. There is a clear dose-response relationship between tobacco exposure and tumor development. A full 90% of patients with oral cancers use tobacco, and many drink alcohol.

Vitamin A Patients with vitamin-A deficiency seem to be at higher risk, whereas diets high in fruits and vegetables seem to be protective.

Chronic irritants, including mouthwash and poor oral hygiene, are associated with tumor development.

Viruses Herpes simplex virus type 1 and human papillomavirus have been implicated in the development of oral cancer.

Anatomy

The oral cavity extends from the cutaneous vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae below. It includes the lips, buccal mucosa, upper and lower alveolar ridges, retromolar trigone, floor of the mouth, hard palate, and anterior two-thirds of the tongue (the "oral" tongue). The primary lymphatic drainage is to the submental triangle, submandibular nodes, and upper deep jugular nodes.

Natural history

The most common presenting complaint is a sore in the mouth or on the lips. One-third of patients present with a neck mass.

The differential diagnosis includes other malignancies and benign diseases or lesions. Other malignancies to be considered include salivary gland tumors,

sarcoma, lymphoma, and melanoma. Benign diseases include pyogenic granuloma, tuberculous disease, aphthous ulcers, and chancres.

Benign mucosal lesions include papillomas and keratoacanthomas, which may be exophytic or infiltrative. The exophytic lesions are less aggressive. The infiltrative papillomas and keratoacanthomas are more often associated with destruction of surrounding tissues and structures. These lesions may progress to malignancy. The TNM staging system for cancers of the lips and oral cavity is outlined in Table 4. T4 lesions have been divided into T4a (resectable) and T4b (unresectable) in the sixth edition of the *AJCC Cancer Staging Manual*.

Treatment

Radiation therapy has been widely used in patients with cancers of the oral tongue and floor of the mouth. Interstitial radiation therapy alone may be used for early (T1-T2) tumors, with local control rates of 80%-95%. A combination of external-beam radiation therapy (60 Gy in 6 weeks) plus interstitial radiotherapy provides excellent local control for early tumors.

Cancers arising at other sites within the oral cavity, such as the gingiva or buccal mucosa, usually are best treated with a primary surgical approach, but postoperative radiation therapy is added when poor pathologic features are present.

Surgical approaches to the primary cancer include peroral, transcervical, or combined operations. A comprehensive neck dissection should be performed in all patients with palpable cervical metastases. When an N0 lesion approaches the midline, bilateral supraomohyoid dissection should be considered. If the lymph nodes from the contralateral side of the neck contain cancer, contralateral neck treatment is needed. If there are bilateral, palpable nodes, both sides of the neck should be dissected.

Combined-modality treatment, including surgical resection and radiation therapy (60-70 Gy in 6-7 weeks), is advised for the treatment of advanced (stage III-IV) disease.

ORAL CAVITY SITE: LIPS

The lips are the most common site of oral cavity cancer. There are approximately 3,600 new cases per year in the United States. The lower lip is affected most often. The vast majority (90%) of patients with lip cancer are men, and 33% have outdoor occupations.

Natural history

The most frequent presentation is a slow-growing tumor of the lower lip that may bleed and hurt. Physical examination must include assessment of hypo-

esthesia in the distribution of the mental nerve (cutaneous sensation of chin area). Currently, fewer than 10% of American patients with squamous cell carcinoma of the lower lip have cervical metastases.

Treatment

Treatment of the primary tumor The primary tumor may be treated with radiation therapy (60-70 Gy in 6-7 weeks) or surgical resection. Currently, operations are more common than irradiation in the United States.

Resection involves excision with at least 0.5 cm of normal tissue circumferentially beyond the recognized border of the tumor. After the resection of larger lesions, reconstruction may pose a major challenge. Small tumors are excised with a V incision.

Patients with advanced disease (stage III or IV) are usually managed with a combination of surgery and postoperative radiation therapy (60-70 Gy in 6-7 weeks).

Treatment of the neck Elective treatment of the neck is seldom recommended for patients with squamous cell carcinoma of the lower lip and a clinically negative neck because few of these patients have cervical metastases. Neck dissection is recommended only in patients with palpable cervical metastases. In these individuals, the recommended approach often includes neck dissection and radiation therapy.

Results The cure rate for T1-T3 tumors is 90% with surgical excision alone. Smaller lesions (T1-T2) may be treated equally well with radiation therapy. Survival rates for patients with T1 and T2 lesions are 90% and 80%, respectively. Overall, younger patients have a poorer prognosis, as do those with involvement of the mandible and extension of the tumor within the oral cavity.

ORAL CAVITY SITE: TONGUE

The oral tongue (anterior two-thirds) is the site of 75% of all tongue cancers. There are approximately 7,100 new cases of oral tongue cancer each year in the United States.

Epidemiology and risk factors

Gender and age The male-female ratio is 3:1. Although the median age of onset is 60 years, tongue cancer may occur in patients younger than 30 years of age. Young patients may have no recognized risk factors.

Risk factors Tongue cancers are associated with poor oral hygiene and with alcohol and tobacco use.

Natural history

The most common presenting symptom in patients with cancer of the tongue is pain. Other symptoms include difficulty with deglutition and speech. There may be a history of leukoplakia, especially in younger women.

Rate of growth Cancer of the tongue seems to grow more rapidly than other oral cavity cancers. Tongue cancers may grow in an infiltrative or exophytic fashion. The infiltrative tumors may be quite large at presentation.

Lesion thickness Thicker lesions have a worse prognosis than thin cancers, and lesion thickness is a more important prognostic factor than is simple tumor stage.

Cervical metastases occur more frequently from tongue cancer than from any other tumor of the oral cavity. At initial evaluation, 40% of patients have node metastases. Bilateral and contralateral metastases from lateral tongue cancers are uncommon.

Treatment

Early-stage disease Treatment usually entails partial glossectomy. Margins should be assessed at the time of resection, as the disease spreads along muscle bundles, leading to more extensive tumor than is appreciated grossly.

Radiation therapy (60-70 Gy in 6-7 weeks) is a suitable option for small or minimally infiltrating tumors. Large, infiltrative lesions should be treated with combined-modality therapy (radiation therapy and surgical resection).

Advanced disease More advanced tumors with mandibular involvement require composite resection, including a partial glossectomy, mouth floor resection, and partial mandibulectomy.

Treatment of the neck A selective neck dissection is often recommended for the clinically N0 disease neck. Comprehensive neck dissection is required in the presence of palpable cervical metastases.

Results Control of disease closely correlates with the extent of the primary tumor and presence of metastases. Rates of local control using radiation therapy or surgery are similar for T1 (~85%) and T2 (~80%) tumors. T3 tumors should be treated using surgery and radiation therapy. Only 10%-15% of local recurrences are amenable to repeat resection.

Overall survival is approximately 50%. Rates of survival at 5 years by stage are stage I, 80%; stage II, 60%; and stage III-IV, 15%-35%. For equivalent primary cancers, the presence of lymph node metastases decreases the survival rate by 50%.

ORAL CAVITY SITE: FLOOR OF THE MOUTH

There are approximately 1,500 cases of floor of the mouth cancer in the United States annually. Mouth floor cancer accounts for 10%-15% of all oral cavity cancers.

Epidemiology and risk factors

Gender and age The male-female ratio is 3:1, but the incidence among women is increasing. The median age at presentation is 60 years.

Tobacco and alcohol Approximately two-thirds of patients with cancer of the mouth floor are heavy smokers and 50% are alcoholics. Alcohol acts synergistically with tobacco. Alcohol may act as a promoter, a direct irritant, or a solvent to increase the solubility of carcinogens from tobacco.

Smokeless tobacco There is a strong association between the use of smokeless tobacco and oral carcinogenesis. Data from the southern United States reveal a 50-fold increased risk of oral cavity cancer in women who use smokeless tobacco.

Pathology

Most lesions are moderately differentiated to well-differentiated squamous cell cancers and are exophytic in character.

Natural history

Patients usually present with a painful mass located near the oral tongue. Since these lesions do not cause pain until they are deep, they are frequently advanced at presentation.

Extension of disease into the soft tissues of the submandibular triangle is not uncommon. Fixation of the tumor to bone suggests possible mandibular involvement. A Panorex film of the mandible may reveal invasion of the mandible via direct extension (through a tooth socket) or via perineural invasion spreading along the mental nerve through the mental foramen. Changes in the mental foramen can be distinct or demonstrate slight asymmetry when compared with the contralateral anatomy. Restricted tongue mobility reflects invasion into the root of the tongue. Palpation demonstrates the depth of infiltration much better than does inspection alone.

Tumors near the midline may obstruct the duct of the submandibular gland, leading to swelling and induration, which may be difficult to distinguish from lymph node metastases. Level I nodes are the first-echelon metastatic sites.

Multifocality Multifocal cancers are more common in the floor of the mouth than in other oral cavity sites. Approximately 20% of patients with mouth

floor tumors have a second primary tumor, half of which are in the head and neck.

Treatment

Early invasive lesions (T1-T2) involving the mucosa alone may be treated with either surgery or irradiation (60-70 Gy in 6-7 weeks) alone, with comparable results. Primary tumors with mandibular involvement should be surgically resected.

Cancer invades the mandible through tooth sockets. Hence, if the tumor merely abuts the mandible, a marginal mandibulectomy (which removes the bone margin but preserves continuity) may be performed. Otherwise, a segmental resection is needed.

Selective neck dissection for treatment planning is advisable for thick stage I or II cancers.

Advanced disease The treatment of choice for advanced disease is combined-modality therapy with surgery and radiation therapy. Complete surgical resection may require a composite resection of the mandible, including a partial glossectomy and neck dissection for advanced primary cancers.

Lesions near the midline with a clinically positive lymph node require ipsilateral comprehensive neck dissection with a contralateral selective (supraomohyoid) neck dissection. Otherwise, both sides of the neck should be treated with irradiation. If there is clinical evidence of bilateral involvement, bilateral comprehensive neck dissection should be performed.

Results Overall, ~40% of patients are cured of their disease; 80% of recurrences appear within the first 2 years. Survival rates at 5 years by stage are as follows: stage I, 85%; stage II, 75%; stage III, 66%; and stage IV, 30%. Signs of poor prognosis include involvement of both the tongue and mandible and extension of the tumor beyond the oral cavity.

NASOPHARYNX

Nasopharyngeal carcinoma is uncommon in most of the world. Endemic areas include southern China, northern Africa, and regions of the far Northern Hemisphere. The incidence (per 1,000 population) ranges from 25.6 in men and 10.2 in women in Hong Kong to 0.6 in men and 0.1 in women in Connecticut.

Epidemiology and risk factors

Gender and age The incidence of nasopharyngeal cancer peaks in the fourth to fifth decades of life, and the male-female ratio is 2.2:1. Both patient age at disease onset and male-female ratio are lower for nasopharyngeal cancer than for other head and neck malignancies.

TABLE 5: TNM staging system for cancers of the pharynx (including base of tongue, soft palate, and uvula)

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Nasopharynx	
T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissue of oropharynx and/or nasal fossa
T2a	Without parapharyngeal extension[a]
T2b	With parapharyngeal extension[a]
T3	Tumor invades bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible (resectable)
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery (unresectable)
Hypopharynx	
T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor involves more than one subsite of hypopharynx or an adjacent site or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue[b] (resectable)
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures (unresectable)

Risk factors Nasopharyngeal carcinoma appears to have different determinants than other head and neck cancers. They include diet, viral agents, and genetic susceptibility. Populations of endemic areas have a diet characterized by high consumption of salt-cured fish and meat. Studies reveal an association between EBV and nasopharyngeal carcinoma. Anti-EBV antibodies have been found in the sera and saliva of patients with this type of carcinoma. Major histocompatibility (MHC) profiles associated with increased relative risk include H2, BW46, and B17 locus antigens.

Regional lymph nodes (N): Nasopharynx	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]
N3	Metastasis in a lymph node(s) > 6 cm and/or to supraclavicular fossa
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa[c]

Regional lymph nodes (N): Oropharynx and hypopharynx	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant metastases (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases

[a] Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilar fascia
[b] Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat
[c] Midline nodes are considered ipsilateral nodes

continued on following page

Anatomy and pathology

The nasopharynx communicates anteriorly with the nasal cavity and inferiorly with the oropharynx. The superior border is the base of the skull. The lateral and posterior pharyngeal walls are composed of muscular constrictors. Posteriorly, the nasopharynx overlies the first and second cervical vertebrae. The eustachian tubes open into the lateral walls. The soft palate divides the nasopharynx from the oropharynx.

TABLE 5: TNM staging system for cancers of the pharynx (including base of tongue, soft palate, and uvula) ***(continued)***

Stage grouping: Nasopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1
Stage grouping: Oropharynx and hypopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Cancers arising in the nasopharynx are classified using World Health Organization (WHO) criteria: type 1 denotes differentiated squamous cell carcinoma; type 2, nonkeratinizing carcinoma; and type 3, undifferentiated carcinoma. The TNM staging system for cancers of the pharynx is outlined in Table 5.

Natural history

A mass in the neck is the presenting complaint in 90% of patients. Other presenting symptoms include a change in hearing, sensation of ear stuffiness, tinnitus, nasal obstruction, and pain.

Cranial nerve involvement Invasion of disease into the base of the skull is seen in ~25% of cases and may lead to cranial nerve involvement. CN VI is the first cranial nerve to be affected, followed by CN III and CN IV. Deficits are manifested by changes in ocular motion. Involvement of CN V may also occur; this is manifested by pain or paresthesia high in the neck or face.

Level V metastases Unlike malignancies of the oral cavity and oropharynx, nasopharyngeal cancers often metastasize to level V lymph nodes. Bilateral metastases are common.

Treatment

Treatment of nasopharyngeal cancer usually involves radiation therapy (65-70 Gy) for the primary tumor and draining lymph nodes. Overall survival is 50% at 5 years. Surgical resection has very high morbidity and is seldom entertained, even after recurrence of a small cancer.

Nasopharyngeal cancer is distinguished from other sites of head and neck cancer by its radiosensitivity and chemosensitivity. Although advanced nodal disease can be controlled by irradiation alone in ~50% of patients, eventual distant metastasis remains a problem.

The final report of the intergroup trial 0099 confirmed that for patients with locally advanced nasopharyngeal cancer, concurrent cisplatin chemotherapy with radiation therapy (followed by systemic chemotherapy) provided a clear survival benefit compared with treatment with irradiation alone. At 5 years, patients who received combined-modality therapy had overall survival rates of 67%, compared with 37% if they received radiation thrapy alone ($P = .001$). Disease-free survival at 5 years was 74% for the chemoradiation therapy arm vs 46% for the radiation therapy-alone arm.

OROPHARYNX

Carcinoma of the oropharynx affects 4,000 patients in the United States annually.

Epidemiology and risk factors

Gender and age Oropharyngeal cancer usually occurs in the fifth to seventh decades of life. The male-female ratio is 3-5:1.

Tobacco and alcohol The most significant risk factors are tobacco and alcohol use.

Anatomy and pathology

The opening to the oropharynx is a ring bounded by the anterior tonsillar pillars (faucial arch), extending upward to blend with the uvula and inferiorly across the base of the tongue (behind the circumvallate papillae). The walls of the oropharynx are formed by the pharyngeal constrictor muscles, which overlie the cervical spine posteriorly. The superior boundary is the soft palate, which separates the oropharynx from the nasopharynx.

Inferiorly, the oropharynx is divided conceptually from the hypopharynx (laryngopharynx) at the level of the epiglottis. Subsites include the base of the tongue, soft palate, tonsillar area, and posterior pharyngeal wall. The extent of a primary tumor may be difficult to assess due to its location.

The jugulodigastric nodes (levels II and III) constitute the first echelon of lymphatic drainage. Metastases may also appear in the parapharyngeal and retropharyngeal nodes and may be detected only through imaging studies.

Premalignant lesions occur in the oropharynx but are less common than in the oral cavity.

Treatment

Radiation therapy External-beam radiation therapy (65-70 Gy over 7 weeks) and interstitial irradiation have been used in the curative treatment of oropharyngeal carcinomas for over 70 years. Radiation therapy represents a reasonable alternative to surgery and may also be required following radical resection of tumors with poor pathologic features to reduce the likelihood of local recurrence.

Altered fractionation schedules (accelerated and/or hyperfractionated) have gained interest in the past several years based on both theoretical grounds and the results of mainly retrospective data. One prospective, randomized trial in patients with oropharyngeal cancer (excluding base of the stongue cancer) documented a 20% increase in locoregional control and a 14% survival benefit at 5 years in patients who receive 8,050 cGy in a hyperfractionated schedule, as opposed to 7,000 cGy in a conventionally fractionated schedule. This improvement in outcome was not offset by any significant increase in acute or late tissue toxicity. Adoption of this strategy as a standard of care awaits confirmation of its superiority in a large, four-arm cooperative group trial that has completed accrual and is under analysis.

Local control rates with radiation therapy for all primary sites (including the tonsil, soft palate, base of the tongue, and posterior oropharyngeal wall) are as follows: T1, 90%; T2, 80%; T3, 65%; and T4, 55%. Cancers of the tonsillar

fossa are better controlled with irradiation than cancers arising in other subsites of the oropharynx.

Chemoradiation Recent additions to the literature support the use of concurrent chemotherapy with irradiation as an alternative to surgery or radiation alone for locally advanced cancers of the oropharynx. Brizel et al reported the results from a phase III randomized prospective study from Duke University. Patients were randomized to receive either hyperfractionated irradiation alone to a total dose of 7,500 cGy or hyperfractionated irradiation to a dose of 7,000 cGy with concurrent cisplatin and 5-FU chemotherapy during irradiation and two cycles of the drugs after radiation therapy. At 3 years, the rate of overall survival was 55% vs 34% in favor of the combined-modality arm; locoregional control was also superior in the combined-therapy arm, 70% vs 44%. Complications were similar between the two treatment arms.

A second study by the RTOG compared three different chemo/radiation therapy regimens for patients with stage III/IV squamous cell carcinoma of the head and neck. RTOG 97-03 randomized patients to receive 70 Gy in 7 weeks with either cisplatin and 5-FU during the last 10 days of treatment, hydroxyurea (Hydrea) and 5-FU with radiation therapy delivered on alternating weeks, or weekly cisplatin and paclitaxel. Two-year survival rates for all three arms ranged from 60%-67%.

Surgery Excision through the open mouth of all but small palatal and tonsillar lesions is generally inadequate. Substantial dissection is needed to provide exposure, and reconstruction is often required. A mandibulotomy, composite resection of the mandible, and/or total laryngectomy are occasionally required.

OROPHARYNGEAL SITE: BASE OF THE TONGUE

Cancer of the base of the tongue is far less common than that of the oral tongue.

Anatomy

The base of the tongue is bordered anteriorly by the circumvallate papillae and posteriorly by the epiglottis. There is a rich lymphatic network, with metastases frequently seen in levels II-V.

Natural history

The base of the tongue is notorious for lesions that infiltrate deeply into muscle and are advanced at diagnosis. This finding is probably due to the relatively asymptomatic anatomic location. Thus, bimanual oral examination with digital palpation is a critical part of the physical examination.

Most patients present with pain and dysphagia. Other symptoms include a neck mass, weight loss, otalgia, and trismus.

All oropharyngeal cancers have a strong propensity to spread to the lymph nodes, and base of the tongue tumors are no exception. Approximately 70% of patients with T1 primary base of the tongue tumors have clinically palpable disease in the neck and 20%-30% have palpable, bilateral lymph node metastases. The risk of nodal metastases increases with increasing T stage and approaches 85% for T4 lesions.

Treatment

Early-stage disease Stage I or II cancers may be treated equally effectively with either surgical resection or radiation therapy (65-70 Gy in 6-7 weeks) alone. Radiation therapy often results in a lesser functional deficit.

With surgery, lymphadenectomy is recommended due to the high frequency of metastatic spread. If irradiation of the primary is employed, both sides of the neck should be treated, even if the nodes do not seem to be involved.

Advanced disease More advanced disease may require total resection of the tongue base with supraglottic or total laryngectomy to ensure complete removal of disease. Limited laryngeal resection may result in recurrent aspiration, which is not tolerated by many patients. Total laryngectomy may be the only way to isolate the airway from oral secretions and eliminate the risk of aspiration. Chemoradiation via external-beam irradiation or irradiation alone combined with an implant can be curative for patients with advanced tumors of the tongue base and is often the treatment of choice.

Results In general, the prognosis of cancers of the tongue base is poor due to their advanced stage at presentation. The extent of nodal disease predicts survival. For T1 and T2 cancers, local control rates approach 85%. The major determinant of treatment failure is the tumor's growth pattern, with a high local control rate for exophytic lesions and a far worse rate for infiltrative tumors.

OROPHARYNGEAL SITE: TONSIL AND TONSILLAR PILLAR

The tonsil and the tonsillar pillar are the most common locations for tumors in the oropharynx.

Natural history

Tonsillar fossa tumors tend to be more advanced and more frequently metastasize to the neck than do tonsillar pillar cancers. At presentation, 55% of patients with fossa tumors have N2 or N3 disease, and contralateral metastases are common. Symptoms include pain, dysphagia, weight loss, a mass in the neck, and trismus.

Treatment

Single-modality therapy (irradiation or surgery alone) is acceptable for T1 and T2 tumors. Irradiation alone (60-70 Gy in 6-7 weeks) may be curative for more advanced tumors, although many of these lesions will require surgery combined with irradiation. The neck should always be included in treatment planning. More advanced disease usually requires surgery combined with irradiation (60-70 Gy in 6-7 weeks).

HYPOPHARYNX

Hypopharyngeal cancers are approximately one-third as common as laryngeal cancers.

Epidemiology and risk factors

Approximately 80% of cases occur in men. Plummer-Vinson syndrome is a known risk factor, and, in endemic areas, the male-female ratio is 1:4, reversing the otherwise 4:1 male-female ratio.

Anatomy

The hypopharynx (or laryngopharynx) is the entrance to the esophagus. The superior aspect (above the plane of the hyoid bone) communicates with the oropharynx, and the inferior border is situated in the plane of the lowest part of the cricoid cartilage (the esophageal inlet). The anterior surface (postcricoid area) is contiguous with the posterior surface of the larynx. The pharyngeal musculature forms the lateral and posterior walls. The piriform sinuses are within the hypopharynx on each side of the larynx.

The hypopharynx contains three subsites: the paired piriform sinuses (lateral, pear-shaped funnels); the posterior pharyngeal wall, from the level of the vallecula to the level of the cricoarytenoid joints; and the postcricoid area (pharyngoesophageal junction), which begins just below the arytenoids and extends to the inferior border of the cricoid cartilage. Seventy percent of hypopharyngeal cancers occur in the piriform sinuses.

Natural history

Hypopharyngeal tumors produce few symptoms until they are advanced (~70% are stage III at presentation). They may cause a sore throat, otalgia, a change in voice, odynophagia, or an isolated neck mass. Subtle changes on physical examination, including pooling of secretions, should be regarded with concern.

Nodal metastases Diffuse local spread is common and is due to tumor extension within the submucosa. Abundant lymphatic drainage results in a higher incidence of lymph node metastases than with other head and neck tumors. At

TABLE 6: TNM staging system for cancers of the larynx

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck [resectable], including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) (resectable)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck, including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus) (resectable)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures (unresectable)

presentation, 70%-80% of patients with hypopharyngeal tumors have palpable cervical lymph node metastases; in half of these patients, palpable cervical nodes are the presenting complaint. Levels II and III are most commonly involved. Bilateral metastases are seen in only 10% of patients with piriform sinus cancers but in 60% of those with postcricoid tumors.

Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node(s), more than 6 cm in greatest dimension
Distant metastases (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Synchronous lesions are common. Overall, 20%-25% of patients with hypopharyngeal cancer develop a second primary within 5 years, usually in the head and neck.

Chemotherapy and external-beam radiotherapy Similar in design to the VA Cooperative Laryngeal Cancer Study, a randomized trial of the European Organization for Research on the Treatment of Cancer (EORTC) has shown that initial therapy with cisplatin and 5-FU, followed by definitive irradiation in patients with complete remissions (or, alternatively, surgical salvage) results in at least equivalent survival relative to immediate pharyngolaryngectomy. Of patients treated with initial chemotherapy, 28% retained a functional larynx at 3 years.

Results In general, even when treatment includes both surgery and radiation therapy, hypopharyngeal cancer is difficult to control. The overall 5-year survival rate is 25%; this rate decreases by 50% in the presence of lymph node metastases.

LARYNX

Laryngeal cancers constitute approximately 1.2% of all new cancer diagnoses in the United States. Approximately 9,500 new cases are expected in the year 2003.

To evaluate nonsurgical management of patients with stage III/IV laryngeal cancer, a phase III study tested three arms: (A) induction cisplatin/5-FU followed by radiation therapy; (B) concurrent cisplatin and radiation therapy; (C) radiation therapy alone. Total radiation dose was 70 Gy in 7 weeks with 2 Gy/fractions in all arms. A total of 507 patients were entered in the study, with 65% of them having stage III disease. Two-year laryngectomy-free survival was 58% for arm A, 66% for arm B, and 55% for arm C. The study concluded that concurrent chemoradiotherapy significantly increased the time to laryngectomy *(Forastiere AA, Berkey B, Maor M, et al: Proc Am Soc Clin Oncol [abstract] 20:2a, 2001).*

Epidemiology and risk factors

Laryngeal cancer most commonly affects middle-aged to older men who smoke tobacco and drink alcohol. There is no racial predominance,s but, in the past, blacks have presented at a younger age with a poorer prognosis. Most laryngeal squamous cell carcinomas result from exposure to carcinogens that cause diffuse mucosal changes (field effect).

Anatomy and pathology

Laryngeal anatomy is complex and includes cartilages, membranes, and muscles. The three subsites of the larynx are the glottis, or true vocal cords; the supraglottis, which includes the false cords, epiglottis, and aryepiglottic folds; and the subglottis, which is the region below the glottis and within the cricoid cartilage. The TNM staging system for cancers of the larynx is outlined in Table 6.

Treatment

Laryngectomy All or part of the larynx may need to be removed to achieve surgical control of laryngeal cancer. Decision-making for partial laryngectomy is complex and depends on the patient's wishes, the extent of local disease, and

the skills of the surgeon and radiation oncologist. Pharyngocutaneous fistula occurs in < 15% of patients but remains the most common complication following total laryngectomy. Spontaneous closure with conservative treatment and local wound care occurs in the majority of patients.

External-beam radiation therapy and chemoradiation With improvements in techniques and fractionation schedules, external-beam radiation therapy, which allows for laryngeal preservation, is an option for all but the most advanced tumors. A combination of induction chemotherapy (cisplatin plus 5-FU) and subsequent radiation therapy (6,600-7,600 cGy) may be used to preserve the larynx in the majority of patients with T3 laryngeal cancer without compromising survival. This approach is complex and requires careful attention during all phases of treatment.

Results In patients with T1 and T2 tumors of the glottic or supraglottic larynx, radiation therapy is associated with local control rates of 75%-95%. Patients with T3 tumors can expect local control rates of 50%-65% with radiation therapy alone.

The VA Cooperative Laryngeal Cancer Study randomized patients with resectable squamous cell carcinoma of the larynx to receive either standard surgery followed by radiation therapy or neoadjuvant therapy with cisplatin and 5-FU followed by radiation therapy for those achieving a good response to chemotherapy. Approximately two-thirds of patients survived 2 years following the combination of either chemotherapy plus irradiation or resection plus irradiation. Of those patients initially treated with chemotherapy and irradiation, one-third required a total laryngectomy because of a lack of response to treatment; the larynx was successfully preserved in two-thirds of these patients.

As in all head and neck cancer patients, the development of second cancers continues to result in mortality for several years following successful therapy.

LARYNGEAL SITE: SUPRAGLOTTIS

Supraglottic tumors occur less frequently than tumors of the true vocal cords. The epiglottis is the most common location for supraglottic cancers.

Natural history

Tumors close to the glottis produce symptoms sooner than tumors at other subsites. However, nearly 60% of patients with supraglottic tumors have T3 or T4 primary tumors at presentation.

The supraglottis has a rich lymphatic network. There is an associated high incidence of lymph node metastases in early-stage tumors (40% for T1 tumors). The incidence of metastases in a clinically N0 neck is about 15%. The incidence of bilateral cervical lymph node involvement is about 10%, and this rate increases to 60% for anterior tumors. The neck is a frequent site of recurrence in patients with supraglottic malignancies.

Treatment

Treatment of the primary tumor Appropriate cancers may be treated with partial laryngectomy. A supraglottic laryngectomy removes the upper portion of the thyroid cartilage and its contents, including the false vocal cords, as well as the epiglottis and aryepiglottic folds. This approach preserves speech and swallowing, but more extensive resections increase the demands on lung function, limiting their utility. Supraglottic laryngectomy is not well tolerated by patients with impaired lung function because of aspiration.

In patients with T1-T2 tumors, local control rates with radiation therapy (65-70 Gy in 6-7 weeks) exceed 80%. Also, as noted above, T3 tumors may be treated with radiation therapy (same regimen). Supraglottic laryngectomy is seldom appropriate as salvage therapy following irradiation due to complications, including swelling, difficulty swallowing, and poor wound healing. The usual salvage operation for persistent supraglottic cancer following radiation therapy is total laryngectomy.

More advanced disease requires combined-modality treatment and often requires total laryngectomy. Radiation therapy may be employed with curative intent, as may induction chemotherapy followed by irradiation, as described earlier.

Treatment of the neck The high incidence of cervical metastases makes treatment of the neck a necessity. About one-third of clinically negative necks contain involved nodes, and the incidence of recurrence in the untreated neck is high. In the surgical treatment of T1-T2 primary tumors, bilateral selective neck dissection is recommended.

Larynx preservation Data from RTOG 91-11 continue to mature, and an update to this trial was reported at the 2002 American Society of Therapeutic Radiology and Oncology (ASTRO) meeting, including rates of locoregional control, laryngectomy-free survival, and overall survival. This three-arm study randomized 517 evaluable patients to receive one of the following regimens: induction chemotherapy (with cisplatin and 5-FU) and conventional irradiation of 7,000 cGy, concurrent chemotherapy (cisplatin given days 1, 22, and 43), or irradiation therapy alone to 7,000 cGy. Locoregional control for the three arms was 61%, 78%, and 56%, respectively ($P < .01$). The number of laryngectomies was 43, 21, and 49, respectively, for the three arms. Overall survival was about 75% for each arm. The authors concluded that concurrent chemoradiation therapy was superior to the other regimens, with the highest locoregional control rates and laryngectomy-free survival.

Results The cure rate for early cancers of the larynx approaches 80% or more. Half of patients with T3 cancer are cured, whereas more than two-thirds of patients with T4 cancer will die of cancer.

LARYNGEAL SITE: GLOTTIS

The glottis is the most common location of laryngeal cancer in the United States, comprising more than half of all cases.

Natural history

The cure rate for tumors of the true vocal cords is high. These cancers produce symptoms early, and, thus, most are small when detected. Approximately 60% are T1 and 20% are T2. Normal cord mobility implies invasion of disease limited to the submucosa. Deeper invasion results in impaired vocal cord motion; this finding is most common in the anterior two-thirds of the vocal cord.

The true vocal cords have very little lymphatic drainage. Cervical metastases are infrequent with T1 and T2 tumors.

Treatment

Treatment of the primary tumor Carcinoma in situ is highly curable and may be treated equally well with microexcision, laser vaporization, or radiation therapy. Treatment decisions should be based on the extent of local disease. Multiple recurrences should heighten suspicion for an invasive component, and a more aggressive approach, such as partial or total laryngectomy, should be employed. T1 and T2 tumors may be treated by partial laryngectomy or radiation therapy (65-70 Gy in 6.5-7 weeks). In selected patients, partial laryngectomy can be performed after irradiation failure for T1-T2 glottic cancer, with excellent tumor control, satisfactory laryngeal function, and no increase in morbidity.

Advanced T4 disease is best treated with total laryngectomy. The standard treatment for T3 glottic cancer has been laryngectomy. However, many T3 lesions are now being treated with concomitant chemoradiotherapy, with salvage laryngectomy required in ~25% of patients for residual/recurrent disease or laryngeal dysfunction. Induction chemotherapy followed by irradiation can also be used, as described earlier.

Treatment of the neck Due to the sparse lymphatic network and low incidence of cervical metastases, elective neck dissection is indicated only for transglottic lesions. Palpable disease obviously requires neck treatment.

Results Cure rates by tumor size alone are as follows: T1, 90%; T2, 80%; T3, 50%; and T4, 40%. Neck involvement worsens the prognosis dramatically.

LARYNGEAL SITE: SUBGLOTTIS

Subglottic cancer is unusual, accounting for fewer than 10% of all laryngeal cancers.

Natural history

These cancers tend to be poorly differentiated, and, as the region is clinically "silent," most present as advanced lesions (~70% are T3-T4). The subglottis also has rich lymphatic drainage, and the incidence of cervical metastases is 20%-30%.

Treatment

Partial laryngectomy is not practical for the treatment of tumors in the subglottis, and, thus, therapy usually includes total laryngectomy plus neck dissection. Combination therapy (surgery plus radiation therapy [60-65 Gy in 6-7 weeks]) is recommended for more advanced disease.

Results The cure rate for the uncommon T1 and T2 tumors is ~70%. Most failures occur in the neck. The cure rate for more advanced lesions is ~40%.

UNKNOWN HEAD AND NECK PRIMARY SITE

The cervical lymph nodes are the most common metastatic site at which squamous cell carcinoma is found.

Natural history

Most patients who present with squamous carcinoma involving cervical lymph nodes, especially in the upper or middle portion of the cervical chain, will have a primary site within the head and neck. When the lower cervical or supraclavicular lymph nodes are involved, a primary lung cancer should be suspected.

In the overwhelming majority of these cases, the primary lesion will be discovered based on history, physical examination, proper radiographic evaluation (CT and/or MRI), and examination with the patient under anesthesia with endoscopy (direct laryngoscopy, nasopharyngoscopy, esophagoscopy, and bronchoscopy). "Silent" primary tumors are most often discovered in the base of the tongue or tonsillar fossa.

Treatment

A substantial percentage of patients achieve long-term disease-free survival after treatment of the involved side of the neck. Locoregional control and survival are diminished by multiple lymph nodes and the presence of extracapsular extension of disease in the involved neck.

Irradiation alone Patients with early-stage neck disease (N1 disease or small, mobile N2a disease) can often be treated with radiotherapy alone. Radiation therapy dosages and techniques should be similar to those used in patients

with advanced primary head and neck cancer. The nasopharynx, oropharynx, and hypopharynx should be included in the irradiated field.

Surgery alone When neck dissection is used at the initial treatment, a primary tumor in the head and neck subsequently becomes obvious in about 20% of patients.

Irradiation alone or combined with surgery Combination therapy (surgery plus radiation therapy [60-65 Gy in 6-7 weeks]) is recommended for patients who are found at surgery to have multiple involved nodes or extracapsular extension or who have suspected residual microscopic disease in the neck without a clinically detectable tumor. Open nodal biopsy does not appear to compromise outcome as long as adequate radiotherapy is delivered subsequently.

In most modern series utilizing predominantly combination therapy, 5-year survival rates exceed 50%. The volume of tumor in the involved neck influences outcome, with N1 and N2 disease having a significantly higher cure rate than N3 disease or massive neck involvement. Regional relapse is usually predicted by extranodal disease.

Chemotherapy The role of chemotherapy for metastatic squamous carcinoma in cervical lymph nodes remains undefined.

RECURRENT HEAD AND NECK CANCER

As mentioned previously, surveillance after treatment of head and neck cancer is mandatory, as early detection of second primary cancers or locoregional recurrence affords the best chance for disease control. Nearly two-thirds of patients whose head and neck cancer recurs develop tumor at (or near) the primary site or in the neck nodes. Eighty percent of head and neck cancer recurrences eventuate within 2 years. Development of recurrent tumor in the neck is the single most common type of treatment failure in patients with squamous cell carcinoma of the upper aerodigestive tract.

Differentiating recurrence from late complications of irradiation Differentiating between recurrent carcinoma and significant sequelae of radiotherapy is a difficult clinical problem at all sites within the head and neck. Any suspicious mucosal changes, enlarged nodes in the neck, or discrete subcutaneous nodules warrant prompt biopsy.

Candidates for surgery Different choices of first treatment (ie, surgery or radiation therapy) and the intensity of follow-up influence success in treating recurrence. Aggressive surgical intervention should be offered to two groups of patients with recurrent local or regional disease: those whose therapy is chosen with curative intent and those who have the prospect for significant palliation.

The types of recurrence that may be approached surgically with the greatest likelihood of success include (1) metastases in the neck after initial treatment limited to the primary tumor alone and (2) reappearance or persistence of cancer at a site previously treated with radiotherapy alone. Salvage resection may also be considered in other situations, however. They include the appearance of cancer in the neck after prior irradiation or neck dissection, at the margins after previous resection, and even at the base of the skull.

Although surgery is the standard of care for the treatment of recurrent disease, there is a growing body of evidence suggesting that reirradiation with concurrent chemotherapy can save selected patients when resection is not possible. Several institutions have reported experiences retreating patients, and these results led to the development of the first multi-institution reirradiation study.

A single-arm, phase II study (RTOG 96-10) evaluated toxicity and therapeutic results for patients with recurrent squamous cell carcinoma of the head and neck. Eighty-six patients received four weekly courses of 1.5 Gy fractions twice daily with concurrent 5-FU and hydroxyurea. Each cycle was separated by 1 week of rest. The median survival was 8.1 months and the 1- and 2-year survival rates were 41.7% and 16.2%, respectively. Compared with patients who experienced early recurrences, patients whose disease recurred 3 years after the original irradiation fared better, with 1- and 2-year survival rates of 48.1% and 32.1%, respectively.

Unless a patient cannot tolerate an operation, resection of discrete local or regional recurrent tumors should be entertained as the first course of treatment. Management of recurrences involves complex decision-making and requires familiarity with multidisciplinary care.

SUGGESTED READING

Al-Sarraf M, LeBlanc M, Giri PGS, et al: Superiority of 5-year survival with chemoradiotherapy (CR-RT) vs radiotherapy in patients (pts) with locally advanced nasopharyngeal cancer (NPC). Intergroup (0099) (SWOG 8892, RTOG 8817, ECOG 2388) phase III study: Final report (abstract). Proc Am Soc Clin Oncol 20:227a, 2001.

Ang KK, Harris J, Garden AS, et al: Concomitant boost radiation and concurrent cisplatin for advanced head and neck carcinomas: Preliminary results of a phase II trial of the RTOG (99-14). Int J Radiat Oncol Biol Phys 54:2–3, 2002.

Cooper JS, Pajak TF, Forastiere AA, et al: Patterns of failure for resected advanced head and neck cancer treated by concurrent chemotherapy and radiation therapy: An analysis of RTOG 95-01/intergroup phase III trial. Int J Radiat Oncol Biol Phys 54:2, 2002.

Corry J, Smith JG, Peters LJ: The concept of a planned neck dissection is obsolete. Cancer J 7:472–474, 2001.

Forastiere AA, Berkey B, Maor M, et al: Phase III trial to preserve the larynx: Induction chemotherapy and radiotherapy vs concomitant chemoradiotherapy vs radiotherapy alone, intergroup trial R91-01 (abstract). Proc Am Soc Clin Oncol 20:2a, 2001.

Garden AS, Pajak TF, Vokes E, et al: Preliminary results of RTOG 97-03: A phase II randomized trial of concurrent radiation (RT) and chemotherapy for advanced squamous cell carcinomas (SCC) of the head and neck (abstract). Proc Am Soc Clin Oncol 20:223a, 2001.

Lin A, Kim HM, Terrell JE, et al: Head and neck cancer-specific quality of life (HN-QOL) and its correlation with xerostomia following parotid-sparing irradiation (RT) of head and neck cancer. Int J Radiat Oncol Biol Phys 54:167, 2002.

Maor MH, Berkey B, Forastiere AA, et al: Larynx preservation and tumor control in stage III and IV laryngeal cancer: A three-arm randomized intergroup trial: RTOG 91-11. Int J Radiat Oncol Biol Phys 54:2–3, 2002.

NCCN practice guidelines for head and neck cancer. Oncology 14(11A):163–194, 2000.

Ozyigit G, Chao CK: Quality of life assessment in head and neck cancer patients treated with definitive or postoperative IMRT. Int J Radiat Oncol Biol Phys 54:167–168, 2002.

Parliament MB, Scrimger R, Kurien E, et al: Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity modulated radiotherapy (IMRT) for head and neck cancer (HNC). Int J Radiat Oncol Biol Phys 54:165–166, 2002.

Shoaib T, Souta DS, MacDonald DG, et al: The accuracy of head and neck carcinoma sentinel lymph node biopsy in the clinically N0 neck. Cancer 91:2077–2083, 2001.

Wheeler RH, Harris J, Spencer S, et al: RTOG 96-10: Phase II study of reirradiation (RRT) with concurrent hydroxyurea (HU) and 5-fluorouracil (FU) in patients (pts) with recurrent squamous cell cancer of the head and neck: Survival results (abstract). Proc Am Soc Clin Oncol 20:222a, 2001.

Wolden S, Pfister D, Zelefsky M, et al: Intensity modulated radiation therapy improves locoregional control for nasopharyngeal carcinoma (abstract). Proc Am Soc Clin Oncol 21:240a, 2002.