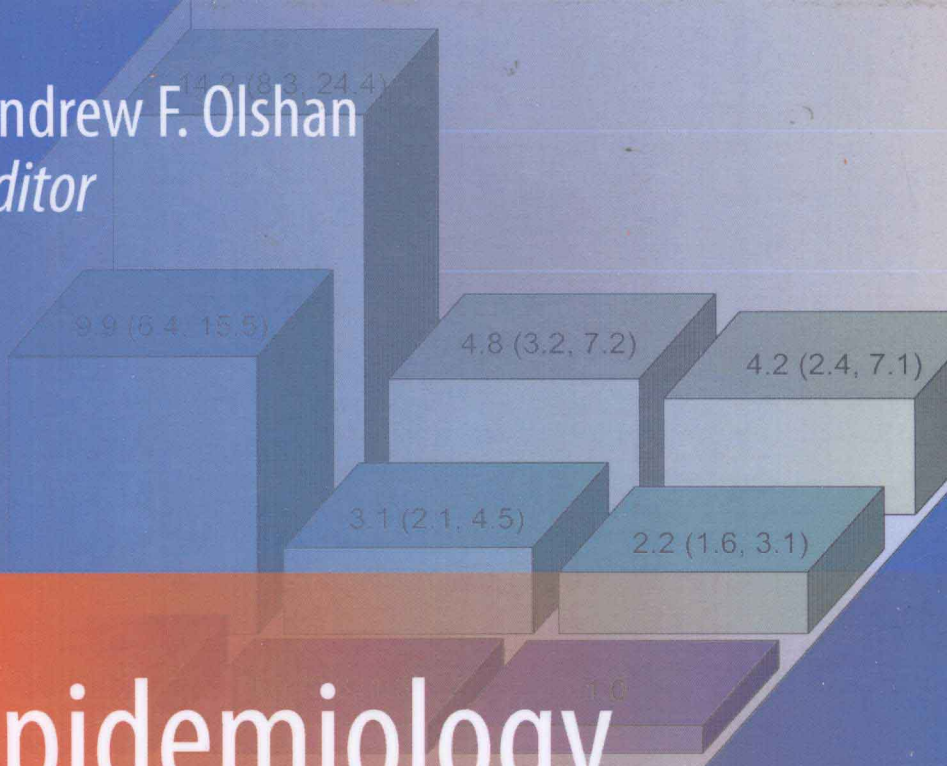
Andrew F. Olshan
Editor



Epidemiology, Pathogenesis, and Prevention of Head and Neck Cancer

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Preface

Head and neck cancer – defined here as cancers of the oral cavity, pharynx, and larynx – comprises a fascinating tumor model. With two well established risk factors – tobacco and alcohol – and the potential for screening, these tumors provide unique opportunities for prevention and control. Further, the known etiological factors also help frame studies of mechanisms and susceptibility. Finally, the role of the human papillomavirus (HPV) offers another cancer model to investigate the viral etiology of cancer.

This context has led to wonderful interdisciplinary research opportunities among clinicians, epidemiologists, and molecular biologists and geneticists. In that spirit, we have brought together the world's experts on the epidemiology, clinical aspects, and molecular biology of head and neck cancer. The book includes a spectrum of research foci from descriptive epidemiology to molecular biology. I hope that active researchers in the field of head and neck cancer will find these current summaries useful to guide their research as well as drawing in those not working on this cancer. The book illustrates much of what is known and also highlights the many unanswered questions.

I wish to thank the authors who worked so hard to develop their chapters. I also thank Rachel Warren of Springer Press for her editorial guidance.

Chapel Hill, NC

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Contents

Classification, Clinical Features, and Molecular Genetic Models

Wayne M. Koch and Melonie Nance

Squamous cell carcinoma of the upper aerodigestive tract (head and neck squamous cell carcinoma, HNSCC) is often considered to be a single disease based on the cell of origin (mucosal epithelium) and histologic features. However, distinctive phenotypic patterns and genotypic correlates increasingly suggest that it might be more accurately thought of as consisting of different entities. These observations have been evolving in the context of the more traditional paradigms of tumor classification based on well established parameters such as primary tumor anatomical site, stage, and histologic features. Taken together, clinicians seek to use new and traditional tumor features to categorize tumors, predict their potential clinical course, and select appropriate strategies for their detection and treatment.

Traditional Concepts of Tumor Classification

Squamous cell carcinoma (SCCA) is the most common malignancy of the head and neck, accounting for 92% of cases [1]. In the head and neck, several types of SCCA present with different tumor behaviors, prognoses, and severities. Traditionally, tumors are classified by stage and anatomic site of origin. Patterns of tumor growth and invasion may vary predictably with the anatomic barriers or pathways that prevent or allow extension. Within the head and neck, these sites are classified based on established anatomic parameters. The upper aerodigestive tract is organized into the following site categories: Nasopharynx, Oral Cavity, Oropharynx, Hypopharynx, Larynx, and Trachea. Beyond the upper aerodigestive tract, the paranasal sinuses, skull base, salivary glands, endocrine glands, skin, ear, and temporal bones are other possible sites where primary SCCA tumors may arise.

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Tumor Stage

Each anatomical site category has its own tumor staging system combining a numerical metric for the primary tumor, nodal basin, and distant metastatic field. The primary lesion stage (T stage) is based on size and location relative to important surrounding structures. The nodal (N) stage is determined by the size, the side (ipsilateral or contralateral to the primary) and the number of suspicious nodes. The distant metastasis (M) stage is generally a plus/minus dichotomy. The overall stage schema takes into account all three components and assigns a Roman numeral Stage I–IV. Staging may be clinical, based on physical examination and radiologic evaluation, or pathological, based on the size and extent of tumor judged after surgical resection. Staging systems as defined by the American Joint Committee on Cancer (AJCC)[1] and the United International Cancer Committee (UICC) have been widely adopted and used. Ideally, tumor stage categories are each distinctly predictive of outcome with poorer survival seen with each increment of advancing stage. This system is imperfect and undergoes periodic scrutiny with suggestions for revision. However, in many clinical outcome studies, stage remains one of the only valuable prognostic parameters.

Anatomical Categories

The boundaries of the oral cavity extend from the mucosal surface of the lips to the junction of the hard/soft palate (above), and the circumvillate papillae of the tongue (below). The oral cavity includes the lips, the gingivobuccal sulcus, the upper and lower alveolus ridges, buccal mucosa, floor of mouth, gingiva, retromolar trigone, and the hard palate. From the oral cavity, tumor may spread via the foramina of the hard or soft palate. Other avenues include circumventing the muscular sling of the floor of mouth, the buccopharyngeal fascia, which is just deep to the buccal mucosa, or into the mandible. Posteriorly, the retromolar trigone is contiguous with the mandibular mucosa, which is closely approximated to the bone; hence, cancer here often invades the periosteum. Lymphatic drainage is most often unilateral from the oral tongue and superficial floor of mouth, and bilateral from the deeper floor of mouth musculature and root of tongue. Tumor staging in the oral cavity is based on the size of the lesion and/or the presence of invasion into deeper structures. The depth of invasion has been shown to be an important prognostic factor as well; it is associated with the likelihood of metastatic nodal involvement, but is not currently included in staging.

The Nasopharynx is continuous with the nasal cavity through the choanae. It is bounded by the skull base superiorly and extends to the level of the soft palate inferiorly, where it is contiguous to the oropharynx. Laterally, the cartilage of the eustachian tube creates a bulge at its opening, the torus tubarius. Just posterior and

[1] AJCC Cancer Staging Manual, 6th edn. Springer-Verlag, New York, NY, 2003.

superior to the torus is the Fossa of Rosenmuller, the site of origin of most nasopharyngeal carcinoma (NPC). NPC is currently classified into three WHO subclassifications based on histologic differentiation: (I) keratinizing, (II) nonkeratinizing, and (III) undifferentiated.

The oropharynx extends from the soft palate to the epiglottis. It is continuous with the posterior oral cavity and demarcated by the circumvallate papillae at the posterior 1/3 of the oral tongue. Within the oropharynx, the tongue base and vallecula are anterior, glossoepiglottic folds are lateral, and the prevertebral pharyngeal wall is posterior.

Additional lymphoid tissue, the lingual tonsil, is located under the mucous membrane of the posterior third of the tongue. Together, the tonsillar tissues of the nasopharynx and oropharynx form a ring of lymphoid tissue that surrounds the entrances into the pharynx from the nose and the mouth known as Waldeyer's ring. The oropharynx is continuous with the hypopharynx below.

The Hypopharynx is a long mucosal region that extends from the epiglottis to the esophageal inlet at the level of C6, running posterior to and wrapping around the larynx. In this region, field cancerization and submucosal lymphatic spread are of paramount importance, and skip lesions are not uncommon. Tumors often spread beyond visible borders of lesion. The hypopharynx is continuous with the esophagus inferiorly, and with the larynx anteriorly through the laryngeal aditus, which is formed by the epiglottis and the aryepiglottic folds. On either side of these folds and medial to the thyroid cartilage are two pyramidal recesses, called the pyriform sinuses. Two-thirds of hypopharyngeal tumors start in the pyriform sinus. From there, tumors may spread laterally to the thyroid cartilage or the thyroid gland. Medial spread can involve the paraglottic space of the hemilarynx, crico-arytenoid joint, or recurrent laryngeal nerve leading to vocal fold immobility. The contralateral pyriform can become involved through spread across the posterior pharyngeal wall or postcricoid mucosa to the other side. The most common sites of metastases from the Hypopharynx are ipsilateral level II–IV nodes. Upon presentation, the incidence of nodal spread is very high: around 75%.

One-third of hypopharyngeal tumors arise from the posterior pharyngeal wall. From this site, tumor spread can affect the prevertebral fascia posteriorly. Retropharyngeal metastases to the nodes of Rouvier are common. Hypopharyngeal tumors that start in the postcricoid region are uncommon (5% of lesions). However, they pose a risk of circumferential spread along and into cricoid and cervical esophagus. They have the lowest rate of regional metastasis and tend to spread to paratracheal nodes first.

The Larynx extends from the epiglottis and the aryepiglottic folds to the cricoid cartilage. It communicates with the laryngopharynx above and the trachea below through the laryngeal aditus . Its lateral walls have two infoldings of mucous membrane, the vestibular folds above and the vocal folds below. The ventricle between the folds has a lateral extension, the saccule, between the vestibular fold and the thyroid cartilage. The mucous membrane of the larynx is primarily ciliated columnar epithelium. The larynx structurally consists of cartilages, muscles, and ligaments that are essential to its role in phonation.

One-third of laryngeal SCCA occurs in the supraglottis, which includes the epiglottis (lingual and laryngeal surfaces), false cords (including ventricle and

saccule), arytenoids, and aryepiglottic folds. Tumors of the infrahyoid epiglottis have poorer prognosis due to the propensity of tumor spread inferiorly into the pre-epiglottic space. Lymphatic spread involves bilateral levels II–IV, with notably frequent involvement of IIB.

Most laryngeal SCCA starts in the Glottis which is comprised of the true vocal cords, ventricular floor, anterior commissure, interarytenoid region, and extends inferiorly to a variable distance below true cords. Clinical presentation usually includes dysphonia. Regional metastases from here are very rare in early-stage disease. However, in advanced lesions (T3-4), metastases are more common and may first involve level VI nodes, before moving laterally. The subglottis is the area from 10 mm below the anterior commissure and 5 mm below posterior true cords and extends to inferior border of cricoid. This region is the most infrequent primary site of the larynx cancer at <5% incidence. Disease in the subglottis most often presents with stridor or shortness of breath. From here, regional metastases are generally seen in levels II–IV and IV of the neck.

Histologic Features

While SCCA has traditionally been categorized by its anatomic site of occurrence, other factors may also be important in determining prognosis. Over the years, several different types of SCCA have been described. Some histopathologic findings have been shown to have prognostic significance. Certain tumor characteristics, such as keratin production; level of differentiation; nuclear appearance; mitoses; and host factors, such as inflammation, desmoplastic reaction, patterns of invasion, and vascular invasion, have been described as adjuncts to clinical staging for predicting outcome. Though this information may be useful, no firm and consistent evidence supports including histologic features in formal cancer classification outside of the nasopharynx. Staging remains based solely on clinical examination and diagnostic imaging.

Histopathologically, SCCA is classified as squamous proliferation that is either keratinizing or nonkeratinizing in nature. Some variants, including basaloid and adenosquamous CA are known to have more aggressive tumor behavior. They are characterized by their small cells with scant cytoplasm, high mitotic rate, and comedonecrosis. Histologic grade is judged according to the degree the squamous cells have departed from their normal appearance. Characteristics that contribute to higher grade malignancy include pleomorphism, hyperchromatism, and increased mitotic activity (especially abnormal mitosis). The presence of keratin is an important determinant, indicating better differentiated lesions (lower grade). Keratin is found within the cytoplasm of well-differentiated cells and scattered throughout many invasive carcinomas in the form of pink-staining, rounded, lamellated "pearls." These epithelial pearls are not characteristic of carcinoma in situ; however, they are seen in some other forms of cancer such as basal cell carcinoma.

Cells present at the deep invasive tumor front have different molecular and morphological characteristics than those in superficial areas of the tumor. For this reason, several studies have shown that the deep invasive tumor front is the most important area

of the tumor for prognostication [2, 3]. Bryne et al. proposed a scoring system that excludes the evaluation of luminal areas of the tumor, demonstrating the prognostic value of grading the deep invasive front. They found that the most important events pertaining to invasion and distant spread occur in this area, and devised a scoring system with high prognostic value. This scoring system assesses cell differentiation, pattern of invasion, and host immune response expressed by peritumoral inflammation [4]. Byrne et al. reported a strong correlation between the total malignancy grade and prognosis in glottic carcinoma. Subsequently, Kurokawa et al. and others used multivariate analysis to support the predictive value of invasive front grading (IFG) in association with the prognosis and survival rates in oral squamous cell carcinoma [5–7]. IFG was shown to provide useful prognostic information when selecting the most appropriate treatment modalities in both glottic and oral cavity squamous cell carcinoma studies [6].

Risk Factors

Etiologic factors and other pathologic agents have been implicated and have an important role in prognosis. Tobacco use, especially in conjunction with alcohol abuse has been the best supported etiologic factor in HNSCCA in the oral cavity and larynx. Over 75% of head and neck squamous cell carcinoma (HNSCC) patients are long-time tobacco users, and many of them ingest alcoholic beverages regularly [8]. The fact that alcohol promotes the carcinogenic effects of tobacco is well established. Numerous studies have found that smoking confers a several fold increased risk of developing HNSCC. Blot and colleagues found a 1.9-fold risk in males and 3.0-fold risk in females [9]. For HNSCC, the cancer risk is directly proportional to the amount of tobacco consumed, measured in pack-years. Compared with nondrinkers, males who consume 1–2 drinks per day have a 1.7-fold HNSCC cancer risk. This risk for heavy drinkers is more than 3.0-fold. Individuals who smoke (2 packs per day) and drink (4 units of alcohol per day) have a multiplicative increase in risk with an odds ratio of 35 for the development of HNSCC, compared to controls [9]. Smokeless tobacco confers approximately a 4.0-fold risk of oral cavity SCCA. When HNSCC is caused by these factors, resulting tumors are often very invasive and can respond poorly to even the most aggressive trimodal therapies, including surgery, radiation, and chemotherapies.

An increasing number of studies suggest that comorbidity is an important prognostic indicator of mortality among head and neck cancer patients [10]. Reid et al. used the American Society of Anesthesiologists'(ASA) class to measure comorbidity for research and clinical purposes and in comparison to the previously validated Charlson index [11]. The ASA class had comparable or even greater prognostic ability for mortality as assessed by multivariate analyses and retained prognostic ability well beyond the peri-operative period. Their study supported the use of the ASA class as a measure of comorbidity and prognostic factor for elderly patient undergoing surgical therapy for HNSCCA.

Some tumors may be described as more indolent due to their relatively predictable response to standard therapies. In 1999, Koch et al. identified distinctive clinical categories in HNSCC patients when comparing groups of nonsmokers with smokers [8]. They found that nonsmokers were more likely to present at extremes of age (old or young), to be female, and to have oral cavity tumors. In this study, they noted that most tumors of the larynx and hypopharynx arose in smokers or former smokers. Additionally, molecular alteration patterns in the tumors of smokers have been found to be distinct from those of nonsmokers. Smokers were more likely to have tumors with p53 mutation, LOH at chromosomes 3p, 4q, and 11q13, and a higher overall percentage of chromosomal microsatellite alterations [8].

The human papilloma virus (HPV) is an epitheliotropic virus detected in samples of oropharyngeal squamous cell carcinoma. Infection alone is not sufficient for malignant conversion; however, results of multiple studies have shown that HPV has an etiologic role in a subset of head and neck squamous cell carcinoma. The rate of HPV DNA presence is slightly higher in the tumors of nonsmokers. Patients with HPV-related tumors are more likely to be nonsmokers and of younger age than the traditional smoker-drinker HNSCC patient. Detailed analyses of tumors for HPV genomic DNA and viral oncogene expression in case–control studies have indicated that HPV infection is nearly exclusively associated with HNSCC of the oropharynx, where it is observed in 40–60% of patients. HPV-positive oropharyngeal tumors are clinically and molecularly distinct.

Analyses of retrospective case series have consistently demonstrated that patients with HPV-positive tumors have a better prognosis than patients whose tumors are HPV negative. This subject is more fully developed in a subsequent chapter. Retrospective survival assessment, though, may be limited by relatively poor quality of collected data and the absence of information on confounding factors of known prognostic value. Recently, Fakhry et al. reported their evaluation of the effect of tumor HPV status on treatment response and survival outcomes among a prospectively collected series of patients with oropharyngeal or laryngeal squamous cell carcinoma [12]. The study participants were uniformly treated with induction chemotherapy and chemoradiation as participants in a phase II trial conducted by the Eastern Cooperative Oncology Group (ECOG). They reported improved survival outcomes for patients with HPV-positive HNSCC and increased tumor sensitivity to chemotherapy and chemoradiation. Several hypotheses have been proposed to explain these differences, including the absence of field cancerization, effective immune surveillance to viral-specific tumor antigens, and an intact apoptotic response to radiation. Because of this distinct tumor behavior, some researchers have proposed a reduction in the intensity of standard therapy in HPV positive disease to reduce the comorbidities caused by chemotherapy and external been radiation therapy. They also propose a modification to the current staging system to include HPV status. These concepts are currently under investigation.

Other proposed etiologic influences include the proximity of tissue to mechanical irritation, thermal injury, and/or chemical exposure. Environmental ultraviolet light exposure has been associated with the development of lip cancer as well as skin SCCA. Solar exposure has been implicated in the pathogenesis of

squamous cell carcinomas arising on the vermilion border of the lower lip, and skin of the nose, scalp, and upper auricles. Other entities associated with SCCA include Plummer–Vinson syndrome (achlorhydria; iron deficiency anemia; and mucosal atrophy of the mouth, pharynx, and esophagus), chronic infection with syphilis, ill-fitting dentures, and long-term immunosuppression (30-fold increase with renal transplant).

Within the oral cavity various benign appearing lesions have some propensity for premalignancy. Leukoplakia, a white mucosal lesion, may occur due to hyperkeratosis and dysplasia. These changes have been estimated to have a variable malignant transformation rate. Erythroplakia is a red appearing lesion of the mucosal surface. The red color is due to increased vascularity due to angiogenesis, which portends a higher likelihood of malignancy than leukoplakia.

A separate class of white lesion, which is a distinct entity, is lichen planus. This is a common affliction, likely of autoimmune inflammatory or multifactorial origin. It has been described as either being (1) induced by drugs or dental materials; (2) associated with chronic liver or other disorders; or (3) idiopathic with immunopathogenesis involving T-cells in particular [13]. The characteristic lesions are most commonly found on the lateral tongue and the buccal mucosa. Lesions are classified as reticular, plaque-like, atrophic, papular, erosive, and bullous. They are characterized by white or gray strands forming a linear or reticular pattern on a violaceous background. Erosive lesions have a shallow, red, ulcerative center. Lichen planus has been found to have a 1% risk of malignant transformation overall, however, rates have been found to be higher in men [14, 15].

Nodal Basin Involvement

Regional metastasis to cervical lymph nodes (LN) occurs commonly, and is often the location of treatment failure or recurrence in HNSCC. At the time of primary tumor presentation the presence and size of cervical LN metastases, quantified by N-stage, is the most accurate predictor of cancer-related outcome (in the absence of distant metastases). The presence of LN metastases reduces disease-related survival per primary site and stage by 50% [1]. Lymph node metastases are undetectable using any means for the first month or even for years. Undetectable nodal disease is termed "occult". Because of the high propensity and danger of occult disease in cervical nodes, standard regimens for all but the earliest cancers include some form of treatment for the neck. Depending on tumor site and likely location of metastases, treatment may be therapeutic or elective and include neck dissection or radiation. When LN metastases are clinically evident, (N+ disease), the path of disease spread is obvious and treatment can be tailored accordingly.

Radiographic imaging is limited with respect to the ability to identify occult metastases in the cN0 setting. Imaging modalities, including MRI and PET/CT are increasingly more sensitive, but may sacrifice specificity. They are not as accurate as histologic evaluation of malignancy. Neck palpation alone has reported error

rate of 20–50%. Analysis of the neck dissection specimen is the most definitive determination of nodal status of the neck. END (Elective neck dissection) provides pathologic staging of the neck, which permits better estimates of patient prognosis. Without clinical or radiologic evidence of cervical LN metastasis the patient is staged as clinically N0 (cN0). In this setting, lymphatic metastases may exist but are too small for radiological or clinical detection. In cN0 cases, there are three therapeutic options; (1) clinical observation; (2) elective neck dissection; and (3) elective neck irradiation. Clinical observation, sometimes referred to as watchful waiting, is the active process of repeated clinical examinations at regularly scheduled intervals. In that paradigm, surgical neck dissection is reserved for those who subsequently develop regional metastases.

Extensive literature exists indicating the likelihood of occult involvement of lymph nodes based on the site and stage of the primary lesion. These estimates are derived from studies of the rate of nodal involvement at the time of neck dissection or after long-term follow-up [16–18]. Anatomic, radiologic, and pathologic investigations of neck dissection specimens have corroborated the classical clinical study by Lindberg published in 1972 [19, 20]. These studies and others have shown that, for example, neck levels II, III, and IV are at greatest risk for metastases from carcinomas of the oropharynx, larynx, and hypopharynx. In addition, the prevalence of level V involvement is low (2–7%), and always lower in a clinically N0 neck compared with a clinically positive neck. In supraglottic and subglottic HNSCC, the risk for regional metastasis is around 50%. This risk is even higher for hypopharyngeal carcinomas. Conversely, this risk in glottic HNSCC is only 25–40%, even for advanced stage (T4) tumors. In addition to surveillance for ipsilateral spread, an appropriate level of suspicion for contralateral metastatic disease must be maintained. Sites such as the soft palate, tongue base, and supraglottis have the highest density of crossing lymph channels. Because of this, approximately 20% of patients with soft palate or tongue base disease already have contralateral cervical lymph node metastases at the time of presentation. Based on anatomic site, tumor stage, and histopathologic characteristics of the primary, a cervical metastatic risk of at least 15–20% is generally accepted as an indication for treatment. For clinically N0 disease, this criterion includes all stages of T3 and some T2 supraglottic and hypopharyngeal carcinomas, T3 and many T2 oral cavity carcinomas, and carcinomas of the tongue thicker than 3 mm.

In light of the estimated risk, elective treatment may be planned for the clinically negative neck. (END) is not only therapeutic, but also a part of the staging process. Pathologic examination of the neck dissection specimen allows for meticulous investigation of each cervical node to understand the extent of disease spread and predict prognosis. Subclinical or occult metastases may be detected on pathologic examination of neck dissection specimens. This is perhaps the most important type of discordance between the clinical and pathologic nodal stages (Koch et al.).

Elective neck irradiation (ENI) is another option that delivers therapy to all possibly affected neck levels. It is often undertaken when radiation is chosen as treatment modality for the primary tumor. These active forms of treatment have expected sequelae such as postoperative pain, stiffness and numbness, or postradiation xerostomia. For many years these management options have been debated among