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histologically by the presence of Paget cells. These tumors present as moist erythematous patches on anogenital or axillary skin of the elderly.

Outcomes are generally good with surgery, and 5-year diseasespecific survival is 95% with localized disease. Advanced age and extensive disease at presentation confer poorer prognosis. RT or topical imiquimod can be considered for more extensive disease. Local management may be challenging because these tumors often extend far beyond clinical margins; surgical excision with MMS has the high est cure rates. Similarly, MMS is the treatment of choice in other rare cutaneous tumors with extensive subclinical extension such as derma tofibrosarcoma protuberans. Kaposi’s sarcoma (KS) is a soft tissue sarcoma of vascular origin that is induced by the human herpesvirus 8. The incidence of KS increased dramatically during the AIDS epidemic but has now decreased tenfold with the institution of highly active antiretroviral therapy. Acknowledgment Walter Urba, MD, PhD, provided valued feedback and suggested improvements to this chapter. Clinical photos were generously provided from the OHSU Swinyer Collection (Leonard Swinyer, MD) and by Drs. Elizabeth Berry, Alexander Witkowski, Joanna Ludzik, Debbie Miller, Alison Skalet, and Justin Leitenberger. Dermoscopic images were pro vided by Elizabeth Berry, Alexander Witkowski, Joanna Ludzik, and Debbie Miller. Reflectance confocal microscopy images were provided by Drs. Alexander Witkowski and Joanna Ludzik. PART 4 Oncology and Hematology ■ ■FURTHER READING Atkins ME et al: Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: The DREAMseq trial—ECOG-ACRIN EA6134. J Clin Oncol 41:186, 2022. Elder DE et al: The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma. Arch Pathol Lab Med 44:500, 2020. Faries MD et al: Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 376:2211, 2017. Harms PW et al: The biology and treatment of Merkel cell carcinoma: Current understanding and research priorities. Nat Rev Clin Oncol 15:763, 2018. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology (NCCN guidelines): Melanoma. Available from https://www.nccn.org/professionals/physician_gls/pdf/melanoma. pdf. Tawbi HA et al: Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 386:24, 2022. Wu YP et al: A systematic review of interventions to improve adher ence to melanoma preventive behaviors for individuals at elevated risk. Prev Med 88:153, 2016. Everett E. Vokes

Head and Neck Cancer Epithelial carcinomas of the head and neck arise from the mucosal surfaces in the head and neck and typically are squamous cell in origin. This category includes tumors of the paranasal sinuses, the oral cavity, and the nasopharynx, oropharynx, hypopharynx, and larynx. Tumors of the salivary glands differ from the more common carcinomas of the head and neck in etiology, histopathology, clinical presentation, and therapy. They are rare and histologically highly heterogeneous. Thyroid malignancies are described in Chap. 397.

■ ■INCIDENCE AND EPIDEMIOLOGY The number of new cases of head and neck cancers (oral cavity, phar ynx, and larynx) in the United States was estimated at 66,920 in 2023, accounting for about 6% of adult malignancies; estimated deaths were 15,400. The worldwide incidence exceeds half a million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx. The incidence of oropharyngeal cancers has been increasing in Western countries. Nasopharyngeal cancer is endemic in East Asia and some Mediterranean countries. ■ ■ETIOLOGY AND GENETICS Alcohol and tobacco use are the most significant environmental risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral can cers. Other potential carcinogens include marijuana and occupational exposures such as nickel refining, exposure to textile fibers, and woodworking. Some head and neck cancers have a viral etiology. Epstein-Barr virus (EBV) infection is frequently associated with nasopharyngeal cancer, especially in endemic areas. EBV antibody titers can be measured to screen high-risk populations and are under investigation to monitor treatment response. Nasopharyngeal cancer has also been associated with consumption of salted fish and indoor pollution. In Western countries, the human papillomavirus (HPV) is associ ated with a rising incidence of tumors arising from the oropharynx, that is, the tonsillar bed and base of tongue. Over 50% of oropha ryngeal tumors are caused by HPV in the United States, and in many urban centers, this proportion is higher. HPV-16 is the dominant viral subtype, although HPV-18 and other oncogenic subtypes are seen as well. Alcohol- and tobacco-related cancers, on the other hand, have decreased in incidence. HPV-related oropharyngeal cancer occurs in a younger patient population and is associated with increased num bers of sexual partners and oral sexual practices. It is associated with a better prognosis, especially for nonsmokers. Vaccination with the nine-valent HPV vaccine may prevent the disease but is not likely to result in a lower incidence for several decades due to long latency of the carcinogenic process. Dietary factors may contribute. The incidence of head and neck cancer is higher in people with the lowest consumption of fruits and vegetables. Certain vitamins, including carotenoids, may be protective if included in a balanced diet. Supplements of retinoids, such as cisretinoic acid, have not been shown to prevent head and neck cancers (or lung cancer) and may increase the risk in active smokers. No spe cific risk factors or environmental carcinogens have been identified for salivary gland tumors. ■ ■HISTOPATHOLOGY, CARCINOGENESIS, AND MOLECULAR BIOLOGY Squamous cell head and neck cancers are divided into well-differentiated, moderately well-differentiated, and poorly differentiated categories. Poorly differentiated tumors have a worse prognosis than well-differen tiated tumors. For nasopharyngeal cancers, the less common differenti ated squamous cell carcinoma is distinguished from nonkeratinizing and undifferentiated carcinoma (lymphoepithelioma) that contains infiltrating lymphocytes and is commonly associated with EBV. Salivary gland tumors can arise from the major (parotid, subman dibular, sublingual) or minor salivary glands (located in the submucosa of the upper aerodigestive tract). Most parotid tumors are benign, but half of submandibular and sublingual gland tumors and most minor salivary gland tumors are malignant. Malignant tumors include muco epidermoid and adenoid cystic

carcinomas and adenocarcinomas. The mucosal surface of the entire pharynx is exposed to alcohol- and tobacco-related carcinogens and is at risk for the development of a premalignant or malignant lesion. Erythroplakia (a red patch) or leukoplakia (a white patch) can be histopathologically classified as hyperplasia, dysplasia, carcinoma in situ, or carcinoma. However, most head and neck cancer patients do not present with a known his tory of premalignant lesions. Multiple synchronous or metachronous cancers can also be observed. In fact, over time, patients with treated

early-stage tobacco- and alcohol-related head and neck cancer are at greater risk of dying from a second malignancy than from a recurrence of the primary disease. Second head and neck malignancies are usually not therapy induced; they reflect the exposure of the upper aerodigestive mucosa to the same carcinogens that caused the first cancer. These second prima ries develop in the head and neck area, the lung, or the esophagus. Thus, computed tomography (CT) screening for lung cancer in heavy smokers who have already developed a head and neck cancer is rec ommended. Rarely, patients can develop a radiation therapy–induced sarcoma after having undergone prior radiotherapy for a head and neck cancer. Much progress has been made in describing the molecular features of head and neck cancer. These features have allowed investigators to describe the genetic and epigenetic alterations and the mutational spectrum of these tumors. Early reports demonstrated frequent overex pression of the epidermal growth factor receptor (EGFR). Overexpres sion was shown to correlate with poor prognosis. However, it has not proved to be a good predictor of tumor response to EGFR inhibitors, which are active in only about 10–15% of patients as single agents. Complex genetic analyses, including those by The Cancer Genome Atlas project, have been performed. p53 mutations are found fre quently with other major affected oncogenic driver pathways including the mitotic signaling and Notch pathways and cell cycle regulation in HPV-negative tumors. HPV oncogenes act through direct inhibition of the p53 and RB tumor-suppressor genes, thereby initiating the carcino genic process. HRAS mutations are detected in 4–8% of patients with recurrent head and neck cancer and may be therapeutically targetable in a small patient subset. While overall mutation rates are similar in HPV-positive and carcinogen-induced tumors, the specific mutational signature of HPV-positive tumors differs, with frequent alteration of the PI3K pathway and occasional mutations in KRAS. Overall, these alterations affect mitogenic signaling, genetic stability, cellular prolif eration, and differentiation. ■ ■CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS Most tobacco-related head and neck cancers occur in patients older than age 60 years. HPV-related malignancies are frequently diagnosed in younger patients, usually in their forties or fifties, whereas EBVrelated nasopharyngeal cancer can occur at all ages, including in teen agers. The manifestations vary according to the stage and primary site of the tumor. Patients with nonspecific signs and symptoms in the head and neck area should be evaluated with a thorough otolaryngologic examination, particularly if symptoms persist longer than 2–4 weeks. Males are more frequently affected than women by head and neck can cers, including HPV-positive tumors. Cancer of the nasopharynx typically does not cause early symptoms. However, it may cause unilateral serous otitis media due to obstruc tion of the eustachian tube, unilateral or bilateral nasal obstruction, or epistaxis. Advanced nasopharyngeal carcinoma causes neuropathies of the cranial nerves due to skull base involvement. Carcinomas of the oral cavity present as nonhealing ulcers, changes in the fit of dentures, or painful lesions and masses. Tumors of the tongue base or oropharynx can cause decreased tongue mobility and alterations in speech. Cancers of the oropharynx or hypopharynx rarely cause early symptoms, but they may cause sore throat and/or otalgia. HPV-related tumors

frequently present with neck lymphade nopathy as the first sign. Hoarseness may be an early symptom of laryngeal cancer, and persistent hoarseness requires referral to a specialist for indirect laryn goscopy and/or radiographic studies. If a head and neck lesion treated initially with antibiotics does not resolve in a short period, further workup is indicated; to simply continue the antibiotic treatment may be to lose the chance of early diagnosis of a malignancy. Advanced head and neck cancers in any location can cause severe pain, otalgia, airway obstruction, cranial neuropathies, trismus, ody nophagia, dysphagia, decreased tongue mobility, fistulas, skin involve ment, and massive cervical lymphadenopathy, which may be unilateral

Physical Examination in Office FNA or excision of lymph node If lymphoma, sarcoma, or salivary gland tumor If squamous cell carcinoma Panendoscopy and directed biopsies. Search for occult primary with biopsies of tonsils, nasopharynx, base of tongue, and pyriform sinus. Specific workup Stage-specific multimodality therapy Consider curative neck dissection Postoperative radiotherapy or chemoradiotherapy CHAPTER 82 FIGURE 82-1 Evaluation of a patient with cervical adenopathy without a primary mucosal lesion; a diagnostic workup. FNA, fine-needle aspiration. or bilateral. Some patients have enlarged lymph nodes even though no primary lesion can be detected by endoscopy or biopsy; these patients are considered to have carcinoma of unknown primary (Fig. 82-1). Tonsillectomy and directed biopsies of the base of tongue can iden tify a small primary tumor that frequently will be HPV related. If the enlarged nodes are located in the upper neck and the tumor cells are of squamous cell histology, the malignancy probably arose from a muco sal surface in the head or neck. Tumor cells in supraclavicular lymph nodes may also arise from a primary site in the chest or abdomen. Head and Neck Cancer The physical examination should include inspection of all visible mucosal surfaces and palpation of the floor of the mouth and of the tongue and neck. In addition to a tumor, leukoplakia (a white muco sal patch) or erythroplakia (a red mucosal patch) may be observed; these “premalignant” lesions can represent hyperplasia, dysplasia, or carcinoma in situ and require biopsy. Further examination should be performed by a specialist. Additional staging procedures include CT or MRI of the head and neck to identify the extent of the disease. Patients with lymph node involvement should have CT scan of the chest and upper abdomen to screen for distant metastases. In heavy smokers, the CT scan of the chest can also serve as a screening tool to rule out a second lung primary tumor. A positron emission tomogra phy (PET) scan can help to identify or exclude distant metastases. CT and PET scans may also be useful in evaluating response to therapy. The definitive staging procedure is an endoscopic examination under anesthesia, which may include laryngoscopy, esophagoscopy, and bronchoscopy; during this procedure, multiple biopsy samples are obtained to establish a primary diagnosis, define the extent of primary disease, and identify any additional premalignant lesions or second primaries. Head and neck tumors are classified according to the tumor-nodemetastasis (TNM) system of the American Joint Committee on Cancer (AJCC) (Fig. 82-2). This classification varies according to the specific anatomic subsite. In general, primary tumors are classified as T1 to T3 by increasing size, whereas T4 usually represents invasion of another structure such as bone, muscle, or root of tongue. Lymph nodes are staged by size, number, and location (ipsilateral vs contralateral to the primary). Overt distant metastases are found in <10% of patients at initial diagnosis and are more common in patients with advanced lymph node stage; microscopic involvement of the lungs, bones, or liver is more common, particularly in patients with advanced neck lymph node disease. HPV-related oropharyngeal malignancies have consistently been shown to have a better prognosis, and in the eighth

Definition of TNM Stage I T1 N0- Tumor ≤2 cm in greatest dimension ≤5 mm depth of invasion (DOI) Stage II T2 Tumor ≥2 cm but not more than 4 cm in greatest dimension OR DOI >5 mm and ≤10 mm PART 4 Oncology and Hematology Stage III T3 Tumor ≥4 cm OR DOI

> 10 mm Stage IVA T4a N2a- Tumor invades skin, mandible, ear canal, fascial nerve, and/or floor of mouth Stage IVB T4b T4b Tumor invades skull base and/or pterygoid plates and/or encases carotid artery Stage IVC M1 M1 Any T Any N FIGURE 82-2 Tumor-node-metastasis (TNM) staging system. (Figure based on the AJCC Cancer Staging Manual, 8th edition.) edition of the AJCC staging manual, a separate staging system that takes into account the more favorable outlook of these patients has been included. According to this system, patients with advanced nodal stage can still be considered to have the equivalent of an overall early stage (and associated good prognosis). In patients with lymph node involvement and no visible primary, the diagnosis should be made by fine-needle aspiration or by

DOI = depth of invasion Stage groupings T1 N0 N0 M0 No regional lymph node metastasis T2 N0 N0 M0 No regional lymph node metastasis N0- N1 T3 N0 M0 Metastasis in a single ipsilateral lymph node, ≤3 cm in greateast dimension N1- N1 T1 M0 N1 T2 M0 T3 N1 M0 ≤3 cm N2 T4a N0 M0 Metastasis in a single ipsilateral lymph node,

> 3 cm but ≤6 cm T4a N1 M0 T1 N2 M0 Metastasis in multiple ipsilateral lymph nodes, none >6 cm N2b- T2 N2 M0 Metastasis in bilateral or contralateral lymph nodes, none >6 cm N2c- T3 N2 M0 T4a N2 M0 ≤6 cm N3 M0 Any N Metastasis in a lymph node >6 cm in greatest dimension or clinically overt extranodal extension N3- N3 M0 Any T 6 cm lymph node excision (especially if only a single node appears involved) (Fig. 82-1). If the results indicate squamous cell carcinoma, a panen doscopy should be performed, with biopsy of all suspicious-appearing areas and directed biopsies of common primary sites, such as the nasopharynx, tonsil, tongue base, and pyriform sinus. HPV-positive tumors especially can have small primary tumors that spread early to locoregional lymph nodes.

TREATMENT Head and Neck Cancer Patients with head and neck cancer can be grossly categorized into three clinical groups: those with localized disease, those with locally or regionally advanced disease (lymph node positive), and those with recurrent and/or metastatic disease below the neck. Comorbidities associated with tobacco and alcohol abuse can affect treatment outcome and define long-term risks for patients who are cured of their disease. LOCALIZED DISEASE Nearly one-third of patients have localized disease, that is, T1 or T2 (stage I or stage II) lesions without detectable lymph node involve ment or distant metastases. These patients are treated with curative intent by either surgery or radiation therapy. The choice of modality differs according to anatomic location and institutional expertise. Radiation therapy is often preferred for laryngeal cancer to preserve

voice function, and surgery is preferred for small lesions in the oral cavity to avoid the long-term complications of radiation, such as xerostomia and osteoradionecrosis and dental decay. Randomized data have shown that a prophylactic staging neck dissection should be part of the surgical procedure to eliminate occult nodal meta static disease. Overall 5-year survival is 60–90%. Most recurrences occur within the first 2 years following diagnosis and are usually local. LOCALLY OR REGIONALLY ADVANCED DISEASE Locally or regionally advanced disease—disease with a large pri mary tumor and/or cervical lymph node metastases—is the stage of presentation for >50% of patients. Such patients can also be treated with curative intent, but not usually with surgery or radiation therapy alone. Combined-modality therapy, including surgery and/ or radiation therapy and chemotherapy, is most successful. Che motherapy can be administered as induction chemotherapy (che motherapy before surgery and/or radiotherapy) or as concomitant (simultaneous) chemotherapy and radiation therapy. The latter is most commonly used and supported by the best evidence. Five-year survival rates exceed 50% in many trials, but part of this increased survival may be due to an increasing fraction of study populations with HPV-related tumors who carry a better prognosis. HPV test ing of newly diagnosed tumors should be performed for patients with oropharyngeal tumors at the time of diagnosis. Clinical trials for HPV-related tumors are focused on exploring reductions in treatment intensity, especially radiation dose, in order to ameliorate long-term toxicities (fibrosis, swallowing dysfunction). In patients with intermediate-stage tumors (stage III and early stage IV), concomitant chemoradiotherapy can be administered as a primary treatment for patients with unresectable disease, to pursue an organ-preserving approach especially for patients with laryngeal cancer (omission of surgery), or in the postoperative set ting for smaller resectable tumors with adverse prognostic features. Induction Chemotherapy In this strategy, patients receive che motherapy (current standard is a three-drug regimen of docetaxel, cisplatin, and fluorouracil [5-FU]) before surgery and radiation therapy. Most patients who receive three cycles show tumor reduc tion, and the response is clinically “complete” in up to half of patients. This “sequential” multimodality therapy allows for organ preservation in patients with laryngeal and hypopharyngeal cancer and results in higher cure rates compared with radiotherapy alone. Concomitant Chemoradiotherapy With the concomitant strategy, chemotherapy and radiation therapy are given simultaneously rather than in sequence. Tumor recurrences from head and neck cancer develop most commonly locoregionally (in the head and neck area of the primary and draining lymph nodes). The concomi tant approach is aimed at enhancing tumor cell killing by radiation therapy in the presence of chemotherapy (radiation enhancement) and is a conceptually attractive approach for bulky tumors. Toxicity

(especially mucositis, grade 3 or 4, in 70–80%) is increased with concomitant chemoradiotherapy. However, meta-analyses of ran domized trials document an improvement in 5-year survival of 8% with concomitant chemotherapy and radiation therapy. Cisplatin is preferentially given weekly during a course of daily radiotherapy over a 6- to 7-week course. In addition, concomitant chemoradio therapy produces better laryngectomy-free survival (organ pres ervation) than radiation therapy alone in patients with advanced larynx cancer. For patients with advanced nasopharyngeal cancer, the addition of neoadjuvant chemotherapy before concomitant chemoradiotherapy has been adopted as standard of care leading to 5-year survival rates exceeding 80% in a Southeast Asian study. The outcome of HPV-related cancers also seems to be favorable following cisplatin-based chemoradiotherapy. However, trials sub stituting cisplatin with the EGFR inhibitor cetuximab in that patient population have shown inferior survival. Similarly, the investigation of immune checkpoint inhibitors in this setting has not yet led to improved outcomes.

The success of concomitant chemoradiotherapy in patients with unresectable disease has led to the testing of a similar approach in patients with resected intermediate-stage disease as a postopera tive therapy. Concomitant chemoradiotherapy produces a signifi cant improvement over postoperative radiation therapy alone for patients whose tumors demonstrate higher risk features, such as extracapsular spread beyond involved lymph nodes, involvement of multiple lymph nodes, or positive margins at the primary site following surgery. CHAPTER 82 A monoclonal antibody to EGFR (cetuximab) increases sur vival rates when administered during radiotherapy compared with radiotherapy alone and has been considered for patients unable to tolerate concurrent chemoradiotherapy. The addition of cetuximab to standard chemoradiotherapy regimens has failed to show further improvement in survival and is not recommended. Head and Neck Cancer TREATMENT APPROACHES FOR HPV-RELATED HEAD AND NECK CANCERS Given consistent observations of high survival rates for patients with advanced HPV-related oropharyngeal tumors using combinedmodality treatment strategies, de-escalation protocols have attracted widespread interest. The goal here is to decrease the long-term morbidity resulting from high-dose radiation therapy, including extensive neck fibrosis, swallowing problems, and osteoradione crosis of the jaw. Current studies are investigating the use of lower radiation doses, the use of induction chemotherapy and subse quent omission of chemotherapy or administration of significantly reduced chemoradiation doses in very good responders, and other strategies. In addition, interest has increased in surgical approaches using robotic surgery, which allows better visualization of the base of tongue and tonsil. While technically feasible, a large number of patients with disease involving multiple lymph nodes will still require postoperative chemoradiotherapy, thus negating the goal of treatment de-escalation. At present, treatment guidelines for HPV-related tumors are identical to carcinogen-induced tumors. It is hoped that de-escalation approaches will be validated by ongoing controlled clinical trials. RECURRENT AND/OR METASTATIC DISEASE Five to 10% of patients present with metastatic disease, and 30–50% of patients with locoregionally advanced disease experience recurrence, frequently outside the head and neck region. Patients with recurrent and/or metastatic disease are, with few exceptions, treated with pal liative intent. Some patients may require local or regional radiation therapy for pain control, but most are given systemic therapy. Combination chemotherapy formerly was the first-line systemic therapeutic approach to patients with recurrent disease after prior curative intent surgery and/or chemoradiotherapy or those present ing initially with metastatic disease. In particular, a combination of cisplatin with 5-FU and cetuximab (the EXTREME regimen) was frequently used.

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