

(or lung cancer) and may increase the risk in active smokers. No specific 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-differentiated tumors. For nasopharyngeal cancers, the less common differentiated 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, submandibular, 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 mucoepidermoid 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 history of premalignant lesions. Multiple synchronous or metachronous cancers can also be observed. In fact, over time, patients with early-stage 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 primaries 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 should be considered. 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 overexpression of the epidermal growth factor receptor (EGFR). Overexpression 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 successful in only about 10–15% of patients. *p53* mutations are also found frequently with other major affected oncogenic driver pathways including the mitotic signaling and Notch pathways and cell cycle regulation. The PI3K pathway is frequently altered, especially in HPV-positive tumors, where it is the only mutated cancer gene identified to date. Overall, these alterations affect mitogenic signaling, genetic stability, cellular proliferation, and differentiation. HPV is known to act through inhibition of the *p53* and *RB* tumor-suppressor genes, thereby initiating the carcinogenic process, and has a mutational spectrum distinct from alcohol- and tobacco-related tumors.

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 EBV-related nasopharyngeal cancer can occur in all ages, including teenagers. 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 exam, particularly if symptoms persist longer than 2–4 weeks. Males are more frequently affected than women by head and neck cancers, including HPV-positive tumors.

Cancer of the nasopharynx typically does not cause early symptoms. However, it may cause unilateral serous otitis media due to obstruction

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. 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 lymphadenopathy as the first sign.

Hoarseness may be an early symptom of laryngeal cancer, and persistent hoarseness requires referral to a specialist for indirect laryngoscopy 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, odynophagia, dysphagia, decreased tongue mobility, fistulas, skin involvement, and massive cervical lymphadenopathy, which may be unilateral 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. 106-1). 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 mucosal surface in the head or neck. Tumor cells in supraclavicular lymph nodes may also arise from a primary site in the chest or abdomen.

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 tumors themselves, leukoplakia (a white mucosal patch) or erythroplakia (a red mucosal patch) may be observed; these “pre-malignant” 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 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 tomography (PET) scan may also be administered and can help to identify or exclude distant metastases. The definitive staging procedure is an

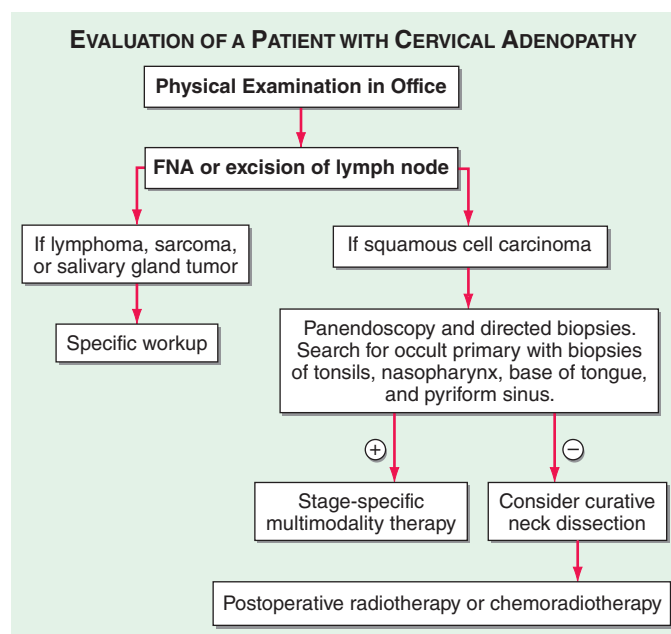


FIGURE 106-1 Evaluation of a patient with cervical adenopathy without a primary mucosal lesion; a diagnostic workup. FNA, fine-needle aspiration.