for RT because of the risks of long-term carcinogenesis and radiodermatitis. Imiquimod can be used to treat superficial and smaller nodular BCCs, although it is not FDA-approved for nodular BCC. Topical 5-fluorouracil therapy should be limited to superficial BCC. PDT, which uses selective activation of a photoactive drug by visible light, has been used in patients with numerous tumors. Intralesional chemotherapy (5-fluorouracil and IFN) for NMSC has existed since the mid-twentieth century, but is used so infrequently that recent consensus guidelines for the treatment of BCC and SCC do not include it. Like RT, it remains an option for well-selected patients who cannot or will not undergo surgery.

SQUAMOUS CELL CARCINOMA

Therapy for cutaneous SCC should be based on the size, location, histologic differentiation, patient age, and functional status. Surgical excision and MMS are standard treatments. Cryosurgery and ED&C have been used for premalignant lesions and small, superficial, in situ primary tumors. Lymph node metastases are treated with surgical resection, RT, or both. Systemic chemotherapy combinations that include cisplatin can palliate patients with advanced disease. SCC and keratoacanthomas that develop in patients receiving BRAF-targeted therapy should be excised, but their development should not deter the continued use of BRAF therapy. Retinoid prophylaxis can also be considered for patients receiving BRAF-targeted therapy, although no prospective studies have been completed thus far.

PREVENTION

The general principles for prevention are those described for melanoma earlier. Unique strategies for NMSC include active surveillance for patients on immunosuppressive medications or BRAF-targeted therapy. Chemoprophylaxis using synthetic retinoids and immunosuppression reduction when possible may be useful in controlling new lesions and managing patients with multiple tumors.

OTHER NONMELANOMA CUTANEOUS MALIGNANCIES

Neoplasms of cutaneous adnexae and sarcomas of fibrous, mesenchymal, fatty, and vascular tissues make up the remaining 1–2% of NMSCs.

Merkel cell carcinoma (MCC) is a neural crest–derived highly aggressive malignancy with mortality rates approaching 33% at 3 years. An oncogenic Merkel cell polyomavirus is present in 80% of tumors. Many patients have detectable cellular or humoral immune responses to polyoma viral proteins, although this immune response is insufficient to eradicate the malignancy. Survival depends on extent of disease: 90% survive with local disease, 52% with nodal involvement, and only 10% with distant disease at 3 years. MCC incidence tripled over the last 20 years with an estimated 1600 cases per year in the United States. Immunosuppression can increase incidence and diminish prognosis. MCC lesions typically present as an asymptomatic rapidly expanding bluish-red/violaceous tumor on sun-exposed skin of older white patients. Treatment is surgical excision with sentinel lymph node biopsy for accurate staging in patients with localized disease, often followed by adjuvant RT. Patients with extensive disease can be offered systemic chemotherapy; however, there is no convincing survival benefit. Whenever possible a clinical trial should be considered for this rare but aggressive NMSC, especially in light of the potential for new treatments directed at the oncogenic virus that causes this malignancy.

Extramammary Paget's disease is an uncommon apocrine malignancy arising from stem cells of the epidermis that are characterized 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 site-directed surgery, and 5-year disease specific survival is approximately 95% with localized disease. Advanced age and extensive disease at presentation are factors that confer diminished 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 highest cure rates. Similarly, MMS is the treatment of choice in other rare cutaneous tumors with extensive subclinical extension such as *dermatofibromasarcoma 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.

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106 Head and Neck Cancer

Everett E. Vokes

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. 405.**

INCIDENCE AND EPIDEMIOLOGY

The number of new cases of head and neck cancers (oral cavity, pharynx, and larynx) in the United States was 53,640 in 2013, accounting for about 3% of adult malignancies; 11,520 people died from the disease. 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 is increasing in recent years. Nasopharyngeal cancer is more commonly seen in the Mediterranean countries and in the Far East, where it is endemic in some areas.

ETIOLOGY AND GENETICS

Alcohol and tobacco use are the most significant risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral cancers. 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 of the Mediterranean and Far East. EBV antibody titers can be measured to screen high-risk populations. Nasopharyngeal cancer has also been associated with consumption of salted fish and in-door pollution.

In Western countries, the human papilloma virus (HPV) is associated with a rising incidence of tumors arising from the oropharynx, i.e., the tonsillar bed and base of tongue. Over 50% of oropharyngeal tumors are caused by HPV in the United States. 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 numbers of sexual partners and oral sexual practices. It is associated with a better prognosis, especially for nonsmokers.

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 *cis*-retinoic acid, have not been shown to prevent head and neck cancers