

**The Bethesda  
Handbook of**

# **Clinical Oncology**

**Fourth Edition**

**Jame Abraham  
James L. Gulley  
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# THE BETHESDA HANDBOOK OF CLINICAL ONCOLOGY

FOURTH EDITION

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THE BETHESDA  
HANDBOOK  

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OF CLINICAL  
ONCOLOGY

FOURTH EDITION

*We dedicate this book to those lives  
that are touched by cancer and to their  
caregivers who spend endless hours  
taking care of them.*

“May I never forget that the patient is  
a fellow creature in pain.  
May I never consider him merely a  
vessel of disease.”

—Maimonides  
(Twelfth-century  
philosopher and physician)



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# P R E F A C E

*The Bethesda Handbook of Clinical Oncology* is a clear, concise, and comprehensive reference book for the busy clinician to use in his or her daily patient encounters. The book has been compiled by clinicians who are working at the National Cancer Institute and National Institutes of Health, Johns Hopkins, Mayo Clinic, and Cleveland Clinic, as well as scholars from other academic institutions. To limit the size of the book, less space is dedicated to etiology, pathophysiology, and epidemiology and greater emphasis is placed on practical clinical information. For easy accessibility to the pertinent information, long descriptions are avoided, and more tables, pictures, algorithms, and phrases are included.

*The Bethesda Handbook of Clinical Oncology* is not intended as a substitute for the many excellent oncology reference textbooks available that are essential for a more complete understanding of the pathophysiology and management of complicated oncology patients. We hope that the reader-friendly format with its comprehensive review of the management of each disease with treatment regimens, including dosing and schedule, makes this book unique and useful for oncologists, oncology fellows, residents, students, oncology nurses, and allied health professionals.

The landscape of oncology has changed substantially since we published the first edition of the book more than 13 years ago. For the fourth edition, we have updated all chapters and added two new chapters, "Clinical Genetics" and "Diagnosis-Driven Individualization of Cancer Care." In addition, we have included multiple-choice questions for most chapters to enhance the learning experience and help clinicians prepare for their board examinations.

As always, we have attempted to capture the advances in the field and listened to the feedback from readers to improve this edition. We hope that anyone needing a comprehensive review of oncology will find *The Bethesda Handbook of Clinical Oncology* to be an indispensable resource.

Jame Abraham  
James L. Gulley  
Carmen J. Allegra

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# SECTION One

## Head and Neck

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### 1

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## Head and Neck Cancer

Carter Van Waes, Karl E. Haglund, and  
Barbara A. Conley

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### EPIDEMIOLOGY

The incidence of head and neck squamous cancer is more than 500,000 cases per year worldwide, and 40,000 to 60,000 cases per year in the United States, where it comprises approximately 3% to 5% of all new cancers and 2% of all cancer deaths. Most patients are older than 50 years, and incidence increases with age; the male-to-female ratio is 2:1 to 5:1. The age-adjusted incidence is higher among black men, and, stage-for-stage, survival among African Americans is lower overall than in whites. Death rates have been decreasing since at least 1975, with rates declining more rapidly in the last decade. Ninety percent of these cancers are squamous cell histology. The most common sites in the United States are the oral cavity, pharynx, larynx, and hypopharynx. Nasal cavity, buccal, paranasal sinus cancers, salivary gland malignancies, and various sarcomas, lymphomas, and melanoma are less common.

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### RISK FACTORS

Heavy alcohol consumption increases the risk of developing squamous head and neck cancer twofold to sixfold, whereas smoking increases the risk 5- to 25-fold, depending on gender, race, and the amount of smoking. Both factors together increase the risk 15- to 40-fold. Smokeless tobacco and snuff are associated with oral cavity cancers. Use of smokeless tobacco, or chewing betel with or without tobacco and slaked lime (common in many parts of Asia and some parts of Africa), is associated with premalignant lesions and oral squamous cancers.

Multifocal mucosal abnormalities have been described in patients with head and neck cancer ("field cancerization"). There is a 2% to 6% risk per year for a second head and neck, lung, or esophageal cancer in patients with a history of cancer in this area. Those who continue to smoke have the highest risk. Second primary cancers represent a major risk factor for death among survivors of an initial squamous carcinoma of the head and neck.

Epstein-Barr virus (EBV) has been detected in virtually all nonkeratinizing and undifferentiated nasopharyngeal cancers but less consistently in squamous nasopharyngeal cancers. Human papilloma-virus (HPV) infection is associated with up to 70% of cancers of the oropharynx and tonsil, and some larynx and squamous nasopharyngeal cancers. The incidence of HPV+ cancers seems to be increasing in several countries, and HPV positivity is more common in cancers in nonsmokers. Disorders of DNA repair (e.g., Fanconi anemia, dyskeratosis congenita) as well as organ transplantation with immunosuppression are also associated with increased risk of squamous head and neck cancer.

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## SCREENING

The U.S. Preventive Task Force makes no recommendations regarding regular screening for oral cancer in the general population, due to the low incidence and lack of sensitivity studies. They do recommend counseling for cessation of tobacco use and limitation of alcohol intake.

The American Cancer Society recommends oral examination during physician or dental appointments. The oral examination should include inspection of all mucosal areas, assessment of range of motion of tongue, bimanual palpation of floor of mouth, palpation of the tongue, and assessment of dental health.

Careful examination of the head and neck is warranted in individuals with risk factors (e.g., tobacco and/or alcohol use) and suggestive symptoms. Any local/regional complaints require evaluation, especially if symptoms persist for more than 4 weeks or after treatment for presumed infection.

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## PREVENTION AND CHEMOPREVENTION

The most important recommendation for prevention of head and neck cancer is to encourage smoking cessation and to limit alcohol intake. As risk for HPV-associated head and neck cancer is associated with multiple sexual partners, education on safer sexual practices may also be helpful. Consideration should be given to prophylactic administration of HPV vaccines to adolescents, a treatment currently approved by the U.S. Food and Drug Administration for prevention of cervical cancer (bivalent or quadrivalent vaccines) in females and genital warts in males (quadrivalent vaccine), as well as for prevention of anal precancers (quadrivalent vaccine). Data are currently being gathered on the effect of vaccination on incidence of HPV-related head and neck cancer.

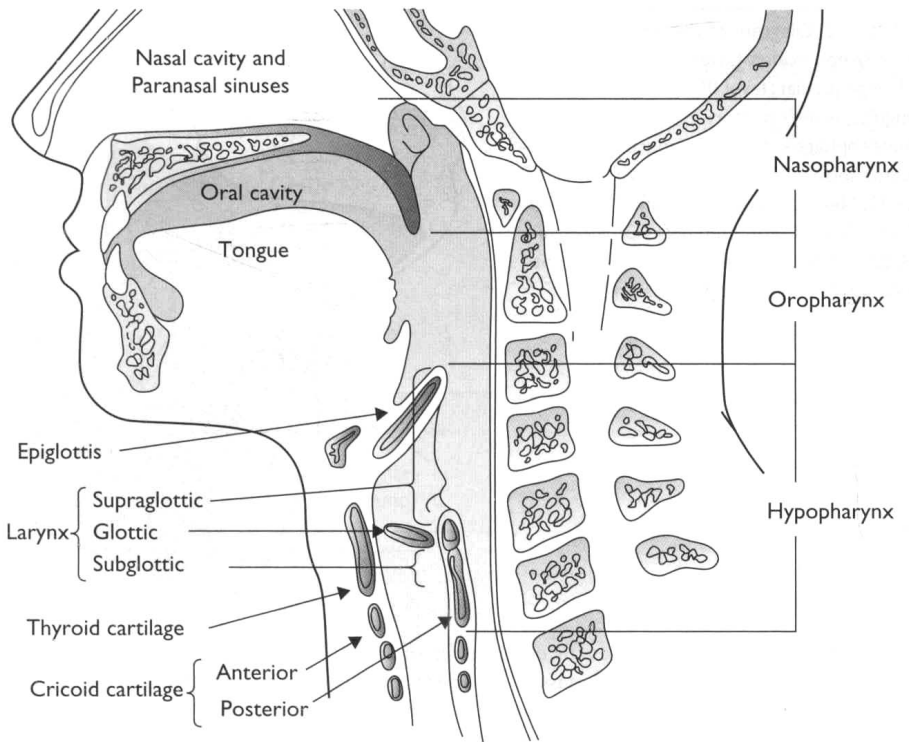
Premalignant lesions occurring in the oral cavity, pharynx, and larynx may manifest as leukoplakia (a white patch that does not scrape off and that has no other obvious cause) or erythroplakia (friable reddish or speckled lesions). These lesions require biopsy and potentially excision. The risk of leukoplakias without dysplasia progressing to cancer is about 4%. However, up to 40% of severe dysplasias or erythroplasias progress to cancer.

Presently, there is no effective chemoprevention for patients at risk for head and neck squamous cancer. A recent trial with PPAR agonist pioglitazone showed regression or reduction in size of leukoplakia in ~80% of subjects. A multicenter phase II study is underway. Chemoprevention outside a clinical trial is not recommended.

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## ANATOMY

A simplified depiction of extracranial head and neck anatomy is presented in Figure 1.1. The major regions and subsites of the upper aerodigestive tract are divided into the nose and paranasal sinuses; nasopharynx (NP); oral cavity (OC; lips, gingiva, buccal areas, floor of mouth, hard palate, and tongue anterior to the circumvallate papillae); oropharynx (OP; soft palate, tonsils, base of tongue and lingual tonsils, and pharyngeal wall between palate and vallecula); hypopharynx (HP; pharyngeal wall and piriform sinuses, between vallecula and esophageal inlet); and larynx (epiglottis, glottis, and subglottic trachea).



**FIGURE 1.1** Sagittal section of the upper aerodigestive tract. (Adapted from Oatis CA. *Kinesiology: The Mechanics and Pathomechanics of Human Movement*. Baltimore, MD: Lippincott Williams & Wilkins; 2004.)

Knowledge of the lymphatic drainage of the neck assists in identification of the site of a primary tumor when a palpable lymph node is the initial presentation, and in staging metastatic spread, enabling the surgeon or radiation oncologist to plan appropriate treatment of both primary and neck disease. The patterns of lymphatic drainage divide the neck into several levels (Fig. 1.2). Level I comprises the submental or submandibular nodes, which are most often involved with lesions of the oral cavity or submandibular salivary gland. Level II (upper jugular lymph nodes) extends from the skull base to the hyoid bone, and is frequently the site of metastatic presentation of naso- or oropharyngeal primaries. Level III (middle jugular lymph nodes between the hyoid bone and the lower border of the cricoid cartilage) and level IV (lower jugular lymph nodes between the cricoid cartilage and the clavicle) are most often involved by metastases from the hypopharynx, larynx, or above. Level V is the posterior triangle including cervical nodes along cranial nerve XI, frequently involved along with level II sites in cancers of the naso- and oropharynx. Level VI is the anterior compartment from the hyoid bone to the supra-sternal notch bounded on each side by the medial carotid sheath, and is an important region for spread of laryngeal and thyroid carcinomas. Level VII is the area of the superior mediastinum, and portends distant metastasis.

## PRESENTATION

Symptoms and signs most often include pain and/or mass effects of tumor, involving adjacent structures, nerves, or regional lymph nodes (Table 1.1). Adult patients with any of these symptoms for more than 4 weeks should be referred to an otolaryngologist. Delay in diagnosis is common due to patient