QUICK REFERENCE GUIDE TO

TNM Staging of Head and Neck Cancer and Neck Dissection Classification

Fourth Edition

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

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Table of Contents

Preface

Staging is the language essential to the proper and successful management of head and neck cancer patients. It is the core of diagnosis, treatment planning, application of therapeutics from multiple disciplines, recovery, follow-up, and scientific investigation. Staging must be consistent, efficient, accurate, and reproducible. The head and neck cancer caregiver can never be too fluent in this mode of communication, as we educate patients and navigate them toward cure. The simple clarification that Stage IV disease is not synonymous with a "death sentence" has powerful impact for patients and their families. With this imperative, the American Academy of Otolaryngology—Head and Neck Surgery Foundation and the American Head and Neck Society present the fourth edition of *Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification.*

Just as our knowledge of and therapeutics for head and neck cancer evolve, so does the language we use in managing the disease. Such terms as "chemo-radiation," "organ preservation," "HPV positive," and "de-escalation" are now central to care planning discussions. Likewise, the staging system evolves to incorporate current knowledge and reflect state-of-the-art treatments.

This new edition of *Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification* incorporates the changes from the seventh edition of the American Joint Commission on Cancer (AJCC) Cancer Staging Manual, as well as updated discussions of site-specific cancers.

We hope this *Quick Reference Guide* will serve the practitioner and the patient equally well as we ready ourselves for further evolution of head and neck cancer staging and management.

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I. Introduction

The tumor, node, metastasis (TNM) staging system allows clinicians to categorize tumors of the head and neck region in a specific manner to assist with the assessment of disease status, prognosis, and management. All available clinical information may be used in staging: physical exam, radiographic, intraoperative, and pathologic findings. Other than histopathologic analysis, biomarkers and molecular studies are not yet included in the staging of head and neck cancers.

Three categories comprise the system: T—the characteristics of the tumor at the primary site (this may be based on size, location, or both); N—the degree of regional lymph node involvement; and M—the absence or presence of distant metastases. The specific TNM status of each patient is then tabulated to give a numerical status of Stage I, II, III, or IV. Specific subdivisions may exist for each stage and may be denoted with an a, b, or c status. T4a disease indicates *moderately advanced disease* and is specific by subsite, but is still considered resectable. T4b disease is *very advanced disease* with findings—such as carotid artery encasement, prevertebral involvement, and skullbase involvement—that previously determined the disease to be unresectable. In general, early-stage disease is denoted as Stage I or II disease, and advanced-stage disease as Stage III or IV disease. Of importance is that any positive metastatic disease to the neck will classify the disease as advanced, except in select nasopharynx and thyroid cancers. T4a disease is staged as IVa. T4b disease is staged as IVb, and any distant metastasis is staged as IVc.

A. Upper Aerodigestive Tract Sites

The majority of tumors arising in the head and neck (other than nonmelanoma skin cancers) arise from the squamous mucosa that lines the upper aerodigestive tract (UADT) and are predominately squamous cell carcinomas. The UADT begins where the skin meets the mucosa at the nasal vestibule and the vermillion borders of the lips, and continues to the junction of the cricoid cartilage and the cervical trachea and at the level of the cricoid

where the hypopharynx meets the cervical esophagus. The UADT is organized into several major sites that are subdivided to several anatomic subsites. The major sites include (1) the oral cavity, (2) the oropharynx, (3) the hypopharynx, (4) the larynx, (5) the nasopharynx, and (6) the nose and paranasal sinuses.

ORAL CAVITY

The oral cavity is a common site for squamous cell cancers of the UADT, probably because it is the first entry point for many carcinogens. The anterior aspect of the oral cavity is the contact point of the skin, with the vermilion of the lips extending posteriorly to the junction of the hard and soft palates, and with the anterior tonsillar pillars and the circumvallate papillae forming the posterior limits. The major subsites of the oral cavity are the lips, anterior tongue, floor of mouth, buccal mucosa, upper and lower alveolar ridges, hard palate, and retromolar trigone. The trigone consists of the mucosa overlying the anterior aspect of the ascending ramus of the mandible. Tumors of the oral cavity tend to spread regionally to lymph nodes of the submandibular region (Level I) and to the upper and middle jugular chain lymph nodes (Levels II and III).

Because of accessibility and the risk of involvement of bony structures, treatment with primary radiotherapy can lead to radionecrosis of the mandible or maxilla. Moreover, oral cavity squamous cell carcinomas may be less sensitive to chemotherapy and radiation, relative to oropharyngeal or laryngeal cancers. Thus, primary treatment for most tumors is surgical. Advanced-stage disease may receive adjuvant radiation therapy. Positive surgical margins, multiple involved lymph nodes, and/or extracapsular tumor extension call for consideration of postoperative chemoradiotherapy, to improve local disease control.

OROPHARYNX

This region begins where the oral cavity ends at the junction of the hard and soft palates superiorly and the circumvallate papillae inferiorly, and extends from the level of the soft palate superiorly, which separates it from the nasopharynx, and to the level of the hyoid bone inferiorly. The subsites of the oropharynx are the tonsil, base of tongue, soft palate, and pharyngeal walls. Cancers of the oropharynx often metastasize to upper and middle jugular chain lymph nodes (Levels II and III), but can also spread to retropharyngeal

lymph nodes, which distinguishes them from oral cavity tumors and must be considered when treating oropharyngeal cancers.

Tumors in the oropharynx have traditionally been treated with radiotherapy, as a single modality for T1/2 or N0/1 staging. For patients with more advanced disease, T3/4 or N2b/c/3 staging, chemoradiotherapy most often with a concomitant approach has become standard. Cisplatin, administered during weeks 1, 4, and 7, has most often been studied and may be considered a standard.

There has been a near epidemic rise in the incidence of oropharyngeal cancer related to human papillomavirus (HPV) infection. Most often occurring in younger patients lacking the traditional risk factors of significant tobacco and alcohol use, HPV-related tumors demonstrate a significantly higher cure rate. Recent advances in surgical techniques, including transoral laser microsurgery and transoral robotic surgery, have allowed for surgery to be considered as an integral part of combined modality treatment.

HYPOPHARYNX

The hypopharynx has its superior limit at the level of the hyoid bone, where it is contiguous with the oropharynx, and it extends inferiorly to the cricopharyngeus muscle, as it transitions to the cervical esophagus. The major subsites of the hypopharynx are the pyriform sinuses, the postcricoid region, and the pharyngeal wall. Tumors often present here at advanced stages and can be difficult to cure, and because of their location can impact swallowing and speech function adversely. Spread to the upper, middle, and lower jugular lymph nodes (Levels II–IV) and the retropharyngeal nodes is common in these cancers. Two other hallmarks of hypopharyngeal cancers are submucosal spread and skip areas of spread. Surgery had been the mainstay of primary treatment for hypopharyngeal cancers for many years, but increasingly radiotherapy and chemoradiotherapy are used to treat cancers in this location with success.

LARYNX

The larynx is the most complex of the mucosal lined structures of the UADT. The important roles of the larynx in speech, swallowing, and airway protection make the treatment considerations of cancers of this structure varied and controversial. The larynx is bordered by the oropharynx superiorly, the trachea inferiorly, and the hypopharynx laterally and posteriorly. The larynx is

comprised of a cartilaginous framework, and is subdivided vertically by the vocal folds into the supraglottic, glottic, and subglottic subsites. The supraglottic larynx includes the epiglottis, which has both lingual and laryngeal surfaces, the false vocal cords, the arytenoids cartilages, and the aryepiglottic folds. Anterior to the supraglottis is the pre-epiglottic space. This is a complex space with a rich lymphatic network that contributes to the early and bilateral spread of tumors that arise from supraglottic structures to upper, middle, and lower jugular chain lymph nodes (Levels II–IV).

The glottic larynx describes the true vocal folds, where they come together anteriorly at the anterior commissure, as well as where they meet the mobile laryngeal cartilages at the posterior commissure. The glottic larynx extends from the ventricle to 1 centimeter (cm) below the level of the true folds. The vocal folds are lined with stratified squamous epithelium, which contrasts with the pseudostratified, ciliated respiratory mucosa lining the remainder of the larynx. Glottic laryngeal cancers tend to metastasize unilaterally, and regional spread is less common than with supraglottic tumors. Between the thyroid cartilage and the vocal fold lies the paraglottic space, which is continuous with the pre-epiglottic space. This serves as a pathway for submucosal spread of tumors from the glottis to the supraglottis and/or subglottis, or vice versa, which is known as transglottic spread.

The subglottic larynx starts 1 cm below the vocal folds and continues to the inferior aspect of the cricoid cartilage. While it is rare for tumors to arise initially in the subglottis, tumors arising in the supraglottic or glottic larynx commonly spread in a "transglottic" fashion to involve the subglottic larynx. Subglottic tumors tend to metastasize to paratracheal (Level VI) as well as middle or lower jugular lymph (Levels III and IV) node groups.

Treatment of laryngeal cancers varies widely from center to center. For early-stage lesions, radiotherapy and transoral endoscopic excision are the most common treatment options. Both yield excellent tumor control, but proponents of each modality often disagree on the functional sequelae of the two types of treatment. However, good long-term functional data are lacking. Treatment of more advanced tumors can be even more controversial, but while total laryngectomy was long held as the gold standard for treating T3 and T4 larynx cancers, chemoradiotherapy has been shown to be quite effective in achieving local regional control, survival, and organ preservation. Concomitant chemoradiotherapy may be most appropriate for T3 and early

T4 primary lesions, while upfront surgery with adjuvant postoperative treatment can have improved disease control for advanced T4 tumors. Treatment of both sides of the neck must be taken into consideration when treating supra- and subglottic tumors, and unilateral neck treatment is considered for patients with advanced glottic tumors.

NASOPHARYNX

The nasopharynx is a cuboidal structure bounded anteriorly by the choanae at the back of the nose, where pseudostratified ciliated columnar cells are found. The roof and posterior walls of the nasopharynx are made up of the sphenoid bone and the upper cervical vertebrae, covered with a stratified squamous epithelial lining. Inferiorly, at the level of the soft palate, the nasopharynx meets the superior oropharynx. The opening of the Eustachian tube is found at the posterior-superior aspect of either lateral nasopharyngeal wall; therefore, impingement of this opening by a nasopharyngeal tumor can lead to Eustachian dysfunction manifested by a middle-ear effusion and hearing loss. Thus, all adult patients with an unexplained unilateral middle-ear effusion, particularly in areas where nasopharyngeal carcinoma is endemic (such as southern China, northern Africa, and Greenland), should have their nasopharynx examined.

The adenoids, consisting of mucosa-covered lymphoid tissue, are found posteriorly and superiorly in the nasopharynx and are more prominent in children than adults. While minor salivary tumors can occur in the nasopharynx, most nasopharyngeal cancers are derived from the mucosal lining and fit into one of the three histologic subtypes described by the World Health Organization (WHO). WHO Type I nasopharyngeal carcinoma (NPC) is keratinizing squamous carcinoma, and WHO Type II is nonkeratinizing squamous cell carcinoma. WHO Type III is an undifferentiated tumor, also known as lymphoepithelioma. The Epstein-Barr virus is thought to play a pathogenic role in the development of Type II and III tumors.

Nasopharyngeal carcinoma may also metastasize to retropharyngeal and parapharyngeal lymph nodes, as well as lymph nodes along the upper, lower, and middle jugular (Levels II–V) chains and the posterior triangle of the neck (Level V). Early-stage NPC is most often treated with radiotherapy alone, and in more advanced cases, such as T3/4 and/or N+ patients, concomitant chemotherapy is being increasingly utilized. Surgery is rarely used in salvage situations at the primary site or neck.

NASAL CAVITY AND PARANASAL SINUSES

The paranasal sinuses consist of the paired maxillary sinuses, the superior frontal sinuses, the bilateral ethmoid system, and the central sphenoids. This region includes the lining of the nasal cavity (medial maxillary walls), as well as the nasal septum. The majority of sinonasal carcinomas arise in the maxillary sinuses and are most commonly squamous cell carcinomas, although adenocarcinomas are described, especially in woodworkers. Because of inherent bone involvement, initial treatment is usually surgical, with consideration for adjuvant radiation therapy based upon stage and pathologic findings. Reconstruction and rehabilitation, especially in cases with orbital involvement, may be prosthetic or tissue based.

Sinonasal carcinomas of the anterior skull base include a variety of pathologies. Standard treatment is multidisciplinary, including craniofacial surgical intervention with adjuvant radiation with or without chemotherapy. Charged-particle radiation, such as proton beam radiation, may be considered in patients with involvement near the anterior skull base and/or orbit. Due to the improved control of the beam's depth of penetration, treatment dose can be optimized, while minimizing collateral damage to adjacent vital structures.

B. Radiation Therapy and Chemotherapy

External beam radiation therapy (RT) alone or in conjunction with chemotherapy has a well-established role in the treatment of head and neck cancer as definitive therapy or as adjuvant to primary surgical treatment. The last two decades have seen tremendous technological developments in targeting and delivery of RT in a complex treatment site, such as the head and neck. Three-dimensional (3-D) conformal RT marked a significant improvement over the conventional two-dimensional, three-field setup in better delineation of tumor volume and nodal volume. This improvement allows limited dosing to normal tissue, while adequately treating the tumor. However, 3-D conformal planning does not always result in optimal shielding of critical normal tissues (e.g., salivary glands and visual apparatus), due to current beam constraints.

Intensity-modulated radiation therapy (IMRT) allows for better sparing of such critical normal tissues by modulating the radiation beam in multiple small beamlets, while at the same time adequately covering the tumor volume. With the advent of IMRT, it is also very important for the clinician

to be acutely aware of radiologic anatomy (levels of nodal disease, pathways of locoregional spread of tumor, and delineation of postoperative tumor bed), while utilizing computed tomography scan, magnetic resonance imaging, and positron emission tomography scan for treatment planning.

Preoperative clinical and radiologic evaluation of disease is extremely important for postoperative radiotherapy planning, as tissue planes may be obscured after surgery. Such evaluation is also valuable in determining whether ipsilateral or bilateral neck disease needs to be addressed based on tumor location, extent, and size; initial nodal presentation; and likelihood of contralateral nodal involvement. Certain primary tumor sites have a high risk of retropharyngeal nodal involvement (nasopharynx, pyriform sinus, and tongue base), and these nodal groups should be covered in RT target volumes for these tumors. Approximately 20 percent of anterior tongue and floor of mouth cancers may have skip nodal metastasis to the Level IV nodal region, and should be included in RT volumes.

Important considerations in RT planning following surgical resection include a thorough evaluation of the surgical pathology report with respect to resection margins, extension to soft tissue/bone, and perineural or lympho-vascular invasion at the primary site and size; extra-capsular spread (ECS); and number and level of nodal involvement. Postoperative patients with ECS are at high risk for locoregional recurrence. Careful adjuvant treatment planning includes consideration of radiation dose (60–66 gray [Gy]), addition of concurrent chemotherapy (Radiation Therapy Oncology Group [RTOG] 95-01), extension of the RT clinical target volume to include overlying skin, and elective irradiation of contralateral neck nodes. The clinical target volume in radiation therapy of a clinically or pathologically involved neck typically extends up to the skull base to treat the highest neck nodes. In the contralateral elective neck irradiation, the highest-treated nodes are jugulo-digastric nodes.

Adjuvant RT should ideally begin within 4–6 weeks following primary surgical resection and neck dissection, unless postoperative complications significantly delay wound healing. Delaying adjuvant therapy has been shown to significantly decrease locoregional control.

While it has not been shown to have the ability to cure head and neck cancer as a sole treatment modality, chemotherapy has been found to provide patients with significant improvement in disease control; organ preservation;

and a potential decrease in late distant metastatic disease, in certain clinic scenarios. The use of chemotherapy typically is through one of the following approaches: *concomitant adjuvant* (given along with RT in the postoperative setting); *adjuvant* (given alone after the completion of surgery, RT, or both); or *palliative* (given to patients with incurable recurrence or metastatic head and neck cancer to improve survival and/or quality of life).

Concurrent chemotherapy is the most commonly used of the chemotherapeutic options, and is utilized to potentiate the effects of RT in order to achieve improved locoregional control and organ preservation. This treatment strategy has been found to have particular application in treating moderately advanced cancers of the pharynx and larynx (Stage III–IV, excluding T4 laryngeal and hypopharyngeal tumors). In these instances, concomitant chemoradiation has been found to provide improved locoregional control and, in some studies, improved overall survival, all while allowing for larynx preservation in one-half to two-thirds of patients. Platinum-based agents, such as cisplatin and carboplatin, are typically the compounds of choice used in these regimens, given on days 1, 22, and 43 of RT.

Concomitant adjuvant chemoradiation therapy is the use of combined chemotherapy and RT in the postoperative setting. As mentioned above, such adjuvant therapy should be instituted within 6 weeks of the primary surgery. The addition of chemotherapy to postoperative radiation has been shown to yield improved locoregional control and overall survival in patients with evidence of positive margins, multiple positive lymph nodes, and/or the presence of extracapsular spread in cervical lymph nodes. Typical agents used are platinum-based compounds (cisplatin or carboplatin) and 5-fluorouracil. The addition of chemotherapy to adjuvant RT has also been shown to result in increased local toxicity.

Although recurrent and/or metastatic head and neck cancers are generally incurable, palliative chemotherapy has been shown to delay the time until cancer progression and to improve survival modestly. Platinum drugs, 5-flourouracil, methotrexate, and cetuximab are frequently offered to otherwise healthy patients with incurable head and neck cancers.

In an effort to focus more specifically on head and neck cancers from a molecular level, additional studies are also ongoing to establish the role of different biologic agents in the treatment of this group of tumors. The epidermal growth factor receptor (EGFR) system is currently the most widely

studied area. EGFR overexpression has been shown to be related to more advanced tumor stage and nodal stage, as well as worse prognosis in terms of locoregional control and overall survival. As a result, numerous compounds are under investigation to evaluate their effect on progression of disease. The most widely studied compound in the treatment of head and neck cancer is cetuximab, a monoclonal antibody that inhibits the EGFR. The use of biologic agents in head and neck cancer is an area of many ongoing research efforts.

The American Academy of Otolaryngology—Head and Neck Surgery Foundation's education initiatives are aimed at increasing the quality of patient outcomes through knowledgeable, competent, and professional physicians. The goals of education are to provide activities and services for practicing otolaryngologists, physicians-in-training, and nonotolaryngologist health professionals.

The Foundation's AcademyU® serves as the primary education resource for otolaryngology–head and neck surgery activities and events. These include expert-developed knowledge resources, subscription products, live events, eBooks, and online education. In addition, the AAO-HNSF Annual Meeting & OTO EXPO℠ is the world's largest gathering of otolaryngologists, offering a variety of education seminars, courses, and posters. Many of the Foundation's activities are available for *AMA PRA Category 1 Credit™*.

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AHNS MISSION

On May 13, 1998, The American Head and Neck Society (AHNS) became the single largest organization in North America for the advancement of research and education in head and neck oncology. The merger of two societies, the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons, formed the American Head and Neck Society. The American Head and Neck Society remains dedicated to the common goals of its parental organizations:

- To promote and advance the knowledge of prevention, diagnosis, treatment, and rehabilitation of neoplasms and other diseases of the head and neck,
- To promote and advance research in diseases of the head and neck, and
- To promote and advance the highest professional and ethical standards.

For more information about the AHNS, visit www.ahns.info.

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