CA
A Cancer Journal for Clinicians

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CA Cancer J Clin 2005;55;242-258

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TNM Staging of Cancers of the Head and Neck: Striving for Uniformity Among Diversity

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This article is available online at http://CAonline.AmCancerSoc.org

ABSTRACT The sixth edition of the tumor-node-metastasis staging system for head and neck cancers incorporates some significant shifts in philosophy. As treatment paradigms shift and data from ongoing clinical and basic research become available, further revisions may be expected in the future. The purpose of this review is to highlight the complexities involved in developing a user-friendly staging system and to report the major changes in the new version. The authors also discuss some areas of current interest that may have the potential to lead to future modifications. (*CA Cancer J Clin 2005;55:242–258.*) *© American Cancer Society, Inc., 2005.*

INTRODUCTION

The tumor-node-metastasis (TNM) staging system was first reported by Pierre Denoix in the 1940s.[1] The International Union Against Cancer (UICC) eventually adapted the system and compiled the first edition of the TNM staging system in 1968 for 23 body sites. It is important to realize that the TNM staging system is simply an anatomic staging system that describes the anatomic extent of the primary tumor as well as the involvement of regional lymph nodes and distant metastasis.[2] Over the years, revisions to the TNM staging system have been based on an improved understanding of the natural history of tumors at various sites aided by advances in technology that have allowed clinicians to better assess the extent of tumors. Changes or revisions of any staging system should ideally be supported by evidence-based information generated from large cohorts of patients, preferably in the setting of prospective randomized clinical trials. Therefore, Level I evidence is available to support changes in the staging system for certain cancers that are common enough to provide large patient cohorts for meaningful data analysis (eg, melanoma, cancers of the colon, breast, and lung).

On the other hand, the head and neck region comprises a variety of anatomic sites. For example, tumors arising from the skin, nasal cavity and paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, esophagus, thyroid gland, salivary glands, soft-tissue tumors, bone sarcomas, and miscellaneous tumors such as neurogenic tumors and paragangliomas are all generically included in the head and neck region. More importantly, these tumors have diverse clinical behavior and outcomes. It is therefore literally impossible to generate a uniform staging system that would be relevant for all tumors arising in the head and neck region. Another effect of this diversity among head and neck tumors is that patient cohorts available for outcomes analysis for most sites are limited in numbers, and on the whole, no Level I evidence is available to support important clinical questions. Thus, changes in the TNM staging system have to be developed based on expert opinions and published reports in the literature while keeping in sight advances in technology for improved assessment of tumor extent and shifting paradigms in therapeutic strategies. To this end, the UICC TNM Committee has established a structured process for continuous improvement of the TNM classification.[3] A panel of experts continuously reviews manuscripts published in the literature that may affect future changes in the TNM staging system.

Like most other cancers, prognosis depends largely on the stage of the tumor, but other factors related to lifestyle such as smoking and alcohol consumption and medical comorbidity also affect outcome. Accurate and reliable stratification of head and neck cancers (HNC) for prediction of outcomes has been challenging, mainly because of

the numerous anatomic sites and subsites from which tumors can arise and the diversity of histologic types of tumors in these locations. The overwhelming majority of mucosal HNCs are squamous cell carcinomas. Therefore, the TNM classification of the UICC and the American Joint Committee on Cancer (AJCC) for most mucosal anatomic sites is designed for squamous cell carcinoma and minor salivary gland cancers. This variety and heterogeneity place a considerable onus on the clinician or cancer registrar involved in staging these tumors to be aware of the principles involved and the basis for modification of accepted staging categories.

Treatment paradigms for head and neck carcinoma, especially for tumors involving certain sites such as the larynx and pharynx, have undergone radical change over the past decade. Preservation of function is a major endpoint of interest, and nonsurgical treatment options using chemotherapy and radiation therapy are now considered as standards of care. Not all patients, however, are suited to organ preservation therapy, and a percentage of them that do not respond ultimately end up having surgical resection of the affected organ. Therapeutic decision making and selection of patients for appropriate therapy need considerably more research. Conventional TNM information has so far proved inadequate in predicting response to nonsurgical therapy. In current practice, information obtained from clinical examination and radiologic imaging is used to assign a clinical stage (cTNM), which is then used to stratify patients for selection of therapy and to report outcomes of treatment. If the patient undergoes surgical resection, the pathologic stage (pTNM) derived from histopathologic examination of the tumor and/or regional lymph nodes is useful in selecting postoperative adjuvant therapy and for estimating prognosis. As nonsurgical therapy gains wider acceptance as the initial definitive treatment of certain head and neck carcinomas, the importance of pathologic information is likely to diminish because the tumor and regional nodes in these patients will not be available for comprehensive pathologic analysis. Better and more reliable methods of pretreatment tumor assessment are therefore crucial to ensure that the clinical assessment of tumor approximates its actual pathologic extent. This is especially relevant for tumors of certain anatomic sites such as the larynx, where considerable heterogeneity in tumor characteristics and response to therapy have been documented within the same T stage.[4] Additionally, future comparisons of clinical outcomes may be expected to experience the effects of this inconsistency between cTNM and pTNM staging.

Staging information must be recorded in detail at the source by the clinician. The absence of detailed and accurate staging information makes it difficult for cancer registrars to interpret clinical records and may increase the chance for error in TNM staging. By the same measure, it is insufficient for the clinician to assign a cTNM stage without documenting the exact anatomic extent of the tumor. Failure to record the characteristics of the tumor from which the TNM stage is derived not only precludes comparisons with previous versions of the staging system and analysis of statistical systematic variations such as stage migration but also prevents use of the data set to generate evidence for modification of the existing system. "Stage migration" occurs when patients are assigned to different clinical stages because of differences in the accuracy of the staging method and the staging method used rather than actual differences in the extent of disease. For example, introduction of newer diagnostics tests such as computed tomography (CT) and magnetic resonance imaging (MRI) or positron emission tomography scans can result in assignment of a higher clinical stage and "improved" outcome for patients in a particular stage group purely because of the increased accuracy of the diagnostic test compared with conventional methods of tumor assessment such as clinical examination. This essentially results in a redistribution of patients to each clinical stage without any change in the overall results of treatment. To this end, the development of "collaborative staging" by the AJCC is an important step forward. Collaborative staging incorporates all features of the tumor that may or may not be currently used in the TNM staging system such as clinical, radiologic, pathologic, biologic, and molecular features and comorbidity information. A more comprehensive and accurate staging/prognostic system that is able to incorporate all this information may be-

come a reality in the future with advances in biocomputational techniques such as artificial neural networks. Until then, anatomic staging will remain the only practical and widely available method for clinicians throughout the world. It is important to realize that an overly detailed and complex system that is very accurate in determining prognosis will by definition be limited in its utility and user-friendliness. Conversely, a very simple staging system would have a high compliance rate but would experience poor prognostic ability. Therefore, any revisions to existing staging systems should be considered a compromise between the ideal and the practical.

For many decades, the AJCC-UICC TNM staging system has been used for staging HNC worldwide. The system has been periodically revised not only to incorporate information available from advances in diagnosis (eg, endoscopy and radiologic imaging) but also from improved understanding of the biologic behavior of the numerous tumors that occur in this anatomic area. The latest version of the TNM system[5] became effective in January 2003, and unlike many other cancers, the staging system for head and neck carcinoma has undergone significant modification. This report, which is the fourth in the series,[6] is aimed at summarizing the salient modifications in staging strategy and the reasons behind these changes.

DIFFERENCES BETWEEN THE FIFTH (1997) AND SIXTH (2002) EDITIONS OF THE AJCC STAGING SYSTEM

Global Changes

The fifth edition of the AJCC staging system[7] for HNC was felt to be deficient in certain areas listed in Table 1. One of the major concerns was that the staging system lacked sensitivity to stratify patients who were placed in Stage IV. For example, the fifth edition placed patients with an advanced primary tumor with no evidence of regional or distant metastasis ($T_4N_0M_0$) in Stage IV along with those who had clearly incurable disease by virtue of extensive nodal metastases (N_{2b} or N_3) or widespread diffuse metastatic disease (M_1).

It is well known that a majority of patients with cancer of the head and neck have recurrent disease at the primary site or in the neck at the time of death. In many patients, local/regional recurrence is indeed the cause of death. Thus, control of tumor above the clavicles in the head and neck region is of paramount importance in the overall management of patients with HNC. Within Stage IV, therefore, there are patients who are salvageable by aggressive surgical treatment for an extensive primary tumor that is felt to be surgically resectable. These patients clearly have a better prognosis compared with those with widespread metastatic disease at distant sites. Similarly, patients with advanced disease at the primary site and/or regional lymph nodes, which is felt to be technically not resectable, are currently managed with a treatment program of radiation therapy and chemotherapy with a reasonable expectation of tumor control and longevity. This is quite in contrast to palliative therapy offered to patients with distant metastatic disease.

Thus, Stage IV has been revised to reflect these therapeutic strategies by defining subcategories: Stage IVA includes tumors that are locally advanced but surgically resectable and therefore salvageable; Stage IVB includes tumors that are locally advanced and surgically unresectable but potentially treatable with a reasonable expectation of locoregional control with chemoradiotherapy; and Stage IVC is assigned to patients with distant metastatic disease that is incurable and therefore only suitable for palliative treatment. While these changes are not supported by evidence-based information, they are based on the opinion of experts involved in the treatment of HNC and clearly reflect the shifting paradigms in management of advanced cancers of the head and neck as practiced today in the United States and worldwide.

Discrepancies in the size descriptor for T staging among various sites in the fifth edition have been eliminated, and uniform parameters (<2 cm, 2 to 4 cm, and >4 cm) are now used for several anatomic sites of the primary tumor (oral cavity, thyroid, and salivary glands).

TABLE 1 The Rationale for Major Modifications in the Sixth Edition of the AJCC Staging System

Deficiencies Observed in the Fifth Edition	Action Taken for the Sixth Edition
Patients with Stage IV disease represent a group with a wide spectrum of biological and clinical behavior and are suited for different treatment modalities with considerably different outcome expectations.	Patients with locoregionally advanced stage disease are therefore stratified into surgically resectable (T4a) (Stage IVA) versus unresectable (T4b) (Stage IVB) disease. Patients with distant metastasis are classified as Stage group IVC.
Tumors arising from the nasal cavity or ethmoid sinuses have a very different clinical course from those arising in the maxillary sinuses.	The nasoethmoid complex is now recognized as a distinct anatomic subsite with two regions: nasal cavity and ethmoid sinuses.
Categorization of T stage by size criteria is largely arbitrary and is based on the inverse relationship of tumor volume to prognosis. The lack of uniform size criteria for different anatomic sites resulted in confusion in their use.	Size descriptor for T categories are now uniform across all sites (oral cavity, oropharynx, salivary glands, and thyroid glands).
Anaplastic thyroid carcinomas behave very distinctly and had been grouped with other differentiated carcinomas of the thyroid.	Anaplastic carcinomas are considered T4a or T4b irrespective of other features such as size.
The implication of involvement of central compartment nodes compared with lateral cervical and superior mediastinal nodes was not considered in N staging of differentiated thyroid cancer.	Metastasis to central compartment nodes is classified as N1a, and involvement of lateral cervical or superior mediastinal nodes is classified N1b.

The fifth edition did not provide any staging system for tumors of the nasal cavity and ethmoid sinuses, and the only staging system available was for tumors of the maxillary sinus. In recognition of the fact that tumors of the nasal cavity and ethmoid sinuses have a natural history, routes of progression, and therapeutic strategies that are distinct from maxillary sinus tumors, it was essential that a separate staging system be introduced for these two sites. The introduction of craniofacial surgery in the management of tumors that approach the skull base has provided prognostic information to support development of the T staging system of the ethmoid sinuses.[8]

The neck node staging system takes into account the size, multiplicity, and laterality of nodal metastasis. The latest edition of the staging system makes no changes in the N staging for any sites except the thyroid, and a descriptor has been added for nodal metastasis in the upper neck or in the lower neck, designated by (U) and (L). The risk of distant metastasis, and thus outcome, is thought to be related to the location of the nodal metastases in the neck. Although the location descriptor is not mandatory for nodal staging in the current edition, the hope is that it will allow collection of information to test this clinical observation in large cohorts of patients for consideration in future revisions.

T Category Issues

Classification of tumors into T stages based on the size of the primary tumor has been largely arbitrary. The size criteria for the T category are based on the inverse relationship of tumor volume to outcome for most HNCs. In the previous editions, the cutoff limits for size criteria used for T staging were different for oral cavity and thyroid and salivary gland tumors. In the sixth edition, a uniform descriptor for size for the above head and neck sites was introduced. In addition, for T4 tumors (larger than 4 cm), subcategories a and b were introduced based on involvement of vital structures and thus their suitability for surgical resection. T4a implies locally advanced but resectable tumor, while T4b implies tumor that is not technically resectable but is suitable for nonsurgical options such as chemoradiotherapy. The obvious problem in using feasibility of surgical resection as a staging parameter is that it is subject to the variability of the level of available expertise. However, the criteria used to define "unresectability" are generally acknowledged as indicative of extension of tumor to vital anatomic structures, where surgical resection is either technically not feasible with a curative intent or not recommended.

Site-specific T Category Changes

Table 2 is a compilation of the modifications that appear in the T category. Figures 1 through 6 illustrate the anatomic details of the head and neck sites, and Tables 3 through 15 list the parameters for T, N, and M staging as defined in the sixth edition of the staging system.[5]

TABLE 2 Site-specific Changes in Description of T4a and T4b Categories

Site	Description
Lip and Oral Cavity	
Lip	T4a: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose)
Oral cavity	T4a: Tumor invades adjacent structures (eg, through cortical bone, into deep [extrinsic] muscle of the tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face) Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4
Oral cavity and lip	T4b: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Oropharynx	T4a: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
	T4b: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Nasopharynx	No subdivision of T4
	Stage groupings same as in fifth edition
Hypopharynx	T4a: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue (including prelaryngeal strap muscles and subcutaneous fat)
	T4b: Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
Larynx	T4a: Tumor invades through the thyroid cartilage (glottic and supraglottic tumors) or cricoid cartilage (subglottic tumors) and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
	T4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Nasal cavity and ethmoid sinus	T4a: Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior fossa, pterygoid plates, sphenoid or frontal sinuses
	T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus
Maxillary sinus	T4a: Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
	T4b: Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of the trigeminal nerve V_2, nasopharynx, or clivus
Major salivary glands	T4a: Tumor invades skin, mandible, ear canal, and/or facial nerve
	T4b: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
Thyroid gland	
Follicular, papillary, and medullary	T4a: Tumor of any size extending beyond thyroid capsule to invade subcutaneous tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
	T4b: Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Anaplastic	All anaplastic carcinomas are considered T4 tumors
	T4a: Intrathyroidal anaplastic carcinoma—surgically resectable
	T4b: Extrathyroidal anaplastic carcinoma—surgically unresectable

Pharynx

The T classification for nasopharynx tumors remains unchanged after the major revisions undertaken in the fifth edition. The description of T2 has, however, been clarified to include extension of tumor into soft tissue outside the nasopharynx other than the parapharyngeal space.

The posterior pharyngeal wall is anatomically continuous across the landmarks (plane of the superior surface of the soft palate and the superior surface of the hyoid bone) that are used to separate the nasopharynx, oropharynx, and the hypopharynx. Reliable identification of the origin of a tumor that straddles these three regions of the pharynx may often be impossible and lends some degree of unreliability to outcomes reporting for this subsite.

Tumors that invade the prevertebral fascia are categorized T4b because the likelihood of curative surgical resection is minimal, if any. However, delivery of a meaningful dose of radiation to this area may be feasible using intensity-modulated radiation therapy in spite of its proximity to the spinal cord. Nonetheless, it is important to point out that the inherent difficulty in detecting early invasion of the prevertebral fascia on radiologic imaging is likely to cause some staging inhomogeneity within this category because most patients will undergo nonsurgical therapy.

Larynx

The prognostic significance of involvement of the paraglottic space by glottic as well as supraglottic tumors is acknowledged in the sixth edition, and these tumors are now staged T3. There was considerable ambiguity in the previous edition regarding the extent of carti-

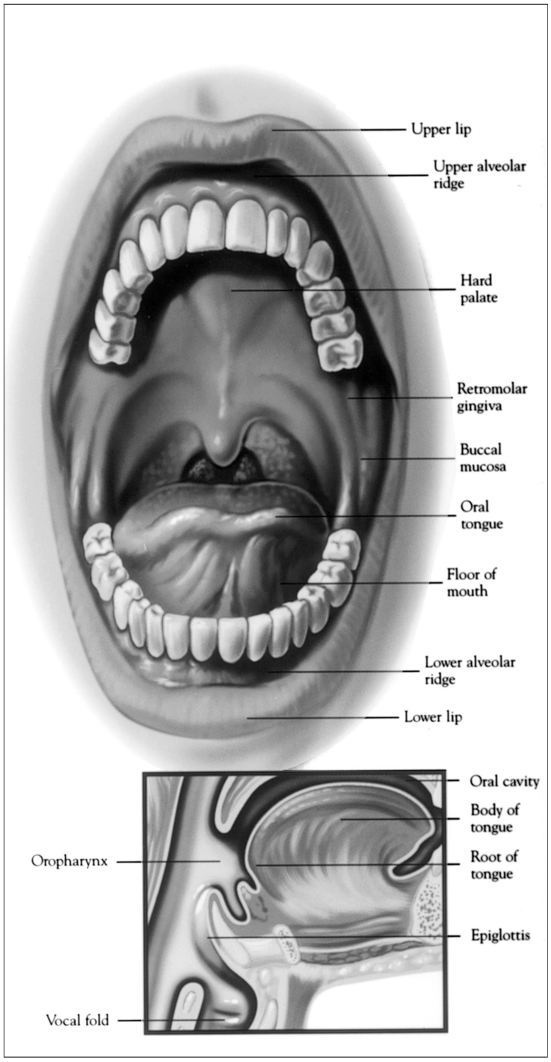

FIGURE **1** Anatomic Subsites of the Lip and Oral Cavity. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

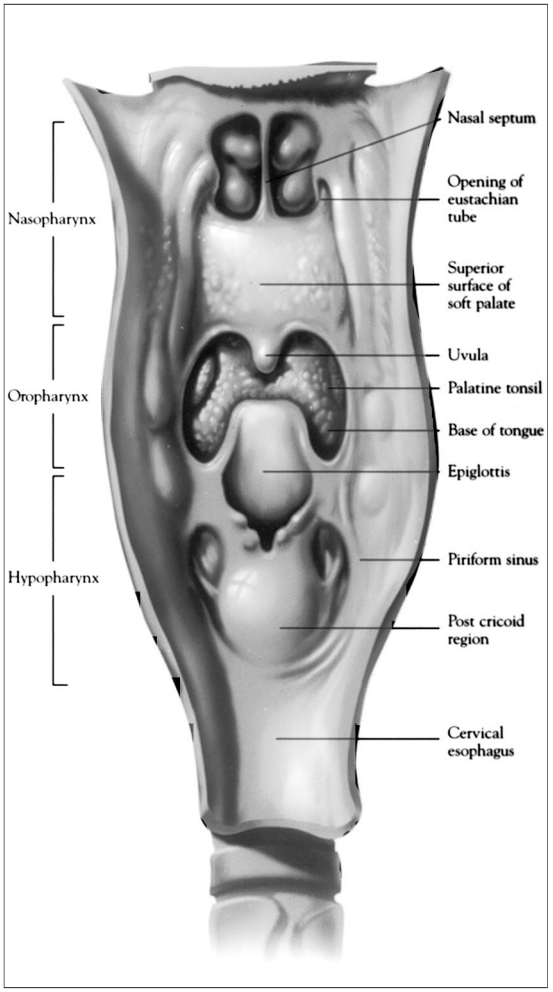

FIGURE **2** Anatomic Subsites of the Pharynx. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

lage invasion required for assigning Stage T4. Tumors that have caused minor cartilage erosion (eg, inner cortex of the thyroid lamina) are now staged T3, while the T4a category is reserved for tumors that actually penetrate through the cartilage.

Nasal Cavity and Paranasal Sinuses

In recognition that tumors of the nasal cavity and ethmoid sinuses are distinct from those of the maxillary sinus, two new anatomic subsites have been added under the category of paranasal sinuses. This revision includes modifications that allow appropriate classification of both nasal cavity and ethmoid sinus tumors. Regarding tumors of the maxillary sinuses, the description of T2 has been reworded to clarify that extension of the tumor to the posterior wall of the maxillary sinus, and involvement of the pterygoid plates qualifies as T3, a distinction that was not explicit and resulted in some ambiguity between the T2 and T3 categories in the previous edition.

Major Salivary Glands

The significant change in staging for major salivary gland tumors is the revision of the size criteria for T3 tumors to eliminate the upper limit of 6 cm. The rationale for this decision was that because of the anatomic dimensions of the major salivary glands, tu-

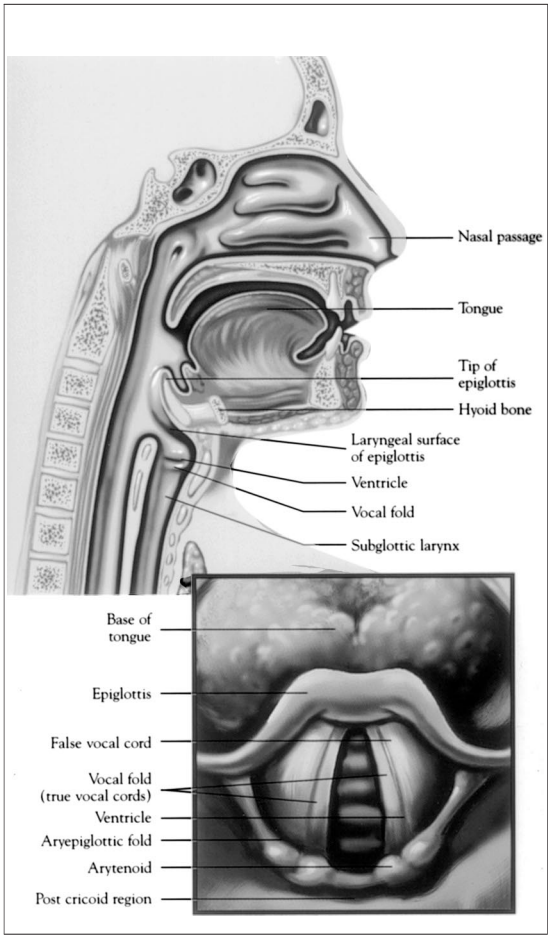

FIGURE **3** Anatomic Subsites of the Larynx. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

mors that are larger than 4 cm in dimension nearly always have extension of the tumor beyond the capsule of the gland. Extension of the tumor beyond the confines of the salivary gland clearly has adverse prognostic significance. With this change, the size criteria for salivary gland tumors are now the same as for other anatomic sites (<2 cm, 2 to 4 cm, and >4 cm). The other major modification is in the reorganization of the T4 category. Tumors that involve the skin of the preauricular region, ear canal, mandible, and/or the facial nerve are amenable to potentially curative surgical resection and are thus classified as T4a. More extensive tumors that involve the skull base and/or the pterygoid plates or those that encase the carotid artery are deemed surgically unresectable for cure and identified as T4b.

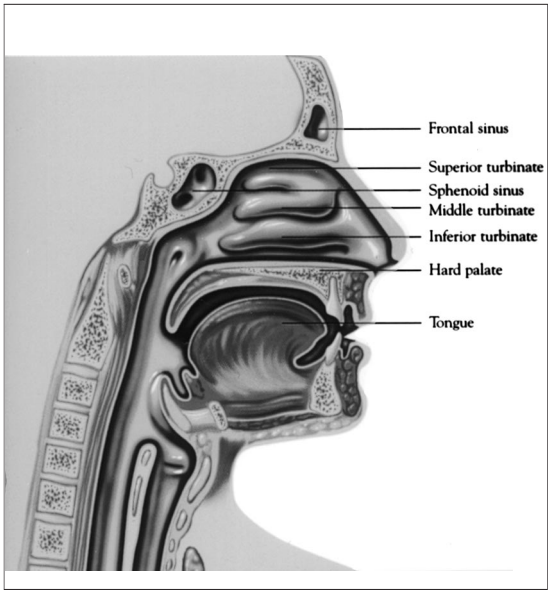

FIGURE **4** Saggital Section Showing the Nasal Cavity and Paranasal Sinuses. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

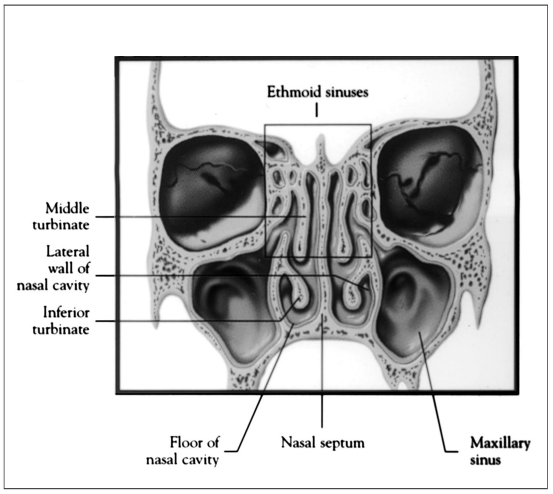

FIGURE **5** Coronal Section Showing the Relationship of the Paranasal Sinuses to the Nasal Cavity and Skull Base. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

Thyroid Gland

Differentiated and Medullary Thyroid Cancer

For differentiated (papillary and follicular) and medullary tumors confined to the parenchyma of the thyroid gland without extrathyroidal extension, there is no evidence to suggest that using a size cutoff of 1 cm provides better

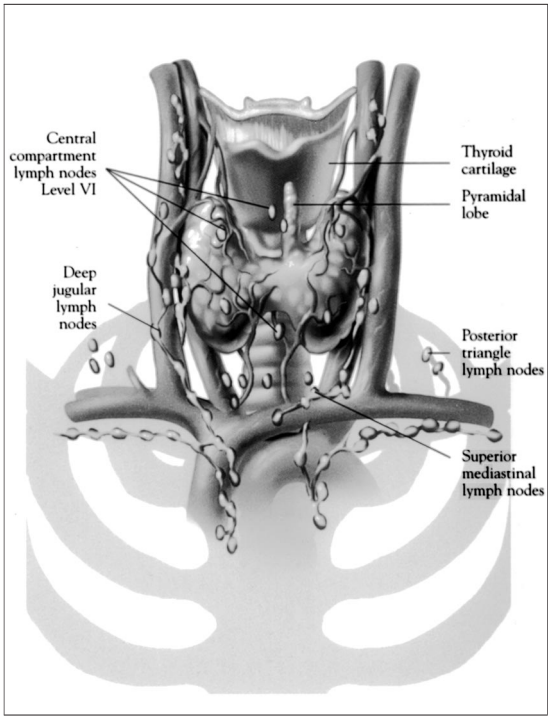

FIGURE **6** The Thyroid Gland and Its Lymphatic Drainage. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

TABLE **3** T Staging for Tumors of the Lip and Oral Cavity

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	
Lip	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose)*
Oral Cavity	Tumor invades through cortical bone, into deep [extrinsic] muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

*Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

prognostic stratification compared with the 2-cm cutoff used for other head and neck sites. Therefore, the T1 through T3 categories were revised to maintain consistency with other sites. Similarly, the fifth edition did not discriminate between minor extrathyroidal extension of tumor (into the sternothyroid muscle(s) that can be easily encompassed in a routine thyroidectomy without any adverse prognostic influence) and more extensive extrathyroidal involvement of structures such as the sternohyoid muscle, larynx, trachea, recurrent laryngeal nerve, or esophagus. The fact that diverse outcomes may be expected in these two groups of patients is now recognized in the sixth edition: tumors that involve the sternothyroid muscle are classified as T3, while extension to larynx, trachea, esophagus, recurrent laryngeal nerve, or subcutaneous soft tissue, all of which are surgically resectable, is classified as T4a. Tumors that invade the prevertebral fascia or encase the carotid artery or mediastinal great vessels are not resectable for cure, and these patients are staged T4b.

Anaplastic Thyroid Carcinoma

Patients with anaplastic thyroid carcinoma have an almost uniformly dismal prognosis irrespective of local features of the primary tumor. Therefore, the only T category available for staging these tumors has been T4. In keeping with the theme of classifying T4 tumors by surgical resectability, the sixth edition divides anaplastic tumors into T4a (a small tumor confined within the thyroid parenchyma) and T4b (extrathyroidal tumor that is surgically unresectable). These two groups of patients are, however, biologically distinct, and the clinician should be aware that an anaplastic tumor confined to the thyroid gland is truly rare and is most often discovered as an incidental histologic finding in the surgical specimen after thyroidectomy for an otherwise unremarkable tumor. The diagnosis of anaplastic carcinoma under these circumstances is by no means comparable to that of the more typical patient who presents with a rapidly growing symptomatic thyroid mass. The T staging system for anaplastic thyroid carcinoma should therefore be tempered with an appreciation of the biology of the tumor and the background in which it has arisen.

TABLE **4** T Staging for Tumors of the Pharynx

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Nasopharynx	
T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissues
T2a	Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension*
T2b	Any tumor with parapharyngeal extension*
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Hypopharynx	
T1	Tumor limited to 1 subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than 1 subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue†
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Parapharyngeal extension denotes posterolateral infiltration beyond the pharyngobasilar fascia.
†Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

TABLE **5** T Staging for Tumors of the Larynx

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or involves mediastinal structures

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TABLE 6 T Staging for Tumors of the Nasal Cavity and Paranasal Sinuses

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Maxillary sinus	
T1	Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V_2, nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumor invades any of the following: orbital apex, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus

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TABLE 7 T Staging for Tumors of the Major Salivary Glands

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staginger Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

TABLE 8 T Staging for Tumors of the Thyroid

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension limited to the thyroid
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3	Tumor more than 4 cm limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Anaplastic carcinomas†	
T4a	Intrathyroidal anaplastic carcinoma—surgically resectable
T4b	Extrathyroidal anaplastic carcinoma—surgically unresectable

All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification). †All anaplastic carcinomas are considered T4 tumors. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

N Category Issues

There have been no modifications to the N staging system except for those on thyroid carcinoma. Figure 7 illustrates the nodal levels that are used to describe regional lymphatic metastatic spread to the neck.[9] Although there was considerable discussion by the AJCC Task Force for Head and Neck Sites regarding the prognostic implications of certain features such as the location of the involved nodes (upper

TABLE **9** N Staging for All Head and Neck Sites Except the Nasopharynx and Thyroid

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph more than 6 cm in greatest dimension

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TABLE **10** N Staging for Tumors of the Nasopharynx

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N3	Metastasis in a lymph node(s) >6 cm and/or to supraclavicular fossa
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa*

*Midline nodes are considered ipsilateral nodes. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

TABLE **11** N Staging for Tumors of the Thyroid

Nx	Regional lymph nodes* cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes

*Regional nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

TABLE **12** M Staging for Head and Neck Tumors

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

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TABLE **13** Stage Grouping for All Head and Neck Sites Except the Nasopharynx and Thyroid

Stage Group	T Stage	N Stage	M Stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

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neck versus lower neck) and extracapsular extension, the Committee agreed that insufficient evidence exists at the current time to merit inclusion of these criteria in this staging system. It was proposed that the location of nodal metastasis be recorded separately ("U" for nodes located in the neck superior to the plane of the lower border of the cricoid cartilage, and "L" for those located inferior to it) from the mandatory N category information in order that this information be available for future analysis.

TABLE **14** Stage Grouping for Tumors of the Nasopharynx

Stage Group	T Stage	N Stage	M Stage
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T1	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IVB	Any T	N3	M0
IVC	Any T	Any N	M1

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Extracapsular extension of nodal metastasis, on the other hand, can be most reliably detected only on pathologic examination of the node in question because current radiologic imaging techniques are not adequately accurate. Additionally, the prognostic impact of extracapsular nodal extension independent of metastatic tumor volume has not been examined satisfactorily. More data will therefore be necessary before this feature can be considered for inclusion in the staging criteria.

Lymph node metastases in general have a limited prognostic impact in differentiated thyroid carcinoma, especially in patients younger than 45 years. The worst possible N category that can be assigned in these patients is therefore only N1, which is now subclassified into N1a (metastasis to first echelon lymph nodes at Level VI) and N1b (metastasis to lateral cervical or superior mediastinal nodes). In recognition of the adverse prognostic impact of nodal metastasis in patients older than 45 years, N1b disease is included under Stage Group IVA for all tumors that are smaller than Stage T4b.

TABLE **15** Stage Grouping for Tumors of the Thyroid*

	Papillary or Follicular Carcinoma		
	Under 45 years		
Stage Group	T stage	N stage	M stage
I	Any T	Any N	M0
II	Any T	Any N	M1
	45 years and older		
Stage Group	T stage	N stage	M stage
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1
	Medullary Carcinoma		
Stage Group	T stage	N stage	M stage
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1
	Anaplastic Carcinoma		
Stage Group	T stage	N stage	M stage
IVA	T4a	Any N	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

*Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinoma. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springeronline.com.

M Category Issues

There have been not modifications in this category except the clarification that all patients with distant metastases are now classified as Stage IVC.

Stage Grouping Issues

The stage grouping strategy has undergone a major change in the sixth edition. As described

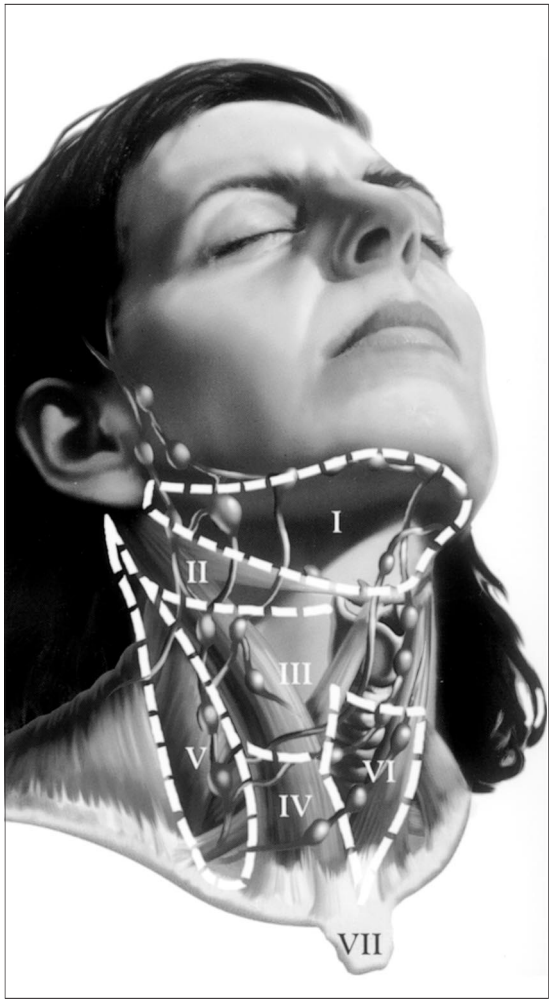

FIGURE 7 Location of Lymphatic Nodal Levels in the Neck. Reproduced with the permission of MedImmune Oncology, Inc., Gaithersburg, MD.

above, Stage IV now includes three subcategories based largely on reorganization of the T category. Therefore, unlike the fifth edition, tumors staged T3 or lower do not qualify for Stage IV in the absence of other adverse features such as N2 or higher neck stage. To maintain consistency with this rule, T3N1 tumors of the major salivary glands are now grouped under Stage III instead of Stage IV as in the previous edition.

Like its predecessor, the sixth edition also recognizes the fact that the age of the host plays a major prognostic role in differentiated thyroid cancer. Papillary and follicular carcinomas of the thyroid in individuals younger than 45 years in age have an excellent outcome on the whole, and therefore Stage Groups III and IV are not applicable to this cohort irrespective of T, N, or M stage of the tumor.

Pretreatment Staging Investigations

The importance of accurate mapping of the tumor before commencing therapy has always been recognized by the AJCC-UICC. Thorough physical examination, including endoscopy if appropriate, should be combined with radiologic imaging to record the precise local (T), regional nodal (N), and distant (M) extent of the tumor. In most instances, the information derived is then assembled by the clinician to assign a pretreatment TNM stage. While recording this information, it is vital that a detailed description of the tumor, including tumor diagrams or photographs, be archived to allow future analysis of modifications to the staging system or comparisons with other systems based on the raw data. While abstraction of stage from clinical records by cancer registrars is an accepted practice, this involves a considerable amount of interpretation. Accurate data collection and pretreatment staging of the tumor should be the responsibility of the physician providing or coordinating the patient's care. The accuracy of these data depends on the expertise and experience of the physician.

Early lesions of the oral cavity and oropharynx are easily amenable to clinical examination including palpation. Clinical assessment of the superficial mucosal extent of these lesions is generally easy, and the depth of invasion into underlying tissue can be approximated by palpation. Radiologic imaging can be helpful in assessing tumors of the tongue for deep extension and for evaluating the status of the mandible in tumors that are in close proximity to the bone. Imaging is also helpful in assessing tumors of the posterior pharyngeal wall for their relationship to the prevertebral fascia. A particular advantage of cross-sectional imaging is its ability to detect nodal metastases that cannot be appreciated on clinical examination, especially in patients who are not amenable to satisfactory examination (eg, thick, muscular neck) or in those who have at-risk nodal basins that cannot be assessed clinically (eg, retropharyngeal nodes in patients with tonsil carcinoma). Most experts consider CT superior to MRI at detecting extracapsular nodal extension,

and there are reports that imaging criteria such as involvement of internodal fat or spiculated margins of metastatic disease are reliable indicators.[10]

Accurate staging of early larynx cancer requires direct visualization of the vocal cords during phonation to assess mobility. The distinction between impaired mobility and vocal cord fixation determines whether a patient with glottic cancer is staged T2 or T3. While this distinction may appear to be relatively straightforward, it does involve a degree of subjectivity that is impossible to standardize. Consequently, T staging in this group of patients involves an inherent heterogeneity that is difficult to remedy. Thus, for glottic tumors that are staged T2 from impaired mobility of the vocal cord, a certain amount of observer-related subjectivity must be anticipated. The prognostic implication of impaired mobility from a bulky tumor that is largely exophytic is appreciably different from a tumor that restricts cord movement secondary to infiltration of the vocalis muscle or arytenoid cartilage. Advances in technology in the future may allow better objective quantification of some of these issues and help standardize staging data. Under the current circumstances, however, it is doubtful that any staging system can be comprehensive enough to account for such variations and still maintain broad usefulness in clinical practice. Radiologic imaging provides little additional staging information for assessment of the mucosal extent of laryngeal tumors. It can, however, provide valuable information to define T staging descriptors related to the depth of the tumor such as invasion of the base of the tongue, preepiglottic and paraglottic spaces, or cartilage invasion.

Contrary to evaluation of tumors of the mucosal surfaces of the remainder of the upper aerodigestive tract, cross-sectional radiologic imaging is mandatory for accurate assessment of tumors of the nasopharynx and paranasal sinuses. Staging information related to therapeutic decision making such as involvement of the dura in an ethmoid tumor or parapharyngeal extension of nasopharynx carcinoma cannot be obtained by clinical or endoscopic examination. CT is excellent in assessing bone, while MRI provides excellent delineation of soft-tissue descriptors such as involvement of the dura or perineural extension of tumor. These imaging modalities should therefore be used to complement each other to answer specific questions related to staging and therapy.

Assessment of tumors of the major salivary glands and the thyroid gland benefits from radiologic imaging if the extent of the tumor in its third dimension cannot be determined clinically. While cross-sectional imaging of a small, well-localized tumor of the parotid gland can provide accurate dimensions for tumor staging, it has little potential to change the treatment algorithm. Conversely, radiologic imaging obtained during the course of investigation of unrelated illness has resulted in an increasing incidence of incidentally discovered tumors ("incidentalomas") of the thyroid and parotid glands. Indeed, only a small percentage of these tumors are malignant, but with the widespread use of imaging for evaluation of common ailments, early detection of some of these malignant tumors will likely result in improved outcomes and the inevitable debate of the effect of "lead-time" bias.[11]

FUTURE MODIFICATIONS

T-category staging for tumors of certain anatomic sites will certainly undergo modification as information from well-conducted clinical studies becomes available. The increasing use of imaging along with improved technology will hopefully be able to provide more accurate data on the third dimension or depth of the tumor. The depth of invasion of the primary tumor is already recognized as an important predictor for risk of nodal metastases in some tumors, such as those of the oral cavity and especially the tongue.[12,13] Other tumor attributes of prognostic relevance include the morphology (exophytic versus endophytic) and the nature of the host-tumor interface (pushing versus infiltrating).[14] Histologic characteristics, such as perineural involvement, vascular and lymphatic invasion, the nature of cellular infiltrate within the tumor, and numerous molecular markers,[15] have also been reported to be indicative of outcome. If one adds to this mix the countless reports supporting the "significance" of a particular biologic or molecular characteristic of

a tumor to predict outcome, it is easy to see the need for discretion in using this information for any future modifications to the staging system. Nonetheless, it is also important to recognize that the anatomic/morphologic features of the tumor that we currently use for staging are only a reflection of underlying genetic and molecular events. While clinical and imaging characteristics of tumors are undoubtedly more vulnerable to subjective interpretation, the incorporation of genetic and molecular characteristics into the staging system will have to await much better understanding of basic tumor and host biology.

As nonsurgical organ-preserving therapeutic approaches gain general acceptance, the relative importance of noninvasive radiologic assessment of the extent of the tumor has increased. Unfortunately, correlative data comparing the accuracy of these approaches to the definitive standard of pathologic examination do not exist for most head and neck sites. This situation is unlikely to change in view of the trend toward nonsurgical therapy for most advanced head and neck tumors. Considerable research is underway to develop chemosensitivity assays[16] and biological and/or molecular predictors of response to nonsurgical therapy.[17] However, a reliable method of identifying patients who are likely to respond to chemoradiation therapy remains elusive. Advanced larynx cancer provides a classic example of this dilemma. It is well recognized that not all patients with advanced laryngeal tumors benefit from organ-preserving chemoradiation therapy. Although there have been attempts to identify clinical (patient- and host-related)[18] and radiologic predictors[19] of response, there is considerable ambiguity regarding their accuracy. Specifically, patients who have involvement of the laryngeal cartilage framework are thought to be at risk for poor response to chemoradiation therapy. A major drawback of all clinical and radiologic studies that evaluate this question in the contemporary era is the lack of pathologic confirmation of their accuracy because index total laryngectomy is no longer accepted as standard practice except in patients with advanced laryngopharyngeal tumors and gross thyroid cartilage destruction. It remains to be seen how clinical staging will have an impact on future analysis of outcomes, and at least for some anatomic sites, the staging criteria may need modification to account for the effects of this conundrum.

Certain tumors, such as malignant tumors, that involve the skull base or temporal bone are relatively uncommon, and because individual institutions are unable to muster enough data for outcomes analysis, staging systems are either nonexistent or relatively basic.[20] The only practical solution to this problem is multiinstitutional, preferably international, collaborative efforts at data collection and reporting.[8] Collection, audit, analysis, and reporting of data from around the world are certainly facilitated by the use of the Internet, and this approach may also be useful to consolidate the staging system for the more common tumors of the head and neck.

Nodal metastasis is the most important predictor of outcome for squamous cell cancer of the head and neck. As discussed above, the relative impact of certain characteristics of nodal metastatic disease such as extracapsular spread and their location in the neck need more investigation. While the prognostic implication of clinically recognized metastases is beyond doubt, the controversy regarding the adverse effect of subclinical nodal disease has not been settled. Sentinel node biopsy is widely accepted as the standard of care in the management of cutaneous malignant melanoma. The procedure is currently under investigation for mucosal HNC, and immunohistochemistry and assessment of molecular markers of metastatic disease in sentinel nodes will identify "submicroscopic" or "molecular" metastases in "sentinel" nodes. The clinical implication of this entity is currently under investigation for malignant melanoma and a similar trend can be expected for HNC.

Whole body functional imaging using techniques such as 18-fluorodeoxyglucose positron emission tomography scanning is becoming increasingly popular in the metastatic workup of patients, especially those undergoing chemoradiation therapy for advanced HNC.[21] One of the advantages of chemoradiation therapy reported in clinical trials completed over the past decade has been the reduction in deaths from distant metastases. It is, however, very likely that some degree of discrepancy existed among

patient groups in these trials regarding their pretreatment distant metastatic status in view of the fact that whole body functional imaging techniques were not available for routine use. A proportion of these patients may have harbored metastatic disease that was never recorded, thus introducing bias in comparing treatment groups. The availability of whole body scanning and its use in patients with advanced HNC may have the effect of homogenizing the "cM0" population that are subject to clinical trials.

Except for differentiated thyroid cancer, where the age of the patient is a critical descriptor, the current TNM staging system for HNC does not take into account any characteristic of the host. It is well recognized that the typical squamous cell carcinoma of the upper aerodigestive tract is etiologically related to the use of tobacco and/or alcohol. Consequently, these patients also have comorbid conditions that although not a feature of the cancer itself, have the potential to impact the type, efficacy, and outcome of therapy. The prognostic influence of comorbidity on outcomes after treatment of several HNCs has been reported in the recent literature.[22] More research and validation of these reports are desperately needed so that the prognostic impact of this parameter can be considered in future modifications of the staging system. The status of the host immune system, on the other hand, is admittedly difficult to quantify but does remain another relatively unexplored characteristic in terms of prognostic impact. The explosive clinical course of an early stage cancer in a patient with human immunodeficiency virus or drug suppression following organ transplantation is the most extreme example of the impact of a compromised immune system on outcome. Lesser degrees of immune dysfunction may be prevalent in some patients with early tumors who have an atypically aggressive clinical course (eg, early stage tongue cancer in a young female who reports no use of tobacco and/or alcohol). As our understanding of the complex interactions that obviously occur between the host and the tumor improves, future staging systems will likely have the advantage of computer technology such as artificial neural networks and will benefit from inclusion of these and other characteristics of the host. The development of collaborative staging by the AJCC is a step in this direction and will allow incorporation of relevant nonanatomic parameters in future revisions of the TNM staging system.

CONCLUSION

The TNM staging system for HNCs is now in its sixth version and is an important tool not only for reporting and comparing outcomes of therapy, but also for improving stratification of patients for inclusion in clinical trials. As technology advances and data from ongoing clinical and basic research become available, in the coming years further revisions may be expected to incorporate as yet unexplored issues related to the host (eg, medical comorbidity and immune competence) and the tumor (eg, biological and molecular markers). Advances in computing technology such as artificial neural networks may facilitate this process. The challenge then will be to maintain sight of the central theme of user-friendliness so that the staging system maintains its role of providing a common language for communication between clinicians and scientists of all specialties around the world.

It is important, however, to realize that no staging system is perfect. The more comprehensive and detailed the staging system, the more accurate and more predictive of prognosis the system becomes. However, a very detailed and complex staging system becomes less user-friendly, and therefore its utility and compliance drops. Thus, the AJCC/UICC staging system is a compromise between the ideal and the practical, and the current revision is no exception. Nevertheless, the changes implemented in this revision offer an incremental gain toward a "perfect" staging system.

ACKNOWLEDGMENTS

The authors would like to acknowledge Ms. Nancy Bennett for her editorial assistance.

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