ARTICLE TITLE: Head and Neck Cancers—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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EDUCATIONAL OBJECTIVES:
After reading the article “Head and Neck Cancers—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual,” the learner should be able to:
1. Summarize significant modifications for clinical and pathological staging of head and neck cancers in the recently released eighth edition of the American Joint Committee on Cancer Staging Manual, Head and Neck Section.
2. Describe the significance and rationale for a separate staging system for high-risk human papillomavirus-associated cancer of the oropharynx.

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Head and Neck Cancers—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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ABSTRACT: The recently released eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section, introduces significant modifications from the prior seventh edition. This article details several of the most significant modifications, and the rationale for the revisions, to alert the reader to evolution of the field. The most significant update creates a separate staging algorithm for high-risk human papillomavirus-associated cancer of the oropharynx, distinguishing it from oropharyngeal cancer with other causes. Other modifications include: the reorganizing of skin cancer (other than melanoma and Merkel cell carcinoma) from a general chapter for the entire body to a head and neck-specific cutaneous malignancies chapter; division of cancer of the pharynx into 3 separate chapters; changes to the tumor (T) categories for oral cavity, skin, and nasopharynx; and the addition of extranodal cancer extension to lymph node category (N) in all but the viral-related cancers and mucosal melanoma. The Head and Neck Task Force worked with colleagues around the world to derive a staging system that reflects ongoing changes in head and neck oncology; it remains user friendly and consistent with the traditional tumor, lymph node, metastasis (TNM) staging paradigm.

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Keywords: American Joint Committee on Cancer (AJCC), depth of invasion, extranodal extension, head and neck cancer, human papillomavirus (HPV), human papillomavirus-associated cancer, oropharynx, prognosis, staging

Practical Implications for Continuing Education

> The 8th Edition staging of HR-HPV associated cancer of the oropharynx will give a much more accurate and reasonable prediction of survival for newly diagnosed patients. For example, a patient that presents with a 2 centimeter, p16+ tonsil cancer and 2 positive lymph nodes in the same side neck is stage IV in the 7th Edition Staging Manual but will become a stage I in the 8th Edition. The psychological benefit of having a stage I versus a stage IV cancer is significant and clinicians can much more readily reassure patients that they have a good prognosis.

> The most significant pathological finding in a positive lymph node is whether it extends outside the capsule (ENE). This will now be an important aspect of staging of non-p16+, non-EBER+ cancers of the head and neck.

> Including depth of invasion in oral cavity will better discriminate the higher risk small cancers as demonstrated by deeply invasive tumors from those with less invasive cancers that have an excellent prognosis.

Introduction

Assigning the proper clinical and pathological stage is one of the key activities for clinicians caring for those afflicted with cancer. Staging entails stratification into...
similar groups based on anatomic and nonanatomic criteria to assist in estimating prognosis and planning treatment.

Head and neck oncology encompasses a group of malignancies that arise in the mucosal surfaces of the upper aerodigestive tract (UADT), including the oral cavity, pharynx, larynx, and paranasal sinuses, as well as cancers of the major and minor salivary glands. As such, the staging of malignancies arising in the UADT was defined in the American Joint Committee on Cancer (AJCC) Staging Manual, seventh edition, in the chapters pertaining to head and neck cancer.

Skin cancer other than melanoma and Merkel cell carcinoma, when staged, has traditionally been addressed using the AJCC tumor, lymph node, metastasis (TNM) approach. However, in practice, clinicians tended not to stage the overwhelming majority of small cancers treated with curettage or cryoablation. Therefore, the Cutaneous Malignancy Task Force of the AJCC recommended eliminating the chapter on nonmelanoma skin cancer (NMSC) from the eighth edition. Because a majority of skin cancers occur in the head and neck, where they can be of significant importance because of competing goals of cancer control and survival versus function and esthetic preservation, the Head and Neck Committee on Staging recommended (and the AJCC leadership agreed to) incorporating skin cancer staging (other than melanoma and Merkel cell carcinoma, which continue to be staged in unique chapters) within the chapters devoted specifically to the head and neck. Hence, the head and neck section addresses NMSCs of the head and neck as well as those malignancies that arise from the mucosal surfaces of the UADT and salivary glands. Thyroid cancers are part of a separate section in the AJCC Cancer Staging Manual, eighth edition.

Recognizing the prognostic power of newly validated pathologic features of some primary tumors and of cervical lymph node metastases, and differentiating high-risk human papilloma virus (HR-HPV)–associated oropharyngeal cancer (OPC) from OPC with other causes, the AJCC Cancer Staging Manual, eighth edition head and neck chapters introduce significant changes from the seventh edition. A new chapter describes the staging of HR-HPV–associated OPC. In addition, a separate chapter for non-HPV–associated OPC and hypopharyngeal cancer and one for nasopharyngeal cancer are included; therefore, pharyngeal cancers are staged in 3 independent chapters. In addition to incorporating the head and neck-specific cutaneous malignancies chapter, other modifications include: changes to the T categories in nasopharynx, oral cavity, and skin; alteration in the N category in nasopharynx; and the addition of extranodal extension (ENE) by tumor in a metastatic lymph node (N category). This review highlights and explains the importance of the major changes introduced with publication of the eighth edition of the AJCC Cancer Staging Manual in the Fall of 2016.

Background on the AJCC Head and Neck Task Force

The AJCC Head and Neck Task Force consisted of 28 specialists selected for their breadth of expertise and depth of knowledge in staging and head and neck cancer biology. This group was guided by the desired tenets for a proper staging system as described by Groome et al. These principles served as guides for determining which aspects of the staging system warranted modification and which should remain unchanged. A comprehensive analysis of each of the chapters, undertaken by subgroups of experts, led to recommendations that were submitted for approval and comment to the full task force. When changes were advised by the task force, additional analyses were performed to determine whether the available data would support the revision. This iterative process led to the changes introduced in the eighth edition.

While personalized nomogram approaches hold promise, the pretreatment assessment of patients using the time-tested TNM framework remains applicable worldwide in diverse medical settings and is relevant to all patients. For evaluating the impact of treatment across populations and time, the revisions in the eighth edition represent a compromise between an accurate but highly complex system (but potentially low compliance) and a simpler, high-compliance system with somewhat diminished predictive capacity.

Cancer Staging Considerations for the Eighth Edition

Cancer staging is an important component of patient care across the world. Preserving universal ability to stage cancers, regardless of a country’s level of resources, and scrupulously assuring harmony between the AJCC and Union for International Cancer Control (UICC) staging systems were crucial goals. Balancing the demand to maintain consistency across past versions of the staging system with the need for innovation and contemporary applicability were important requirements. In this endeavor, members of the UICC and AJCC Head and Neck Committees were linked by a sense of collegiality and unity of purpose. Both groups strove to balance global applicability with the need for incremental improvement. The committees held numerous
teleconferences and e-mail exchanges to solicit worldwide participation, ultimately adopting recommendations that represented compromises all could support.

The nature and type of treatment determines the variety and quality of data available for use in prognostication and staging. For head and neck cancers that are largely treated using nonsurgical modalities (eg, nasopharyngeal cancer), pathological staging data, such as the number of involved lymph nodes or microscopic ENE, are seldom available; therefore, such diseases are staged using only the clinical TNM (cTNM) system. Cancers that are usually treated surgically (eg, oral cavity cancer [OCC]) provide robust pathological and clinical staging information; therefore, separate cTNM and pathological TNM (pTNM) systems are described for these situations.

**Changes to Staging in HR-HPV–Associated OPCs**

Since 1990, the incidence of cancers of the tonsil and tongue base associated with HR-HPV has risen at an alarming 5% per year in the United States and elsewhere.5-7 HPV types 16 and 18 are the most commonly detected, transcriptionally active HR-HPV types in head and neck cancer.7 Demographically, HR-HPV–associated OPC represents a novel disease that occurs more often in younger, healthier individuals with little or no tobacco exposure. The entity is highly responsive to treatment and carries an excellent prognosis.

While the seventh edition TNM staging of OPC adequately reflects the behavior of those cancers typically associated with tobacco and alcohol abuse (not caused by HR-HPV), it does not properly describe HR-HPV disease with respect to prognosis or behavior.1,7,8 As the number of OPCs caused by HPV rose, the seventh edition staging algorithm lost the ability to differentiate between stages (hazard discrimination), and the numerical balance was skewed toward stage III and IV, reducing the predictive features of any specific stage. Therefore, a new staging system was needed for HR-HPV OPC.

Because site or histology alone cannot differentiate the 2 entities, it was imperative to identify an accurate or characteristic test to distinguish the 2 types of OPC. The test should be simple, inexpensive, and reproducible. One option was to consider tobacco exposure versus no tobacco exposure to define the 2 types of oropharynx disease. However, tobacco use is found among patients with HR-HPV–associated tumors, and non HR-HPV–associated tumors emerge in nontobacco users (yet behave like classical tobacco-associated tumors). Hence, tobacco exposure fails as a differentiating characteristic. Direct HR-HPV detection can be performed on tissue samples by in situ hybridization (ISH), but it is expensive and is not universally available, rendering ISH suboptimal for worldwide adoption. In many institutions, HPV-ISH is “sent-out,” which increases turnaround time. Immunohistochemistry for overexpression of the tumor suppressor protein p16 (cyclin-dependent kinase 2A) is an established, robust surrogate biomarker for HPV-mediated carcinogenesis; it is also an independent positive prognosticator in the context of OPC.8-10 Immunohistochemical staining for p16 is inexpensive, has near universal availability, and is relatively straightforward to interpret. Hence, OPCs are now staged according to 2 distinct systems, depending on whether or not they overexpress p16.2 Staging by the HR-HPV–associated OPC system should only be assigned when p16 overexpression is determined using established criteria.11-13 Specifically, the cutoff point for p16 overexpression is diffuse (≥75%) tumor expression, with at least moderate (+2/3) staining intensity. This coincides with the usual staining pattern seen in HR-HPV–associated OPC. Overexpression of p16 is usually localized to tumor cell nuclei and cytoplasm, and p16 staining localized only to the cytoplasm is considered nonspecific and thus not diagnostic (negative).

In the seventh edition of the AJCC Cancer Staging Manual, the oropharynx chapter addressed cancers arising in the nasopharynx, oropharynx, and hypopharynx.1 To reflect the very different biological and etiological differences between nasopharyngeal carcinoma, HR-HPV–associated OPC and non-HR-HPV–associated OPC, and hypopharyngeal cancer, the eighth edition staging manual has been divided into 3 separate chapters—nasopharynx, HR-HPV–associated (p16-positive) OPC, and hypopharynx and non-HR-HPV–associated (p16-negative) OPC—to better reflect the variety of diseases arising in the pharynx.

T categories in both p16-positive, HR-HPV–associated OPC and p16-negative, non-HR-HPV–associated OPC were equally valid from a prognostic standpoint and thus remain the same with 2 exceptions: the p16-positive classification includes no carcinoma in situ (Tis) (because of the nonaggressive pattern of invasive of p16-positive OPC and the lack of a distinct basement membrane in the epithelium of Waldeyer ring), and the T4b category has been removed from p16-positive OPC (because the curves of the T4a and T4b categories proved indistinguishable) (Tables 1 and 2).2 p16-Negative cancers of the oropharynx, like other non-HR-HPV–associated cancers in the head and neck, such as those of the oral cavity, larynx, hypopharynx, and paranasal sinus, will no longer include a T0 category. The rationale for the change is elucidated below (see Unknown Primary).

A variety of treatment approaches for p16-positive, HR-HPV–associated OPC are currently used. The National Comprehensive Cancer Network Guidelines consider radiation-based or surgically based treatment equally acceptable as first-line therapy.14 The data that led to the need for a new staging system and the data to create and validate the staging systems
were broad based and came from centers treating primarily with radiation or primarily with surgical resection as the initial, definitive form of therapy.\textsuperscript{15–18} In view of the rising frequency of p16-positive oropharynx cancer, the urgency to define staging criteria necessitated use of data from both published and unpublished sources. Therefore, access to large data bases for validation was obtained with the approval of the multi-institutional consortia but before their publication.\textsuperscript{17,18}

The p16-positive, HR-HPV-associated OPC cTNM classification is applicable to all patients before treatment (regardless of the intended form of treatment). cTNM employs information from physical examination and whatever imaging is performed. Clinically involved lymph nodes, whether one or multiple, as long as they were ipsilateral and less than 6 cm in size, had similar impact on survival (\textit{similar hazard consistency}) and thus are included in the same N category: N1. Survival with clinically palpable and/or radiographically evident, bilateral or contralateral lymph nodes was distinguishable with a worse outcome than N1. Therefore, contralateral or bilateral lymph nodes are classified as N2. Lymph nodes greater than 6 cm in size, or more than five lymph nodes, were classified as N3. This represents a significant change from the non-HR-HPV–associated (p16-negative) OPC N category (Tables 3 and 4).\textsuperscript{2}

pTNM is obviously applicable only to patients who are managed with surgery (after examination of the resected specimens, like all other pathologically staged tumors). Neither lymph node size (lymph nodes >6 cm in greatest dimension did not confer any difference in survival from a smaller, single lymph node) nor presence in the contralateral neck was predictive of survival, unlike the situation for lymph nodes treated with radiation. However, a fundamental difference in outcome was observed based on the number of pathologically positive lymph nodes. The breakpoint in behavior appeared at 1 to 4 (N1) versus 5 or more (N2) lymph nodes (Table 5).\textsuperscript{2} Because accurately counting the number of involved lymph nodes preoperatively is not possible for a pretreatment clinical stage classification, and because these data were exclusively derived by analyzing pathological lymph node numbers, this classification approach will be confined to pTNM. Therefore, the eighth edition for p16-positive tumors will have 2 separate staging systems, one for cTNM and one for pTNM. The unusual difference in behavior seen in the N3 neck between the clinical and pathological data sets (reflecting radiation treatment rather than surgical lymph node dissection) is unexpected. Prospective data collection will be needed to resolve this issue.

Combining T and N into stage groupings was then accomplished using both the clinical and pathological data sets described above (Tables 6, 7, and 8). The significantly better overall survival seen in HR-HPV–associated OPC allowed for much clearer discrimination into 3 curves representing stages I, II, and III. The paradigm reserves stage IV for patients with distant metastatic disease, a group known to have a much poorer survival. This represents a sharp contrast with non-HR-HPV–associated (p16-negative) cancers of the oropharynx, as described above (Tables 6, 7, and 8).

### TABLE 1. Clinical and Pathologic T Category for Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual\textsuperscript{a}

| T CATEGORY | T CRITERIA |
|------------|------------|
| T0         | No primary identified |
| T1         | Tumor 2 cm or smaller in greatest dimension |
| T2         | Tumor larger than 2 cm but not larger than 4 cm in greatest dimension |
| T3         | Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis |
| T4         | Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond\textsuperscript{b} |

\textsuperscript{a}Table 1 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission). \textsuperscript{b}Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

### TABLE 2. Clinical and Pathologic T Category for Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual\textsuperscript{a}

| T CATEGORY | T CRITERIA |
|------------|------------|
| Tx         | Primary tumor cannot be assessed |
| Tis        | Carcinoma in situ |
| T1         | Tumor 2 cm or smaller in greatest dimension |
| T2         | Tumor larger than 2 cm but not larger than 4 cm in greatest dimension |
| T3         | Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis |
| T4         | Moderately advanced or very advanced local disease |
| T4a        | Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible\textsuperscript{b} |
| T4b        | Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery |

\textsuperscript{a}Table 2 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission). \textsuperscript{b}Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.
hypopharynx, oral cavity, paranasal sinuses, larynx, and salivary gland, in which stage IV is subdivided into IVA, IVB and IVC, and IVC is reserved for distant metastatic disease (Tables 6, 7, and 8).

**Unknown Primary**

Squamous cell carcinoma in lymph nodes arising from an undetected primary cancer is a well recognized clinical entity in the head and neck. The typical presenting finding is of an enlarged cervical lymph node with carcinoma identified by biopsy. A search through history, physical examination, appropriate imaging, and biopsy of candidate sites must yield no evidence of a primary tumor. These patients are categorized as T0 but cannot be assigned to a specific anatomic site. Currently, greater than 90% of these T0 (unknown primary) designations (lymph nodes in patients with no detectable primary) reflect HR-HPV–associated cancers.19,20 A large majority of nasopharyngeal cancers are positive for Epstein–Barr virus (EBV) by Epstein–Barr–encoded RNA (EBER) on ISH.21 Consequently, in the proper clinical context, demonstrating the presence of either EBV or HPV can establish an anatomic site of origin.19,21 HPV-ISH, p16 immunohistochemistry, and EBER-ISH are recommended for all cervical lymph nodes with carcinoma of unknown primary site. Thus, one key change from prior editions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HR-HPV–associated OPC, and salivary gland cancers (which can be identified by their unique histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the oropharynx and nasopharynx. The specificity of p16 overexpression alone as a surrogate HR-HPV biomarker is limited to OPC.

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| N CATEGORY | N CRITERIA |
|------------|------------|
| NX         | Regional lymph nodes cannot be assessed |
| N0         | No regional lymph node metastasis |
| N1         | One or more ipsilateral lymph nodes, none larger than 6 cm |
| N2         | Contralateral or bilateral lymph nodes, none larger than 6 cm |
| N3         | Lymph node(s) larger than 6 cm |

*Table 3 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission).*

| N CATEGORY | N CRITERIA |
|------------|------------|
| NX         | Regional lymph nodes cannot be assessed |
| N0         | No regional lymph node metastasis |
| N1         | Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative |
| N2         | Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative |
| N2a        | Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative |
| N2b        | Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative |
| N2c        | Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative |
| N3         | Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive |
| N3a        | Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative |
| N3b        | Metastasis in any node(s) and clinically overt ENE-positive |

*Table 4 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission).*

Occasionally, cancers from other sites may express p16, potentially giving rise to such a lymph node. Therefore, in the context of assigning a primary anatomic site, HPV-ISH is also recommended as additional confirmatory testing to attribute the lymph node to a p16-positive

| N CATEGORY | N CRITERIA |
|------------|------------|
| NX         | Regional lymph nodes cannot be assessed |
| pN0        | No regional lymph node metastasis |
| pN1        | Metastasis in 4 or fewer lymph nodes |
| pN2        | Metastasis in more than 4 lymph nodes |

*Table 5 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission).*
oropharyngeal origin. Cervical lymph node metastases that are HR-HPV ISH-positive/p16-positive with no primary tumor identified through history, physical examination, or available imaging studies will be staged as p16-positive, HR-HPV–associated OPC, which includes a T0 category. EBV-positive cancers identified in a cervical lymph node with no detected primary tumor will be staged according to the nasopharynx classification in which the T0 category remains. Squamous carcinoma in a cervical lymph node that is negative for EBER and p16 cannot be assigned to any specific head and neck primary site and will be staged according to the system detailed in the cervical node and unknown primary chapter.

**Changes to the T Category**

Primary tumor (T) categories (for size/extent of the primary tumor) have been revised in OCC, NMSC, and nasopharyngeal cancer. The T category for OCC acknowledges the different biological behavior of deeply invasive but small tumors and incorporates depth of invasion (DOI). It has been recognized for decades that the prognosis of OCC worsens when the tumor is thicker. More recent data suggest that DOI is a better predictive parameter than tumor thickness. Starting in the sixth edition of the staging manual, DOI has been recorded and is available for analysis. DOI is distinct from tumor thickness, and the ambiguity in definition has undermined the accuracy of registry-level data. The precise definition of DOI has been clarified in the eighth edition, as described below. Assessing DOI by clinical

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### TABLE 6. Anatomic Stage and Prognostic Groups for Clinical TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual

| T CATEGORY | N CATEGORY | N0 | N1 | N2 | N3 |
|------------|------------|----|----|----|----|
| T0         | NA         | I  | I  | II | III|
| T1         | I          | I  | I  | I  | III|
| T2         | I          | I  | I  | II | III|
| T3         | II         | I  | I  | I  | III|
| T4         | III        | III| III| III| III|

*Any M1 is stage IV.

### TABLE 7. Anatomic Stage and Prognostic Groups for Pathologic TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual

| T CATEGORY | N CATEGORY | N0 | N1 | N2 | N3 |
|------------|------------|----|----|----|----|
| T0         | NA         | I  | I  | II | III|
| T1         | I          | I  | I  | I  | III|
| T2         | I          | I  | I  | II | III|
| T3         | II         | I  | I  | I  | III|
| T4         | III        | III| III| III| III|

*Any M1 is stage IV.

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### TABLE 8. Anatomic Stage and Prognostic Groups for Clinical and Pathologic TNM Grouping of Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual

| T CATEGORY | N CATEGORY | N0 | N1 | N2 | N3 |
|------------|------------|----|----|----|----|
| T1         | I          | I  | III| IVA| IVB|
| T2         | II         | II | III| IVA| IVB|
| T3         | III        | III| III| IVA| IVB|
| T4a        | IVA        | IVA| IVA| IVA| IVB|
| T4b        | IVB        | IVB| IVB| IVB| IVB|

*Any M1 is stage IVC.

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### TABLE 9. T Category for Oral Cavity Cancer, 8th Edition Staging Manual

| T CATEGORY | T CRITERIA |
|------------|------------|
| TX         | Primary tumor cannot be assessed |
| Tis        | Carcinoma in situ |
| T1         | Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness) |
| T2         | Tumor ≤2 cm, DOI >5 mm and ≤10 mm or tumor >2 cm but ≤4 cm, and ≤10 mm DOI |
| T3         | Tumor >4 cm or any tumor >10 mm DOI |
| T4         | Moderately advanced or very advanced local disease |
| T4a        | Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4 |
| T4b        | Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery |

*Table 9 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission*).
examination requires palpation and attention to detail. Clinicians will need to distinguish a thick, exophytic, but less invasive tumor from one that is ulcerated and deeply invasive through careful palpation supplemented by radiographic assessment. Since the inception of the TNM system, clinicians have been using physical examination to reflect subtle differences in size and extension of tumors, so distinguishing less invasive lesions (<5 mm), from those of moderate depth (from >5 to ≤10 mm) or deeply invasive cancers (>10 mm) should not be problematic. DOI will affect T category, accentuating the distinction between superficial or exophytic tumors and those that are more invasive. Staging will no longer depend solely upon greatest surface dimension (Table 9).2 Because data reported from a large international collaborative study of OCC demonstrated a significant distinction in outcomes between T1 tumors with more than 5 mm DOI and T2 through T4 tumors with greater than 10 mm DOI, the T category for OCC is being modified in the eighth edition to improve hazard discrimination.25 Therefore, for every 5-mm increase in DOI, both cT and pT categories will increase one level according to the following: ≤5 mm, >5 mm but ≤10 mm, and >10 mm. Pathologically, DOI is measured from the level of the basement membrane of the closest adjacent normal mucosa. A “plumb line” is dropped from this plane to the deepest point of tumor invasion. The T category increases with every interval of 5 mm (Figs. 1, 2, and 3). The tumor illustrated in Figure 1 is now upstaged to T2 based on a DOI of 9 mm. Figure 2 demonstrates a small, exophytic cancer;

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** To Measure Depth of Invasion, Establish the Horizon That Is at the Level of the Basement Membrane Relative to the Closest Intact Squamous Mucosa. The greatest invasion is measured by dropping a “plumb line” from the horizon. For printable rulers, see vendian.org/mncharity/dir3/paper_rulers/UnstableURL/rules_cm_narrow_20cm.pdf.

![Figure 2](https://example.com/figure2.png)

**FIGURE 2.** The Terms “Depth of Invasion” and “Tumor Thickness” Have Been Used Interchangeably, Which Is Incorrect. The white bar represents maximum tumor thickness, which here is greater than the depth of invasion (blue bar).
FIGURE 3. Depth of Invasion in an Ulcerated Carcinoma. Notice how “tumor thickness” would be deceptively thinner than depth of invasion.

TABLE 10. Regional Lymph Nodes Pathologic Category Criteria (pN)\textsuperscript{a}

| N CATEGORY | N CRITERIA\textsuperscript{b} |
|------------|-----------------------------|
| 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 and ENE-negative |
| N2         | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative |
| N2a        | Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative |
| N2b        | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative |
| N2c        | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative |
| N3         | Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive |
| N3a        | Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative |
| N3b        | Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive |

Abbreviations: ENE, extranodal extension. \textsuperscript{a}Table 10 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission). \textsuperscript{b}Note that a designation of “U” or “L” may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as ENE-negative or ENE-positive.
DOI is less than tumor thickness in this example. Finally, Figure 3 shows a small, ulcerated carcinoma, which was upstaged to T2 based on a DOI of 6 mm. Tumor thickness underestimates aggressive potential; DOI is superior to tumor thickness. Generous preoperative biopsies of small tumors may interfere with DOI determination; therefore, it is important that, when pathologists examine the original biopsies, attention should be directed to DOI to incorporate all available information and to arrive at the most accurate DOI. As with staging of all sorts, the general TNM principle of selecting the less advanced attribute (in this case, the lesser DOI categorization) should always be observed when the clinician harbors doubt. Extrinsic muscle infiltration is no longer a staging criterion for T4 designation in OCC, because DOI supersedes it, and limited extrinsic muscle invasion is difficult to assess (either clinically or pathologically).

As mentioned above, NMSC will be staged with the head and neck chapters in the eighth edition. NMSC includes many types of skin malignancies but is largely composed of basal cell carcinoma and cutaneous squamous cell carcinoma. Regardless of their anatomic site of origin, Merkel cell cancer and melanoma continue to be represented by their own distinct chapters in the eighth edition. Most of the staging criteria remain the same as those in the seventh edition, with the exception of the addition of DOI beyond 6 mm and perineural invasion (PNI) as components of the T category, both of which elevate a lesion as T3, even if the tumor is of limited diameter. Furthermore, a
size criterion is reintroduced, as was previously the case in the sixth edition TNM classification, but with a cutoff point greater than 4 cm (as opposed to 5 cm) to distinguish T3 from T2 lesions, analogous to the size designations in other head and neck cancers.2,24 Similar to OCC, DOI has been shown to have a 6.0-fold higher risk of local recurrence and lymph node metastasis on multivariate analysis.26,27 PNI of larger nerves has also been shown to increase the risk of recurrence and metastasis.28,29 The data for nerves <0.1 mm were less robust;30 therefore, >6 mm DOI and PNI in large-caliber nerves (≥0.1 mm) are considered T3.

There are 2 changes in nasopharynx T classifications relating to anatomic markers rather than DOI. The previous T4 criteria “masticator space” and “infratemporal fossa” were used as synonyms, but their anatomic descriptions differ, sowing confusion among clinicians. These terms will now be replaced by a specific description of soft-tissue involvement to avoid ambiguity. In addition, adjacent muscle involvement (including medial pterygoid, lateral pterygoid, and prevertebral muscles) will now be “down-staged” to T2 based on a recent analysis showing them to have a more favorable outcome using current treatment.31

**Neck Classification Change in the Nasopharynx**

In the N classification of nasopharynx, the iconic, traditional description of the supraclavicular fossa that was unique...
to this site will be replaced by contemporary definitions used for other head and neck sites and more suited to axial cross-sectional imaging. In addition, low neck involvement and >6 cm size will be merged into a single N3 designation (formerly N3a and N3b), and T4 and N3 will both designate stage IVA (formerly IVA and IVB) in stage grouping.31

**ENE in N Categorization**

The status of the regional lymph nodes in head and neck cancer has tremendous prognostic significance, so the cervical lymph nodes must be assessed for each patient. ENE has been added as a prognostic variable for regional lymph node metastases in addition to the number and size of metastatic lymph nodes (Tables 4 and 10).2 Evidence has existed for decades that ENE profoundly affects prognosis for head and neck cancers, with the recently recognized exception of p16-positive, HR-HPV–associated OPC.16,32-35 The risk that newer staging versions would move those patients who had cancers with a worse outcome into more advanced stages, thus artificially creating better outcomes in early stage disease (a concept known as *stage migration*), was balanced against the need for better hazard discrimination and consistency. To minimize stage migration, incorporating ENE into the clinical staging system requires a high bar for inclusion. Current imaging modalities have significant limitations and lack sensitivity and specificity in their ability to identify early or minor ENE.36 Radiological evidence alone may be supportive but is not sufficient. Therefore, for clinical staging, only unambiguous ENE, as determined by physical examination (eg, invasion of skin, infiltration of musculature/dense tethering to adjacent structures, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve) and supported by radiological evidence, should be present to assign a status of ENE-positive.

Pathological ENE is defined as extension of metastatic carcinoma from within a lymph node through the fibrous capsule and into the surrounding connective tissue, regardless of the presence of stromal reaction. Metastatic carcinoma that stretches the capsule but does not breach it does not constitute ENE (Fig. 4A and 4B). An additional feature of ENE that will be collected is minor or major extension. Pathologically, minor ENE (ENE\text{mi}) is defined as extension ≤2 mm from the capsule. Major ENE (ENE\text{ma}) is defined as either extension apparent to the pathologist’s naked eye and feel when accessioning the surgical specimen or >2 mm

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**TABLE 11. Characteristics of Patients With Oral Cavity Cancer**

| CHARACTERISTIC | COMBINED | MSKCC, NY | PMH, TORONTO |
|---------------|----------|-----------|--------------|
| Total no. of patients | 1792 | 1119 | 673 |
| Follow-up: Median [range], mo | 44.30 [0.03-307.75] | 51.02 [0.13-307.75] | 38.23 [0.03-197.61] |
| Years treated | 1985-2012 | 1985-2012 | 1993-2011 |
| Age: Median [range], y | 60 [15-96] | 60 [16-96] | 61 [15-89] |
| Sex: Men, no. (%) | 1064 (59) | 642 (57) | 422 (63) |

Abbreviations: MSKCC, Memorial Sloan Kettering Cancer Center, NY; PMH, Princess Margaret Hospital, Toronto. *Table 11 is 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, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission).
beyond the capsule microscopically (Fig. 5A and 5B). ENE also includes deposits of carcinoma in soft tissues without attendant nodal architecture. The 2 subcategories for ENE are for data collection purposes only, and either is considered ENE-positive for definition of pN.

Validation of Staging Algorithms Using an Oral Cavity Data Set

OCC is largely a surgically treated disease. Therefore, ample histopathologic data from relatively large data sets are available. Most OCC, like cancers of the larynx, hypopharynx, and paranasal sinuses, are HR-HPV-negative or, when positive, tend to behave similarly to their negative counterparts. Consistent with seventh edition staging for oral cavity, larynx, paranasal sinus, and hypopharynx and adopting the premise that nonvirus-associated tumors tend to behave in a similar fashion, the N categorization for all sites has been changed based upon the data from oral cavity sites. OCC outcomes were analyzed using a large data set of patients (treated at 2 tertiary care cancer centers in North America) approached with a common staging and treatment strategy (Table 11).2 Comparable cancer registry data sets for sites other than the oral cavity are not available; therefore, the eighth edition revisions have been based on single-institutional data that have not yet been validated in broader registry data sets. The following is a description of the process of stage revision undertaken for oral cancer to illustrate how the modifications previously discussed using DOI and ENE were assessed.

The influence on overall survival upon incorporation of DOI into the eighth edition oral cavity staging was interrogated in the Memorial Sloan Kettering Cancer Center-Princess Margaret Hospital (MSKCC-PMH) institutional data set (Fig. 6). The addition of ENE to the N category was performed on a data set of patients with OCC from the NCDB, including patients who were treated in 2010 and 2011 (Fig. 7A). The data on ENE from other sites also have been widely published in institutional data sets and also were examined using the NCDB, both of which support inclusion of ENE in all such tumors (Fig. 7B). The new N criteria were then validated using the MSKCC-PMH institutional data set (Fig. 7C). After validation of the N criteria, the next step was to examine the interplay of these new T and N criteria for stage grouping. The NCDB could not be used for this purpose because of the lack of information on DOI of the primary tumor. Therefore, the MSKCC-PMH data set was used for stage group analysis using seventh edition AJCC/UICC criteria (without DOI or ENE) (Fig. 8A). As seen in Figure 8A, the seventh edition stage groupings do not discriminate between stages II and III, an effect that may be attributable to the failure to account for DOI and ENE, which were lacking in the T and N categories.
In recognition of these newer prognostic factors, the MSKCC-PMH institutional data were re-interrogated after appropriate adjustment of the stage groups, which resulted in better discrimination of stage groups (Fig. 8B). However satisfying, these stage groupings could not be validated through cancer registry data, because comparable data on DOI of the primary tumor and ENE were not consistently available from the NCDB. Therefore, although there are institutional data to support restructuring stage groups for OCC, the stage groupings will remain unchanged in the eighth edition pending evaluation of additional cancer registry data sets.

Conclusion
The eighth edition Head and Neck AJCC Cancer Staging Manual incorporates significant changes based on advances in our understanding of the etiology and certain histologic attributes of tumors. These include a separate staging algorithm for HPV-associated cancer of the oropharynx; changes to the tumor T categories in the nasopharynx, oral cavity, and skin; and the addition of tumor ENE to the lymph node category for most sites. The revisions included in the eighth edition were based on evidence available from large institutional and collaborative data sets.

The process that led to these changes highlights the need to collect high-fidelity cancer registry-level data that can be used to confirm prognostic observations identified in institutional data sets. Future versions of the staging system may well incorporate nomograms and personalized approaches; but for now, the eighth edition strikes a balance between a personalized, complex system and a more general, simpler one that maintains the user-friendliness and worldwide acceptability of the traditional TNM staging paradigm.

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