

Staging Head and Neck Cancers

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INTRODUCTION AND OVERVIEW OF KEY CONCEPTS

Cancers of the head and neck may arise from any of the mucosal surfaces of the upper aerodigestive tract. The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition (8th Edition) introduces a number of significant changes. These include a separate staging algorithm for human papilloma virus–associated cancer, restructuring of the head- and neck- specific cutaneous malignancy chapter, division of the pharynx staging system into three components, changes to the tumor (T) categories, addition of depth of invasion as a T characteristic in oral cancer, and the addition of extranodal tumor extension to the node (N) category.

Maintaining a balance between hazard discrimination, hazard consistency, desirable spread in outcomes, prediction of cure, and the highest possible compliance was paramount.¹ As the world moves toward personalized medicine, demand will increase for individualized prediction of risk and outcomes, which may ultimately eclipse the traditional groupings of cancers used in staging. The complexity associated with defining individual risk, prognosis, and benefit from treatment is undeniable but it may eventually be mitigated by relying on computerized algorithms presented in a user-friendly format on the handheld devices so ubiquitous in modern society.² These may be applied through nomograms relying on key anatomic, biologic, and clinical factors. Nonetheless, a feasible pretreatment approach (i.e., clinical TNM) applicable in all medical settings and to all patients should be maintained both for defining treatment and for evaluating the effect of treatment across populations and time. Thus, the 8th Edition represents a compromise between a very accurate, but very complex system (where compliance would be low) and a very simple system, which would permit high compliance at the expense of reduced predictive capacity.

Cancer staging is used worldwide in countries with widely varying levels of resources. Assuring harmony between the AJCC and Union for International Cancer Control (UICC) staging systems was an important goal and it could not have been accomplished without the wisdom, collegiality, and sense of purpose displayed by members of the UICC Head and Neck Committee. We are especially indebted to the tremendous work ethic and attention to detail exhibited by members of the AJCC Head and Neck Expert Panel and its many subcommittees and disease site leaders. Both groups have balanced the need for a worldwide system with the need for incremental improvement.

KEY CHANGES TO HEAD AND NECK CANCER STAGING

The major changes in the 8th Edition for head and neck cancer reflect the changing environment of head and neck oncology. The areas highlighted in this section include general changes and additions to cancer staging that apply across most Head and Neck sites. The specific changes for each site are detailed in the respective chapters.

New and Restructured Chapters

A major addition is a restructured head- and neck-specific cutaneous malignancy chapter. This acknowledges the increasing need for head and neck oncologists to stage cutaneous malignancies.

The Pharynx chapter has been divided into three separate anatomic regions that better reflect the different diseases arising in the pharynx.

- Nasopharynx has its own chapter recognizing the unique biology and etiology of this disease.

To access the AJCC cancer staging forms, please visit www.cancerstaging.org.

- HPV-negative oropharynx and hypopharynx remain together in view of their shared biology and typical risk factors.
- A new chapter describing the staging of human papilloma virus–associated (HPV) oropharyngeal cancers (OPC) has been added.

The rapidly increasing incidence of high-risk HPV (HR-HPV) associated cancers of the tonsil and tongue base has posed numerous challenges in diagnosis, management strategies, and outcomes reporting.³ The AJCC Cancer Staging Manual, 7th Edition (7th Edition) TNM staging of OPC tumors lacks hazard discrimination, hazard consistency, and capacity to predict outcome. HR-HPV associated cancers occur more often in younger, healthier individuals with little or no tobacco exposure. HPV16/18 are the most commonly detected transcriptionally active HR-HPV types. The established staging criteria defined in the 7th Edition are insufficient to adequately stage and define the biology of this emerging disease. Immunohistochemistry for p16 overexpression has emerged as a robust surrogate biomarker for HPV-mediated carcinogenesis and as an independent positive prognosticator in this specific context.⁴ Direct detection of HPV is not used as a defining factor due to limited availability of the test, cost, and lack of additional ability to predict survival compared with p16 overexpression. p16 overexpression was chosen as the best identifier of disease because of its low cost, universal applicability, and ease of reading compared with other HPV identifiers. It is important to remind clinicians, however, that p16 overexpression is context-specific and currently applicable only to the tonsillar and base of tongue regions of the oropharynx. Designation of p16 overexpression should occur only when there is significant staining following established criteria.⁴ To increase the utility of staging and acknowledge the emergence of a distinct disease, the p16+ and p16– OPCs are now separately described. OPC with p16 expression of weak intensity or limited distribution (<75% of cells) should be staged using oropharyngeal carcinoma p16– guidelines.

The 8th Edition TNM staging system for HPV-related cancers of the oropharynx provides better discrimination between stages. T categories remain the same for both p16+ and p16–, except that the p16+ classification includes no Tis category and no T4b, and p16– oropharynx, like other non-HPV associated cancers in the head and neck, includes no T0 category.

The p16+ clinical TNM classification is applicable to all cases before treatment (both surgically and non-surgically treated cases). The pathological classification is confined to cases managed with surgery (following examination of the resected specimens, as with all other pathologically staged tumors).

A unique and potentially perplexing feature of pathological staging in HPV+ is that in the data set, pN3 category

behaves as Stage I while pN2 behaves as Stage II. This finding is unprecedented, and only prospective collection of data will help clarify this apparent paradox.⁵

Rules for Classification

Because a fundamental difference in outcome was observed for cases based on the number of nodes confirmed pathologically and the clinical presence of contralateral nodes and nodes larger than 6 cm, two systems were developed for these two clinical scenarios. Pathological TNM (pTNM) applies only if the patient undergoes surgery and uses the pathological characteristics of the primary tumor and the number of positive nodes obtained from pathological examination of the surgically resected tissue. Clinical TNM (cTNM) utilizes information from available history, physical examination, and whatever imaging is performed. It is clear that to accurately enumerate clinically involved lymph nodes is not possible for a worldwide pretreatment clinical stage classification; that parameter, therefore, is confined to pTNM. It is recommended that clinical staging data be collected on ALL patients for the purposes of pretreatment assessment, providing a uniform standard for comparing cases across treatment centers around the world and for treatment planning, including selection of postsurgical treatment and prediction of prognosis.

Definition of Primary Tumor (T): Changes

Throughout the head and neck chapters, the Primary Tumor (T) categories (for size and extent of the primary tumor) are generally similar, with changes in the skin, nasopharynx, and oral cavity chapters. A key change from prior editions of the TNM system is the elimination of the T0 category in sites other than nasopharynx and HPV+ oropharynx. Specific changes include the following:

- T categorization for skin cancer recognizes the critical importance of depth of invasion beyond 6 mm and perineural invasion, both of which upstage a lesion to T3.
- In nasopharynx, the previous T4 criteria “masticator space” and “infratemporal fossa” are replaced by a specific description of soft tissue involvement to avoid ambiguity. Adjacent muscle involvement (including medial pterygoid, lateral pterygoid, and prevertebral muscles) is designated as T2.
- The biggest change in T category is for the oral cavity. Depth of invasion (DOI) has been added as a modification to T to enhance the distinction between the superficial or exophytic tumors and those that are more invasive. Clinicians have long recognized the very dif-

ferent biological behaviors between these types of lesions, and this is now acknowledged by increasing the T category for every 5-mm increase in DOI in three categories: less than or equal to 5 mm; greater than 5 mm, but not greater than 10 mm; and greater than 10 mm). It is important to recognize the distinction between tumor thickness and true DOI. It has been recognized since the early work of Spiro and co-workers, in the mid-1980s, that prognosis of oral cancers worsens as the tumor grows thicker, as with skin malignancies.⁶ The somewhat more sophisticated measure of DOI has been recorded for oral cavity cancers since the AJCC Cancer Staging Manual, 6th Edition (6th Edition). Clinicians experienced with head and neck cancer generally will have few problems identifying a superficial and less invasive lesion (≤ 5 mm) from those of moderate depth (> 5 mm and ≤ 10 mm) or deeply invasive cancers (> 10 mm) through clinical examination alone. Such experts have estimated the maximum dimensions for complicated lesions of the tonsil or palate for many years. In applying the DOI modifier, if there are doubts or ambiguity, the clinician should apply the general TNM uncertainty staging rule of using the lower attribute for a category (in this case a lower DOI categorization).

- Extrinsic muscle infiltration is no longer a staging criterion for T4 designation in oral cavity, because depth of invasion supersedes it and extrinsic muscle invasion is difficult to assess (both clinically and pathologically).
- An additional change is the elimination of the T0 category for all oral cavity, skin, larynx, HPV– oropharynx, hypopharynx, and sinus. This change affects cases where a cervical lymph node has metastatic squamous cell carcinoma, but no primary tumor is identified despite thorough history, examination, and available imaging studies. Assigning these cases to a specific head and neck site is not possible. Previous editions of TNM staging included a T0 category in each of these disease sites. However, it is seldom used and, if it is, the cancer could not be assigned to a stage group. Therefore, for the 8th Edition, the Expert Panel eliminated the T0 category from the head and neck staging systems. A separate staging system for those cases with an involved cervical node without a known primary tumor has been added to the chapter entitled Cervical Node and Unknown Primary of the Head and Neck. These cases should be classified under the TNM rules for a cancer of unknown primary outlined in that chapter.
- The exceptions where T0 continues to be used as a T-category are HPV-associated cancer and Epstein-Barr Virus (EBV) associated cancers. For HPV-associated cancers identified in a cervical lymph

node (defined as p16 positive), the case is staged using the p16 positive oropharynx system, which continues to include a “T0” category. EBV-positive cancers identified in a cervical node with no obvious primary are staged using the EBV-related nasopharynx system, in which the “T0” category is maintained. T0 is allowed for salivary gland cancers identified by their unique histology.

Regional Lymph Node (N) Category: Introduction of Extranodal Extension

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The 8th Edition introduces the use of extranodal extension (ENE) in categorizing the “N” category for metastatic cancer to neck nodes. The effect of ENE on prognosis in head and neck cancers is profound, except for those tumors associated with HR-HPV.⁷ Including this important prognostic feature was considered critical for improving staging.

Most of the evidence supporting ENE as an adverse prognostic factor is based on histopathological characterization of ENE, especially the distinction between microscopic and macroscopic (or gross) ENE. For clinical staging only, the presence of unquestionable ENE as determined by physical examination and supported by radiological evidence is to be used. As per the standard rules of cancer staging, if there is uncertainty or ambiguity for categorization of T, N, or M, the lower category is assigned.

Stringent criteria for clinical examination must be met to assign a diagnosis of ENE. Current imaging modalities have significant limitations in their ability to accurately identify ENE.⁸ This mandates that radiological evidence alone is insufficient. Unambiguous evidence of gross ENE on clinical examination (e.g., invasion of skin, infiltration of musculature or dense tethering to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk, or phrenic nerve invasion with dysfunction) supported by strong radiographic evidence is required to permit clinical classification of disease as ENE(+).

Pathological ENE also must be clearly defined as extension of metastatic tumor (tumor present within the confines of the lymph node and extending through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction). Again, when there is doubt or ambiguity in the reporting, the lesser or lower category is assigned, in this case ENE(–).

PRINCIPLES OF STAGING

All staging systems presented in this section are for clinical staging, based on the best possible estimate of the extent of disease before initiation of first treatment. Imaging tech-

niques—computed tomography (CT), magnetic resonance (MR) imaging, positron emission tomography (PET), and ultrasonography—may be employed, but clinical examination is sufficient to assign clinical stage. In advanced tumor stages, imaging studies add to the accuracy of primary tumor (T) and nodal (N) categorization, especially in the nasopharyngeal and paranasal sinuses primary sites, as well as for regional lymph nodes. Endoscopic evaluation of the primary tumor and examination under anesthesia when appropriate may be needed for accurate T categorization. These may be supplemented by needle biopsy (most often fine-needle aspiration biopsy [FNAB]) to confirm the presence of tumor and its histopathologic nature, while recognizing that a negative needle biopsy cannot rule out the presence of tumor. When imaging studies are not done or not available, as in low-resource regions, clinical stage may be based solely on careful history, physical examination, and/or endoscopy.

Clinical stage should be reported for all cases, as well as pathological stage when surgery is performed. Any diagnostic information that contributes to the overall accuracy of the pretreatment assessment should be considered in clinical staging and treatment planning. When surgical treatment is carried out, cancer of the head and neck can be staged pathologically (pTNM) using all information available from clinical assessment, as well as from the surgeon's operative findings and pathological study of the resected specimen.

With the exception of p16+ OPC (a recently recognized disease entity), no major changes in the stage groupings are recommended. The current stage groupings reflect recent practices, clinical relevance, and contemporary data. T4 tumors continue to be subdivided into moderately advanced (T4a) and very advanced (T4b) categories. Stage IV disease is divided into moderately advanced, local/regional disease (Stage IVA), very advanced local/regional disease (Stage IVB), and distant metastatic disease (Stage IVC).

The following chapters present the staging classification for nine major head and neck sites and disease entities:

- Oral Cavity
- Major Salivary Glands
- Nasopharynx
- HPV-Mediated (p16+) Oropharyngeal Cancer
- Oropharynx (p16-) and Hypopharynx
- Nasal Cavity and Paranasal Sinuses
- Larynx
- Mucosal Melanoma of the Head and Neck
- Cutaneous Carcinoma of the Head and Neck
- An additional chapter explaining Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck is included for additional clarity and staging information.

COLLECTION OF KEY PATIENT AND TUMOR FACTORS

An ongoing effort to evaluate the effect on prognosis of both tumor and non-tumor-related factors is underway. Cancer registrars should continue to perform chart abstraction to collect information regarding specific factors related to prognosis as outlined in each chapter. These data will be used to enhance the predictive power of the staging system in future revisions. Key domains of information to collect include the following:

- Comorbidity: In addition to the importance of the TNM factors outlined previously, the overall health or presence of comorbid conditions of patients influences outcome. Comorbidity can be assessed and semi-quantified using validated standardized tools applied by review of medical records.⁹ Accurate reporting of all major illnesses in the patient's medical record is essential. General performance measures are helpful in predicting survival.
- Performance Status: In addition, the AJCC strongly recommends that the clinician report performance status using the Eastern Cooperative Oncology Group (ECOG), Zubrod, or Karnofsky performance measures, along with standard staging information.
- Lifestyle factors: Tobacco and alcohol abuse adversely influence survival. Accurate recording of smoking (in pack-years) and alcohol consumption (in number of days drinking per week and number of drinks per day) will provide important data for future analysis. However, exactly how these should be incorporated in staging remains undefined. Smoking is known to have a deleterious effect on prognosis, but valid data are insufficient to allow it to be readily introduced into the staging systems. Smoking history should be collected as an important element of the demographics and may be included in Prognostic Groups in the future. For practicality, the minimum standard should classify smoking history as follows: never, ≤ 10 pack-years, > 10 but ≤ 20 pack-years, > 20 pack-years.
- Nutrition: Nutrition also is important to prognosis and can be indirectly measured by weight loss of > 10 % of body weight over 3 months.¹⁰
- Depression: Depression adversely impacts quality of life and survival.^{11, 12} A previous or current diagnosis of depression should be recorded in the medical record.

REGIONAL LYMPH NODES

The status of the regional lymph nodes in head and neck cancer is of such prognostic importance that the cervical nodes must be assessed for each patient and tumor. The lymph

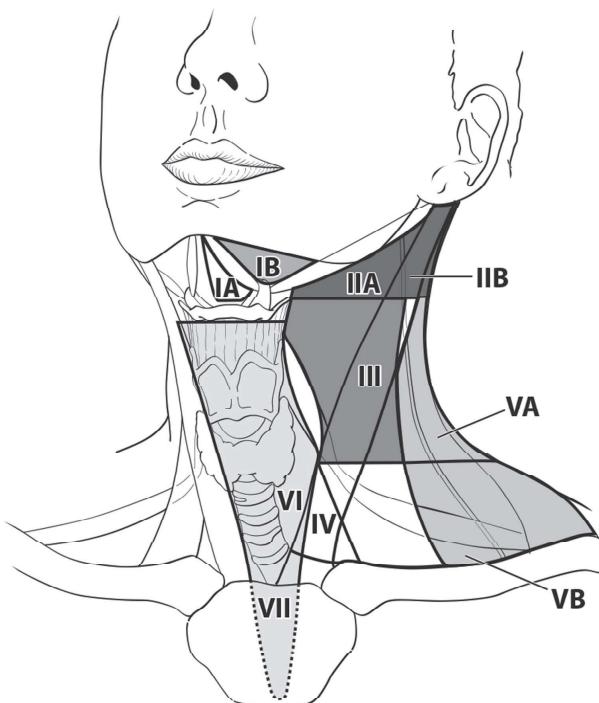
nodes in the head and neck are subdivided into specific anatomic subsites and grouped into seven levels for ease of description (Fig. 5.1, Tables 5.1 and 5.2).

In addition to the standard groups listed in Tables 5.1 and 5.2, other lymph node groups are defined by their specific anatomic location. Numbers of nodes are counted toward N category, but they are listed separately using the following descriptors.

- Suboccipital
- Retropharyngeal
- Parapharyngeal
- Buccinator (facial)
- Preauricular
- Periparotid and intraparotid

Other General Rules for Assessing Regional Lymph Nodes

Histopathologic examination is necessary to exclude the presence of tumor in lymph nodes for pathological categorization (pN0). No imaging study (as yet) can identify microscopic tumor foci in regional nodes or distinguish between small reactive nodes and small malignant nodes.



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Fig. 5.1 Schematic indicating the location of the lymph node levels in the neck as described in Table 5.1

Table 5.1 Anatomical structures defining the boundaries of the neck levels and sublevels

Boundary Level	Superior	Inferior	Anterior (medial)	Posterior (lateral)
IA	Symphysis of the mandible	Body of the hyoid	Anterior belly of the contralateral digastric muscle	Anterior belly of the ipsilateral digastric muscle
IB	Body of the mandible	Posterior belly of the digastric muscle	Anterior belly of the digastric muscle	Stylohyoid muscle
IIA	Skull base	Horizontal plane defined by the inferior border of the hyoid bone	Stylohyoid muscle	Vertical plane defined by the spinal accessory nerve
IIB	Skull base	Horizontal plane defined by the inferior body of the hyoid bone	Vertical plane defined by the spinal accessory nerve	Lateral border of the sternocleidomastoid muscle
III	Horizontal plane defined by the inferior body of the hyoid	Horizontal plane defined by the inferior border of the cricoid cartilage	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of the cervical plexus
IV	Horizontal plane defined by the inferior border of the cricoid cartilage	Clavicle	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of the cervical plexus
VA	Apex of the convergence of the sternocleidomastoid and trapezius muscles	Horizontal plane defined by the lower border of the cricoid cartilage	Posterior border of the sternocleidomastoid muscle or sensory branches of the cervical plexus	Anterior border of the trapezius muscle
VB	Horizontal plane defined by the lower border of the cricoid cartilage	Clavicle	Posterior border of the sternocleidomastoid muscle	Anterior border of the trapezius muscle
VI	Hyoid bone	Suprasternal notch	Common carotid artery	Common carotid artery
VII	Suprasternal notch	Innominate artery	Sternum	Trachea, esophagus, and prevertebral fascia

Modified from Robbins KT, Clayman G, Levine PA, et al.¹³ with permission from the American Medical Association.

Table 5.2 Lymph node groups found within the seven levels and sublevels of the neck

Lymph node group	Description
Submental (sublevel IA)	Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone. These nodes are at greatest risk for harboring metastases from cancers arising from the floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, and lower lip.
Submandibular (sublevel IB)	Lymph nodes within the boundaries of the anterior and posterior bellies of the digastric muscle, the stylohyoid muscle, and the body of the mandible. These include the preglanular and the postglanular nodes and the prevascular and postvascular nodes. The submandibular gland is included in the specimen when the lymph nodes within the triangle are removed. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, anterior nasal cavity, skin, and soft tissue structures of the midface, as well as from the submandibular gland.
Upper Jugular (sublevels IIA and IIB)	Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve, extending from the level of the skull base (above) to the level of the inferior border of the hyoid bone (below). The anterior (medial) boundary is stylohyoid muscle (the radiologic correlate is the vertical plane defined by the posterior surface of the submandibular gland) and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. Sublevel IIA nodes are located anterior (medial) to the vertical plane defined by the spinal accessory nerve. Sublevel IIB nodes are located posterior lateral to the vertical plane defined by the spinal accessory nerve. (The radiologic correlate is the lateral border of the internal jugular on a contrast-enhanced CT scan.) The upper jugular nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, and parotid gland.
Middle Jugular (level III)	Lymph nodes located around the middle third of the internal jugular vein, extending from the inferior border of the hyoid bone (above) to the inferior border of the cricoid cartilage (below). The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.
Lower Jugular (level IV)	Lymph nodes located around the lower third of the internal jugular vein, extending from the inferior border of the cricoid cartilage (above) to the clavicle below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk for harboring metastases from cancers arising from the hypopharynx, thyroid, cervical esophagus, and larynx.
Posterior Triangle (sublevels VA and VB)	This group is composed predominantly of the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes also are included in the posterior triangle group. The superior boundary is the apex formed by the convergence of the sternocleidomastoid and trapezius muscles; the inferior boundary is the clavicle; the anterior (medial) boundary is the posterior border of the sternocleidomastoid muscle; and the posterior (lateral) boundary is the anterior border of the trapezius muscle. Thus, sublevel VA includes the spinal accessory nodes, whereas sublevel VB includes the nodes following the transverse cervical vessels and the supraclavicular nodes, with the exception of the Virchow node, which is located in level IV. The posterior triangle nodes are at greatest risk for harboring metastases from cancers arising from the nasopharynx, oropharynx, and cutaneous structures of the posterior scalp and neck.
Anterior Compartment (level VI)	Lymph nodes in this compartment include the pretracheal and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerves. The superior boundary is the hyoid bone; the inferior boundary is the suprasternal notch; and the lateral boundaries are the common carotid arteries. These nodes are at greatest risk for harboring metastases from cancers arising from the thyroid gland, glottic and subglottic larynx, apex of the piriform sinus, and cervical esophagus.
Superior Mediastinal (level VII)	Lymph nodes in this group include pretracheal, paratracheal, and esophageal groove lymph nodes, extending from the level of the suprasternal notch cephalad and up to the innominate artery caudad. These nodes are at greatest risk of involvement by thyroid cancer and cancer of the esophagus.

Modified from Robbins KT, Clayman G, Levine PA, et al.,¹³ with permission from the American Medical Association.

When enlarged lymph nodes are detected, the actual size (measured as the maximum dimension in any direction) of the nodal mass(es) should be recorded. Pathological examination is necessary for documentation of tumor extent in terms of the location or level of the lymph node(s) involved and the number of nodes that contain metastases. The pathological presence or absence of ENE should be designated as ENE(+) or ENE(-).

Definition of Regional Lymph Nodes (N)

Clinical N (cN)

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(-)