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# Data Set for the Reporting of Nodal Excisions and Neck Dissection Specimens for Head and Neck Tumors

## Explanations and Recommendations of the Guidelines From the International Collaboration on Cancer Reporting (ICCR)

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**• Standardized, synoptic pathologic reporting for tumors greatly improves communication among clinicians, patients, and researchers, supporting prognostication and comparison about patient outcomes across institutions and countries. The International Collaboration on Cancer Reporting is a nonprofit organization whose mission is to develop evidence-based, universally available surgical pathology reporting data sets. Within the head and neck region, lymph node excisions and neck dissections are frequently performed as part of the management of head and neck cancers arising from the mucosal sites (sinonasal tract, nasopharynx, oropharynx, hypopharynx, oral cavity, and larynx), along with bone tumors, skin cancers, melanomas, and other tumor categories. The type of specimen, exact location (lymph node level), laterality, and orientation (by suture or diagram) are essential to accurate classification. There are significant staging differences for each anatomic site within the head and neck when lymph node sampling is considered, most importantly related to human papillomavirus–associated oropharyngeal carcinomas and mucosal melanomas. Number, size, and site of affected lymph nodes, including guidelines on determining the size of tumor deposits and the presence of extranodal extension and soft tissue metastasis, are presented in the context of prognostication. This review elaborates on each of the elements included in the data set for *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours*.**

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The International Collaboration on Cancer Reporting (ICCR) was established in 2011 through a collaboration among the College of American Pathologists, the Canadian Association of Pathologists–Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer, and the Royal Colleges of Pathologists of Australasia and the United Kingdom, joined in 2013 by the European Society of Pathologists, and followed by the American Society of Clinical Pathology and the Royal College of Physicians of Ireland, Faculty of Pathology, as sustaining members. The goal of the ICCR is to produce and maintain a single, internationally agreed-upon, structured pathology data set for cancer specimens of all major sites. Doing so provides opportunities for international collaboration and agreement on data set elements and for international comparison of treatments protocols and outcomes. It also avoids duplication of work by multiple entities and assists countries that lack the resources to create their own structured reporting protocols.[1]

This data set was developed for the reporting of *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours*[39] of patients with carcinomas and melanoma of head and neck mucosal and major salivary gland sites, excluding lymphomas and sarcomas. It is not intended for use in reporting lymph node core needle biopsies or fine-needle aspiration samples. It may be used as a stand-alone document or with other data sets in the head and neck series that address relevant primary tumor sites: oral

cavity[40]; hypopharynx, larynx, and trachea[41]; nasopharynx and oropharynx[42]; malignant odontogenic tumors[43]; nasal cavity and paranasal sinuses[44]; major salivary glands[45]; ear and temporal bone tumors[46]; and mucosal melanomas.[47] Carcinomas covered by the data set include squamous cell carcinoma (SCC) of all upper aerodigestive tract sites, salivary- and nonsalivary-type adenocarcinomas, and neuroendocrine tumors. Pathologists may also apply the data set to cutaneous SCC and other cutaneous carcinomas (excluding Merkel cell carcinoma) metastatic to lymph nodes of the head and neck. It is not applicable to metastatic cutaneous melanoma.

Lymph node excisional biopsies or neck dissections may precede, accompany, or follow the biopsy or resection of a primary head and neck tumor. Concurrent reporting of the lymph node and primary tumor data set elements—ideally in the same report—is preferable, as it provides clinicians with the most comprehensive information for tumor stage categorization. Pathologists should consider the impact of prior intervention (eg, prior diagnostic lymph node excisional biopsy, as well as prior systemic or regional therapy in a patient with a neck mass) on the pN category, referring to the previous surgical pathology specimen if available.

## METHODS

The data set was developed according to the guidelines established by the ICCR by a Dataset Authoring Committee (DAC) comprising expert pathologists and clinicians from the countries and regions represented by the ICCR, as well as from the additional sponsoring organizations or societies: the North American Society of Head and Neck Pathology, the American Academy of Oral and Maxillofacial Pathology, the British Society for Oral and Maxillofacial Pathology, and the International Association of Oral and Maxillofacial Pathologists. A series champion, with support from the ICCR Dataset Steering Committee, coordinated the production of the multiple data sets in this series. In particular, the author panel for the *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours* data set included expert pathologists, a radiation oncologist, and a head and neck surgeon representing 4 countries and 2 continents.[39]

The data sets have a uniform format across sites and consist of both core and noncore elements (Table 1 lists core and noncore elements for this data set). Core elements are essential for the clinical management, staging, or prognosis of the cancer. Based on prognostic factors in the National Health and Medical Research Council levels of evidence,[2] these core elements have evidentiary support at level III-2 or above. In rare circumstances, where level III-2 evidence was not available, an element may have become core through unanimous agreement of the DAC. An appropriate staging system was included as a core element, using the harmonized American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) 8th edition TNM classifications of malignant tumors as the standard reference.[3,4] Including all core elements is considered the minimum reporting standard for a specific cancer.

Noncore elements may be clinically important and recommended as good practice, but have not yet been validated or regularly used in patient management. Accompanying commentary (including tables, diagrams, and microscopic images) was designed to provide contextual guidance to the reporting pathologist.

Members of the DAC were provided with copies of existing data sets that incorporate lymph node reporting for head and neck specimens from the College of American Pathologists and the Royal Colleges of Pathologists of Australasia and the United Kingdom,[5–7] with a rough draft of the data set initially created, and then developed further with successive teleconferences where the merits of proposed core and noncore elements were debated, with relevant commentary and figures for inclusion in the data set discussed. Drafts were circulated several times to members of the DAC, as well as the DAC chairs of other sites in the head and neck series and the series champion. The final DAC draft was submitted to the Dataset Steering Committee for approval before obtaining open consultation by stakeholders, whose comments and questions were addressed before the final data set was published.

**Table 1. Summary of Core and Noncore Data Elements**

| Core Elements (Required) | Noncore Elements (Recommended) |
|---|---|
| Specimen submitted | Operative procedure |
| Histologic tumor type | Primary tumor site |
| No. of nodes examined (per level) | Margin status |
| No. of nodes positive (per level) | Ancillary studies |
| Maximum dimension of largest involved lymph node | |
| Maximum dimension of largest metastatic deposit (for each side of neck, if applicable) | Nonlymphatic structures involved by ENE |
| ENE (present/not identified; major or minor) | Greatest extent of ENE, mm |
| Soft tissue metastasis (present/not identified) | No. of nodes with ENE |
| Regional lymph node categorization | |

Abbreviation: ENE, extranodal extension.

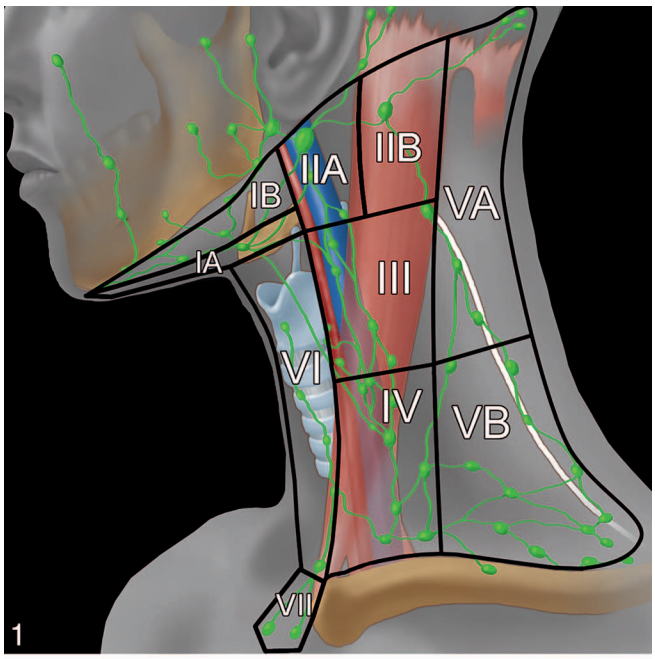
## DATA SET ELEMENTS

### Core (Required) Elements

**Specimens Submitted.**—This section provides a listing of all lymph node groups and the associated nonlymphoid tissue received as part of a single surgery, and should correlate with the operative procedure designation (noncore item, see below). Figures 1 and 2 illustrate the lymph nodes of the head and neck area. Accurate identification of the lymph node levels requires orientation of the specimen(s) by the surgeon, either with the use of sutures, with a diagram, or by submitting each level in a separate specimen container.[8,9] In cases in which orientation is not possible (for instance a level II through IV neck dissection unoriented as to superior versus inferior), consultation with the surgeon is recommended. In some cases, presurgical imaging that describes the location of a mass may help orientation. When possible, specific naming of nonlymphoid tissues is desirable (eg, internal jugular vein, sternocleidomastoid muscle).

Lymph nodes are often received as multiple specimens from a single operative procedure, and may include nodes from both sides of the neck. This happens more frequently in level I and central neck dissections and can depend on the site and extent of the primary tumor. The data set reporting guide groups the lymph nodes submitted into right, left, and central, each with a section for nonlymphoid tissue received. The specific levels received are documented for each side as applicable. If a patient is known to have had a prior lymph node excisional biopsy (eg, for diagnostic purposes), a comment to this effect is strongly recommended. The result of prior excision should be considered in the pN category assigned, with reference to the surgical pathology report number, when possible.

**Histologic Tumor Type.**—Identification of the histologic tumor type is crucial for several reasons, including (1) confirmation that a metastasis is of the same type as the



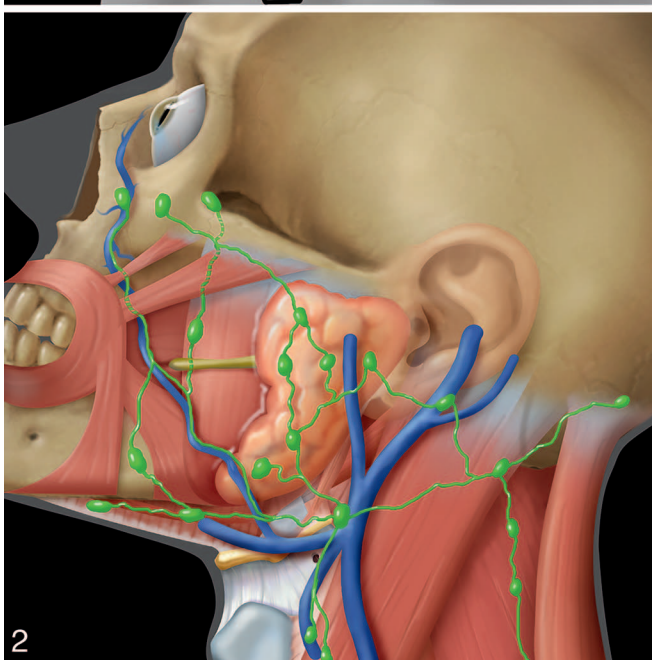




**Figure 1.** *Illustration of the major neck lymph node levels, with anatomical boundaries. Reproduced with permission: This figure was published in Gordon H, Harnsberger HR.* Imaging Anatomy: Brain, Head and Neck, Spine: Diagnostic and Surgical Imaging Anatomy, Cervical Lymph Nodes. *Vol II. 2006:253. Copyright Amirsys/Elsevier (2006).*

**Figure 2.** *Head and neck lymph node groups of the facial area, including the parotid, buccofacial, retroauricular, and occipital groups. These nodes are more commonly involved with tumors of the head and neck skin and parotid gland. Reproduced with permission: This figure was published in Gordon H, Harnsberger HR.* Imaging Anatomy: Brain, Head and Neck, Spine. Diagnostic and Surgical Imaging Anatomy, Cervical Lymph Nodes. *Vol II. 2006:253. Copyright Amirsys/Elsevier (2006).*

resected primary tumor; (2) facilitating a clinical search in cases of unknown primary tumors; (3) determining the correct pT and pN categories (see below); and (4) guiding treatment, which varies by tumor type and lymph node status.[3]

**Table 2. Suggested Presentation of Lymph Node Data[a]**

| Level and Side | No. of Nodes | No. Positive | No. With ENE | $ENE_{mi}$ or $ENE_{ma}$ |
|---|---|---|---|---|
| II right | 12 | 3 | 1 | $ENE_{ma}$ |
| III right | 14 | 2 | 0 | |
| Additional sites | | | | |

Abbreviation: ENE, extranodal extension; $ENE_{mi}$, microscopic ENE (≤2 mm in extent); $ENE_{ma}$, macroscopic ENE (>2 mm in extent).

[a] A tabular format is suggested for clearly presenting the lymph node data. Separate tables can be used for each side of the neck or a single table used for both sides, depending on the circumstance.

Histologic type and grade is typically determined from the histology of the primary site, but this is not possible for tumors of unknown primary. Tissue from a neck metastasis may be required for ancillary testing (eg, p16 immunohistochemistry, in situ hybridization for high-risk human papillomavirus [HPV], in situ hybridization for Epstein-Barr virus [EBV]–encoded RNA). For patients with occult primary SCC (pTX or pT0) in level II or III, the cN or pN categories are determined by EBV and HPV status.[10] Epstein-Barr virus–related and HPV-related carcinomas are given the N category that applies to nasopharyngeal and HPV-related oropharyngeal carcinomas, respectively.[3,4] The most recent (4th edition) World Health Organization (WHO) *Classification of Head and Neck Tumours*[11] was used for tumor classification. Verrucous carcinoma was not included in the list of SCC variants because of its limited capacity to involve regional nodes.

**Lymph Node Status.**—Lymph node status includes multiple core components. For each nodal level, record the number of nodes examined, the number of nodes affected by tumor (positive), and the presence or absence of extranodal extension (ENE) (Table 2). For cases in which an involved lymph node or tumor deposit straddles more than one level, it is recommended to assign it the level in which the bulk of the deposit is found, with an explanatory comment. In some cases, it may not be possible to divide a neck dissection into individual levels, and they must be combined (for example, "levels II/III"). As stated above, if a neck dissection is received without any level designation, orientation by the surgeon is preferred. If this cannot be obtained, the data may be reported without further qualification, such as "right neck dissection, not further specified." Prior neck surgery can make precise designation of the levels difficult and somewhat arbitrary. For tumor deposits in which there is residual lymph node tissue with widespread ENE, a combined gross and microscopic estimate of the number of involved lymph nodes is suggested. Correlation with presurgical imaging studies may be of benefit.

**Maximum Dimension of Largest Metastasis and Involved Lymph Node.**—The maximum dimensions of both the largest involved lymph node and the largest metastasis have been included as core elements in the data set. With rare exceptions (cN for nasopharyngeal carcinoma and pN for HPV-mediated oropharyngeal carcinoma), the N categorization requires measurement of involved lymph nodes. The UICC and AJCC staging systems base the pN and cN category for most upper aerodigestive tract carcinomas on the size of the involved nodes, rather than the size of the tumor deposit. The former measurement

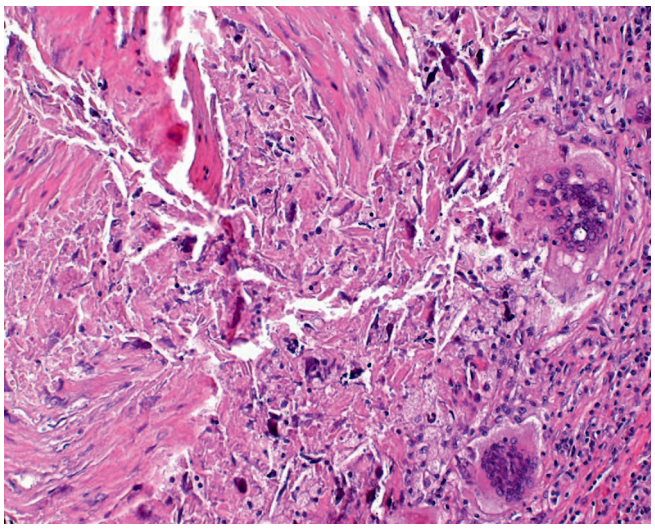


**Figure 3.** *A keratin granuloma, typical of treated lymph nodes found in salvage surgery of the neck. Note multinucleated giant cells at right. This should not be interpreted as residual viable tumor (hematoxylin-eosin, original magnification ×400).*

should be determined grossly at the time of specimen submission. Careful gross and microscopic correlation is required, as the largest lymph node may be reactive, with no metastatic tumor.

In some instances, especially with smaller metastatic lymph nodes, there may be a significant discrepancy between the sizes of the largest involved lymph node and the largest tumor deposit. On rare occasions, this may affect the pN category (for instance pN1 versus pN2a for an oral cavity tumor). With both dimensions provided, the oncologist will have the maximum information upon which to plan treatment. In some centers, there is a movement toward documenting the size of the largest lymph node submitted, then the largest lymph node affected by tumor, and then the largest tumor deposit.

Maximum dimension of the largest metastasis can be difficult to determine in cases where multiple tumor deposits are identified in a single lymph node. Options include (1) measuring the greatest dimension of the largest deposit, (2) combining the sizes of the deposits to give an aggregate dimension, and (3) measuring the greatest dimension end to end from a single slide, including discontinuous tumor deposits. The latter is recommended by the committee.

The prognostic significance of isolated tumor cells (foci $\leq$0.2 mm diameter or $\leq$200 cells) and micrometastases (tumor foci $\leq$2 mm in greatest dimension) is currently unknown for head and neck cancers, and their designation is not required as part of the TNM staging.[3,4,12,13] Isolated tumor cells are uncommon in metastatic SCC, but they do occur in some less-common primary tumors (eg, small cell carcinoma of salivary origin). As such, a tumor deposit of any size is considered a positive lymph node for staging purposes.[3,14] Specific identification of tumor deposits as isolated tumor cells, micrometastases, and cytokeratin-positive nonnucleated cells was not required as part of this data set, but can be recorded as per local practices for data collection.

Neck dissections may be performed as salvage surgery for a persistent neck mass following radiation therapy. In this circumstance, only viable tumor—not necrotic keratinous debris or keratin granulomas—should be categorized as a positive lymph node (Figure 3). Extra sampling or deeper levels of residual neck deposits may be required to evaluate these specimens. The prefix yp should be added to the TNM category.

**Soft Tissue Metastasis.**—Soft tissue metastasis refers to a deposit of tumor in connective tissue, without a microscopically identifiable residual lymph node. When small, this may represent vascular invasion, lymphatic invasion, or a discontinuous focus of ENE. However, most commonly (especially when grossly identifiable), soft tissue metastasis represents a totally replaced node (or nodes) with extensive ENE. It does not refer to intralymphatic tumor emboli in adipose tissue surrounding the lymph nodes.

In many cases, a soft tissue metastasis is the largest focus of tumor in the specimen, and it can be a challenge to accurately determine the number of positive nodes. The committee recommends considering this as a single positive node with macroscopic (major) ENE.

Rarely, there are small, isolated soft tissue metastases (eg, $<$1 mm in greatest dimension) that appear unlikely to be of nodal origin. Special stains and deeper levels may help to identify a vascular origin for these deposits, and the pathologist is discouraged from labeling these as positive lymph nodes (Figure 4, A and B).

**Extranodal Extension.**—Extranodal extension refers to extension of tumor outside the capsule of a lymph node and into the perinodal soft tissue. It is also known as extracapsular extension/spread, but the term *ENE* has been adopted in the 8th edition of the AJCC[3] and UICC[4] staging manuals, and therefore was included here. Extranodal extension is a poor prognostic factor in cervical node-positive head and neck carcinoma, except in HPV-mediated oropharyngeal cancer, where its clinical significance has yet to be established.[15–17] The presence of ENE in head and neck cancers correlates with the risk of regional recurrence and risk of distant disease. It is an important factor for oncologists when considering treatment with postoperative radiotherapy or chemoradiotherapy.[18,19] Extranodal extension can be subcategorized pathologically as microscopic ($\leq$2 mm in extent) or macroscopic ($>$2 mm in extent). These subcategories are usually not required for pN categorization but are recommended by the AJCC for data collection and future analysis. It is unclear if the extent of ENE will influence the decision to recommend systemic therapy or influence the dose of radiotherapy. As such, microscopic versus macroscopic (major) ENE for each level is a core element of the data set. The more detailed 5-point grading system of ENE (Lewis et al[20]) has not yet been validated and as such was not included. There is evidence that in nonoropharyngeal head and neck cancer, Lewis grade 4 ENE (soft tissue metastasis) is predictive of worse overall survival versus all lower grades of ENE, despite intensified adjuvant therapy.[21]

Interobserver variation in the determination of ENE may be minimized if the following guidance is used.

1. Lymph nodes, especially smaller nodes and those in the parotid area, may not have a complete capsule. The node hilum may merge with adipose tissue, or there may be a rim of lymphoid tissue external to the capsule (Figure 5, A and B). In general, a conservative approach is recommended. For instance, tumor within fat near the hilum of a node should be considered intranodal if

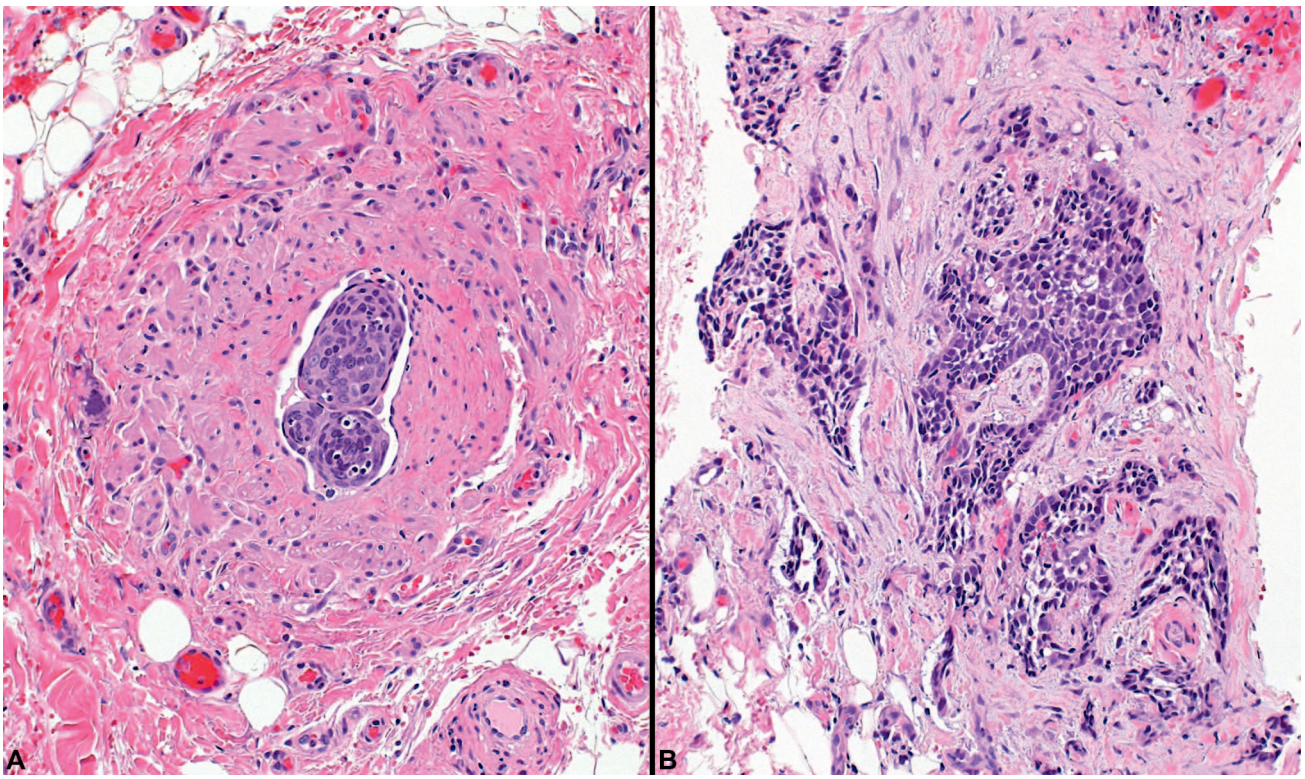



**Figure 4.** *A clearly intravascular tumor deposit within extranodal soft tissue (A). This extranodal soft tissue tumor deposit is less than 1 mm in greatest dimension and is not associated with a visible lymph node. This may represent seeding of the soft tissue via vessels or extranodal extension of tumor that is discontinuous from a node-based mass (B) (hematoxylin-eosin, original magnification ×400).*

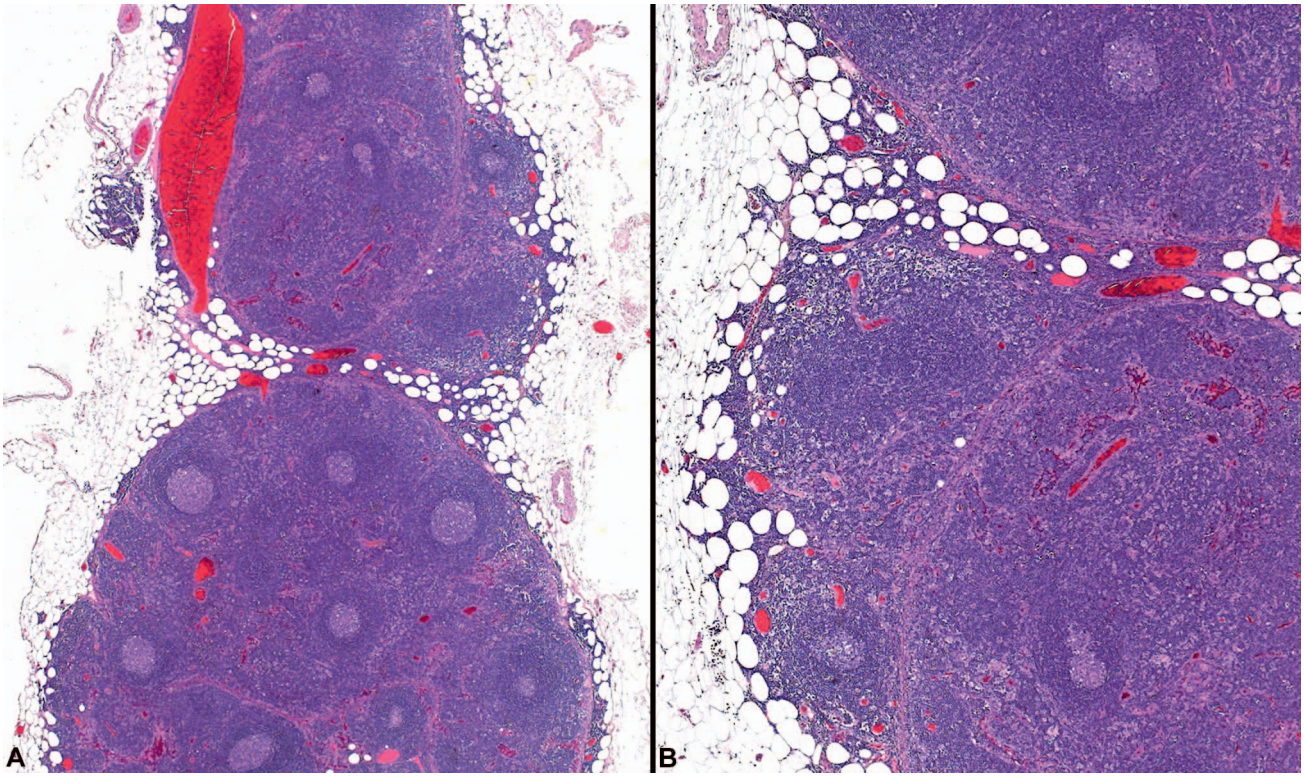



**Figure 5.** *A, Low-power image of a neck lymph node with an indistinct rim of lymphoid tissue peripheral to the capsule. B, Same lymph node at higher power, showing curvilinear fibrous capsule and reactive lymphoid tissue merging with adipose tissue. Tumor in the latter area, external to the capsule, is best considered extranodal (hematoxylin-eosin, original magnifications ×20 [A] and ×40 [B]).*

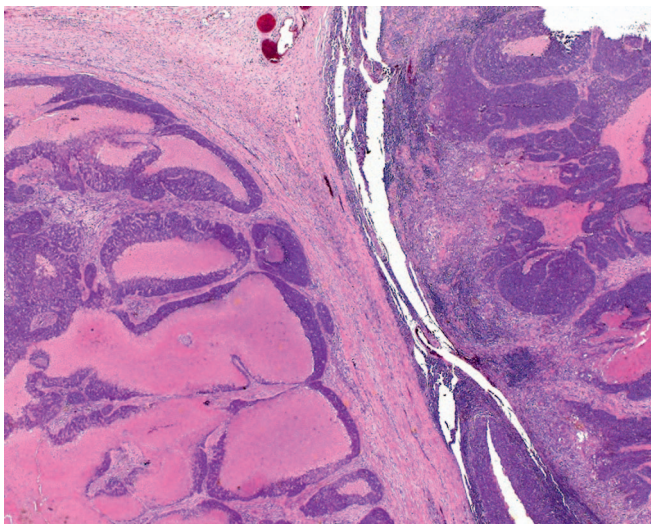


**Figure 6.** *This low-power image is of 2 grossly fused lymph nodes, both replaced and expanded by tumor and with thickened fibrous capsules, but without identifiable extranodal extension (hematoxylin-eosin, original magnification ×20).*

benign lymphoid tissue is identified nearby. Tumor within lymphatics near an involved lymph node should not be considered ENE. However, tumor extending beyond a clearly identifiable fibrous capsule is extranodal, even if there is a surrounding lymphoid response. A stromal desmoplastic reaction is not required.[3]

2. Grossly matted lymph nodes. Grossly adherent lymph nodes may represent true macroscopic ENE or several closely aggregated lymph nodes with thickened capsules, but without microscopic evidence of ENE (Figure 6). Additional levels and sections are recommended to exclude ENE. The presence of matted nodes, their site, and an estimate of the number involved should be included in the gross description. The greatest dimension for pN category should be that of the entire matted deposit. At least one study has shown that radiographically matted lymph nodes are a risk factor for distant metastases and decreased survival in oropharyngeal cancer.[22]
3. Lymphatic spread to lymph nodes versus direct extension from the primary tumor. Some tumors may extend directly into lymph nodes without intervening normal tissue. This is not uncommon in parotid tumors, as there are multiple lymph nodes within the parotid parenchyma itself, but it also occurs with large oral and oropharyngeal primaries. Direct extension into lymph nodes is staged in the same manner as discontinuous metastases.[3] Determination of ENE is subjective, but one method is to base determination of ENE on any component of the capsule that is discontinuous with the primary tumor. A free-text comment is recommended for clarity.
4. The lymph node capsule is often markedly thickened and altered by large metastases with obliteration of the subcapsular sinus. Extranodal extension is measured as the greatest extent of tumor spread perpendicular to the external aspect of the node capsule (Figure 7, A and B). The exact site of the latter can be subjective. It may be estimated by examination of the remaining intact capsule and contour of the node. If the greatest extent of ENE is provided (noncore), the measurement can be rounded to

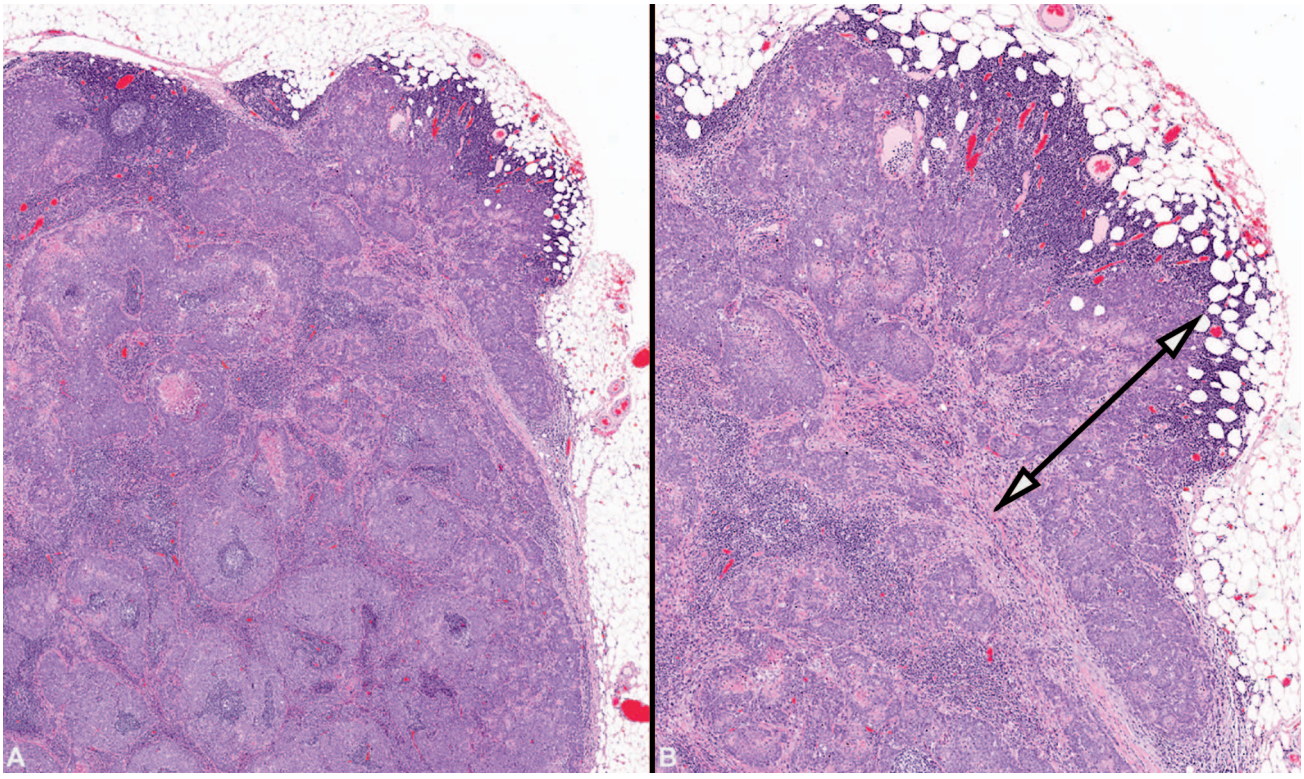



**Figure 7.** *A, Low-power image of a lymph node containing metastatic squamous cell carcinoma, with extranodal extension into perinodal adipose tissue. B, The extent of extranodal extension should be measured from the external aspect of the capsule, or estimated site thereof, to the furthest point of tumor extension into the surrounding tissue (arrow) (hematoxylin-eosin, original magnifications ×20 [A] and ×40 [B]).*

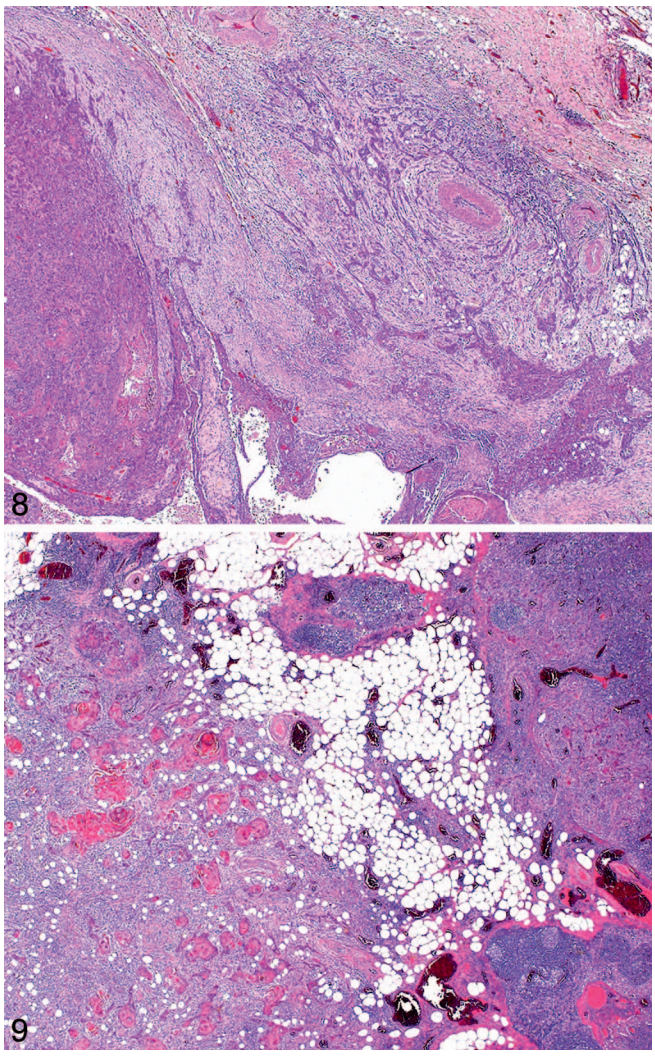



**Figure 8.** *Macroscopic (major) extranodal extension, with tumor encircling extranodal blood vessels at right. In this circumstance, determining the distance from the thickened and distorted lymph node capsule is challenging and subjective (hematoxylin-eosin, original magnification ×100).*

**Figure 9.** *Widespread (macroscopic) extranodal extension from a neck lymph node. Measurement of extranodal extension is subjective as the original capsule is not readily identifiable (hematoxylin-eosin, original magnification ×100).*

the nearest millimeter. More precise measurements are probably not warranted because of the inherent subjectivity required (Figures 8 and 9) and lack of known clinical relevance.

**Regional Lymph Node Categorization.**—The lymph node categorization (Table 3) conforms with the 8th edition of the AJCC and UICC cancer staging manuals,[3,4] recognizing that there are major changes affecting the staging of head and neck cancers from the previous edition. These changes include, among others, (1) restructuring oropharyngeal carcinoma by separating p16-positive from p16-negative carcinoma; (2) inclusion of ENE in the pN categorization for p16-negative oropharyngeal, hypopharyngeal, oral cavity, larynx, skin, major salivary gland, nasal cavity, paranasal sinus, and unknown primary cancers; (3) introduction of a separate category for occult primary tumors of the head and neck, with p16 and EBV tumor testing recommended in patients whose diagnosis remains unknown primary squamous or undifferentiated carcinoma after clinical and radiographic evaluation; and (4) introduction of a separate chapter for cutaneous SCC and other carcinomas (with the exception of Merkel cell carcinoma). Assignment of a pN category is applicable for patients who are treated surgically with a cervical lymph node dissection, rather than single lymph node excisional biopsy, in which case the cN category is used.[3] Nasopharyngeal carcinoma commonly presents with bulky nodal neck disease, and a lymph node biopsy may precede biopsy of the primary site. Nasopharyngeal carcinoma is not a surgically treated disease,[23] and therefore pathologists are rarely called upon to provide a pN category for nasopharyngeal carcinoma. A single positive lymph node biopsy would contribute to the cN categorization.

### Noncore (Recommended) Elements

**Operative Procedure.**—Accurate designation of the operative procedure requires appropriate information from the head and neck surgeon, ideally with specimen orientation. A single operation may encompass more than one of the designated procedures, and the terminology may vary by institution. Some experts have proposed eliminating the operative procedure terminology in favor of a more simplistic designation that includes just the lymph node levels received and a listing of nonlymphatic structures that accompany them.[24] In some cases, it will not be possible to be certain of the operative procedure, and thus this element was considered noncore.

The best-known classification of lymph node groups in the neck is the so-called Robbins classification, originally proposed by the American Academy of Otolaryngology–Head and Neck Surgery[25] and modified over time by that academy and the American Head and Neck Society. The lymph node basins of the neck are divided into levels I to VII, as illustrated in Figure 1. This classification includes only lymph nodes commonly removed during neck dissection procedures, and therefore it does not include all the head and neck node groups. Additional node groups include parotid, buccofacial, retroauricular, and occipital nodes (Figure 2).[26] Precise anatomical boundaries of the head and neck node levels are provided in the new AJCC manual[3] and in the data set notes.

Level VII in the American Head and Neck Society classification refers to pretracheal, paratracheal, and esophageal groove lymph nodes, extending from the level of suprasternal notch cephalad and up to the innominate artery caudad. These are considered superior mediastinal lymph nodes and are essentially an extension of the paratracheal nodes below the suprasternal notch. These nodes are most commonly involved by metastatic thyroid or esophageal cancer and rarely by head and neck mucosal cancers. They are uncommonly submitted with primary head and neck cancer resections.

The subdivisions of several node levels (I, II, and V), indicated in Figure 1, are based on specific anatomical landmarks that are typically not provided to pathologists. The presence of the submandibular gland in level IB may assist in orientation. The subdivisions have clinical significance because they tend to be involved preferentially by tumors of specific primary sites. For instance, level IIB is more commonly involved by primary tumors of the oropharynx or

**Table 3. Union for International Cancer Control (UICC) pTNM 8th Edition[a]**

| Category | Description |
|---|---|
| pNX | Regional lymph nodes cannot be assessed |
| pN0 | No regional lymph node metastasis |
| Lip, oral cavity, p16-negative oropharynx, hypopharynx, larynx, nasal cavity and paranasal sinuses, major salivary glands, cutaneous SCC | |
| pN1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without ENE |
| pN2 | |
| pN2a | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension with ENE, or more than 3 cm but not more than 6 cm in greatest dimension without ENE |
| pN2b | Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension, without ENE |
| pN2c | Metastasis in bilateral lymph nodes, none more than 6 cm in greatest dimension, without ENE |
| pN3 | |
| pN3a | Metastasis in a lymph node more than 6 cm in greatest dimension without ENE |
| pN3b | Metastasis in a lymph node more than 3 cm in greatest dimension with ENE, or multiple ipsilateral or any contralateral or bilateral node(s) with ENE |
| HPV-mediated (p16+) oropharyngeal carcinoma | |
| pN1 | Metastasis in 1–4 lymph node(s) |
| pN2 | Metastasis in 5 or more lymph nodes |
| Nasopharyngeal carcinoma | |
| pN1 | Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage |
| pN2 | Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage |
| pN3 | Metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage |
| Mucosal melanoma | |
| pN1 | Regional lymph node metastasis present |

Abbreviations: ENE, extranodal extension; HPV, human papillomavirus; SCC, squamous cell carcinoma.

[a] Reproduced with permission from Union for International Cancer Control (UICC) from Brierley JD, Gospodarowicz MK, Wittekind C, eds.[4] *UICC TNM Classification of Malignant Tumours*. 8th ed. 2017. Publisher Wiley-Blackwell.

nasopharynx than by primaries of the oral cavity, hypopharynx, or larynx.[27] It is significant to note that newer guidelines for the delineation of neck node levels have been developed and are in use by radiation oncologists.[28]

The most widely used classification of neck dissection procedures was based on the original system[25] proposed by the Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology–Head and Neck Surgery in 1991. This was revised[29] in 2002 and updated[9] in 2008. The classification includes 4 basic procedures: *radical* neck dissection, *modified radical* neck dissection, *extended* neck dissection, and *selective* neck dissection. The term *comprehensive* neck dissection refers to any neck dissection in which all nodes in levels I to V are removed, and therefore it includes radical, modified radical, and extended neck dissections, as explained below.[30]

A radical neck dissection involves removal of levels I to V, as well as the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein. A modified radical neck dissection spares at least one of the above nonlymphatic structures. An extended neck dissection involves removal of additional lymph nodes or nonlymphatic structures beyond those removed as part of a radical neck dissection.

A selective neck dissection is a more limited procedure, in which one or more of the level I to V lymph node groups are spared, typically for malignancies of specific locations and with no or limited clinical evidence of lymph node involvement (N0 or N1).[8,31] *Supraomohyoid* neck dissection refers to removal of levels I to III, and is commonly performed for tumors of the oral cavity. *Lateral* neck dissection refers to removal of levels II to IV, performed for tumors of the larynx, oropharynx and hypopharynx. *Posterolateral* neck dissection refers to removal of levels II to V, frequently performed for skin malignancies of the posterior scalp or upper, posterolateral neck.

*Central* or *anterior compartment* neck dissection removes level VI (pretracheal, paratracheal, precricoid/Delphian, and perithyroidal nodes) and is most commonly performed during surgery for thyroid carcinoma. Level VI lymph nodes are uncommonly received as neck dissections for head and neck skin or mucosal malignancies, but these nodes may be involved by primary cancers of the larynx or hypopharynx. Superior mediastinal nodes (level VII) may also be removed in central neck dissections, particularly for thyroid cancer.

A conspicuous member of the "other" category is the parotid lymph node basin, which is usually received as part of a parotidectomy specimen for primary salivary gland tumors or for metastatic skin cancers of the face and scalp (Figure 2).

**Primary Tumor Site.**—Primary tumor site, if known, should be reported for cases in which the primary tumor resection was not received with the neck dissection. Examples of this situation might include salvage surgery for a persistent neck mass following radiation or concurrent chemoradiation, a delayed neck dissection following resection of a high-risk primary tumor, or surgery for a neck recurrence.

**Margin Status.**—Although neck dissections are not typically margin surgeries, tumors with ENE must be excised with a clear margin. Margin positivity increases the risk of local recurrence and is an indication for additional radiotherapy to that site.[32,33] The site of margin positivity can be used by the radiation oncologist to direct treatment to the area of greatest risk.

**Ancillary Studies.**—Ancillary testing for head and neck cancers most commonly refers to testing for high-risk HPV status in tumors of the oropharynx (typically using the surrogate marker of p16 immunohistochemistry or in situ hybridization) and EBV status in tumors of the nasopharynx (typically using in situ hybridization for EBV-encoded RNA). If ancillary testing was performed, it is recommended to include the type of testing, the result, and interpretive guidelines, if applicable.[34]

Oropharyngeal carcinoma is frequently HPV associated, with these tumors having improved survival versus HPV-negative cases.[35] Testing for p16 status in oropharyngeal SCC is a requirement of the 8th edition of the AJCC and UICC TNM staging systems, and separate staging categories

have been devised for p16-negative and p16-positive tumors.[3,4]

Overexpression of p16 by immunohistochemical analysis is a reliable surrogate for high-risk HPV–associated SCCs of the oropharynx (including types 16 and 18 and others). Overexpression of p16 is defined as moderate to strong, nuclear and cytoplasmic expression (2–3+ intensity) in 70% of tumor cells or more.[9] p16 expression is not applicable as a surrogate for HPV in other head and neck subsites (ie, oral cavity, sinonasal, hypopharynx skin, etc) as HPV is much less frequent and p16 expression is nonspecific.[9]

Strong p16 expression in non–HPV-associated SCC of nonoropharyngeal sites does occur with unclear significance. Thus, although HPV-specific testing would be ideal in the assessment of neck nodes in patients with unknown primary SCC, the lack of testing availability and cost make this impractical for many institutions. The p16 status should be reported in all oropharyngeal primary SCCs (testing either the primary site or from a metastatic focus). Additionally, metastatic SCC to cervical upper or midjugular chain neck lymph nodes (levels II and III) with an unknown primary site should also be tested for p16 overexpression by immunohistochemistry. For nonkeratinizing SCC, a positive p16 result is interpreted as HPV-positive metastatic SCC and should prompt a search for an oropharyngeal primary. For keratinizing SCC, a positive result should prompt HPV-specific testing, such as by RNA in situ hybridization.[9] In situ hybridization for EBV-encoded RNA is recommended for p16-negative, nonkeratinizing, or undifferentiated carcinomas, or if there is clinical suspicion of a nasopharyngeal primary.

**Greatest Extent of Extranodal Extension.**—Extranodal extension is an important predictor of regional recurrence and distant metastasis, and may be an indication for adjuvant combined chemotherapy and radiation, particularly in non–HPV-mediated SCC. The risk of both regional recurrence and distant metastasis is higher with macroscopic versus microscopic ENE.[36] One large study of oral cavity carcinomas determined that adverse prognosis was significant only with ENE more than 1.7 mm beyond the capsule of the node.[37] The latter is similar to the microscopic and macroscopic ENE cutoffs mentioned above. Measurement of the extent of ENE is subjective, especially when there is extensive ENE from a markedly distorted node. As there are no data to support more specific measurements of ENE, it is considered a noncore element.

**Nonlymphatic Structures Involved.**—Nonlymphatic structures including nerves, skeletal muscle, blood vessels, and salivary tissue (such as submandibular gland or tail of parotid, the latter often found in level II) are commonly found in neck dissection specimens and may be helpful landmarks to confirm ENE. The presence of perineural invasion may predict a higher risk of regional recurrence, and venous invasion may confer a greater risk of distant metastases; however, the literature on the topic to support inclusion as a core item is currently insufficient.

## DISCUSSION

### Extent of Staining Required for p16 Positivity in Oropharyngeal SCC

The extent and intensity of p16 staining required to consider the test positive and a surrogate for high-risk HPV varies among studies and institutions. There was debate about the optimal interpretation of a positive result. The cutoff given in the 8th edition of the AJCC *Cancer Staging Manual*[3] is nuclear expression with 2+/3+ positivity (+/− cytoplasmic staining) and 75% distribution or higher. The recent College of American Pathologists guideline for HPV testing head and neck carcinomas states "at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity."[10] The panel felt that as pathologists were making a semiquantitative judgement, there would be little discrepancy between a 70% and 75% cutoff, but the more conservative and commonly used College of American Pathologists interpretation was included.

### Node Level Classification

Most neck dissection specimens are limited to nodes from levels I through V. They come with varying degrees of labeling and orientation, which reduces the precision with which pathologists can divide the nodes into levels. It is important to recognize that very precise anatomical delineation of neck node levels, to include nodes beyond the American Head and Neck Society classification, are used by radiation oncologists to deliver therapy. Readers are referred to the articles by Gregoire et al[27,28] in which levels I through X are delineated. Practically, nodes submitted for pathologic examination from outside the American Head and Neck Society levels are typically named by site and not number.

### Submission of Specimens

Correct submission of neck dissection specimens is required to obtain the most accurate and clinically useful information. Although there is no defined minimum number of lymph nodes required to use the term *neck dissection*, a selective neck dissection should normally contain 10 or more nodes and a comprehensive neck dissection should contain 15 or more nodes.[12] Reference texts are available with grossing guidelines for neck dissection specimens.[38] However, a few points are emphasized here:

1. Inking of neck dissection specimens. Most neck dissections without lymph node involvement or with limited involvement (in which nodes are freely mobile and not matted or grossly involving nonlymphatic structures) do not need to be inked. However, as margin assessment is suggested (noncore item), specimens with large tumor deposits and/or those in which ENE is considered likely should be inked (at least surrounding the mass itself). If evaluation is for metastatic melanoma, an ink color other than black may make interpretation easier.
2. Grossly negative lymph nodes should be submitted in toto. Nodes 5 mm or more should be bisected or multisected to give tissue sections of 2 to 3 mm thickness. Grossly involved lymph node and soft tissue metastases need not be submitted in toto, but 1 section per centimeter in greatest dimension is a reasonable approach. Sections should focus on potential areas of ENE, involvement of nonlymphatic structures, and the margin.
3. When submitting lymph nodes that cannot be removed from the surrounding tissue (eg, parotidectomy specimens), care should be taken not to double count nodes that may be bisected and present in 2 cassettes. Careful gross description, with an estimate of the number of nodes in each block, is recommended. In general, the gross estimate of the number of lymph nodes is most

accurate, except when tissue originally designated as a node is clearly another tissue type (eg, parathyroid gland or skeletal muscle).

## CONCLUSIONS

Lymph node resections and neck dissections are common specimens that are usually received with primary head and neck cancer resections. Proper orientation and submission, using standardized node level terminology, is required for optimal results. Standardized reporting data sets, such as the one presented here, provide the best opportunity to accurately convey crucial information to treating physicians. Pathologists should adhere to the most recent AJCC and UICC cancer staging manuals for pTNM categorization.

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