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Data Set for the Reporting of Carcinomas of the Nasopharynx and Oropharynx

Explanations and Recommendations of the Guidelines From the International Collaboration on Cancer Reporting

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• The International Collaboration on Cancer Reporting was established to internationally unify and standardize the pathologic reporting of cancers based on collected evidence, as well as to allow systematic data collection across institutions and countries to guide cancer care in the future. An expert panel was convened to identify the minimum data set of elements that should be included in cancer reporting from tumors of the nasopharynx and oropharynx. Specifically, there has been a significant change in practice as a result of identifying oncogenic viruses, including human papillomavirus and Epstein-Barr virus, because they preferentially affect the oropharynx and nasopharynx, respectively. For these anatomic sites, when viral association is taken into account, usually reported elements of in situ versus invasive tumor, depth of invasion, and degree of differentiation are no longer applicable. Thus, guidance about human papillomavirus testing in oropharyngeal carcinomas and Epstein-Barr virus testing in nasopharyngeal carcinomas is highlighted. Further, the clinical and the pathologic differences in staging as proposed by the 8th edition of the Union for International Cancer Control are incorporated into the discussion, pointing out several areas of continued study and further elaboration. A summary of the International Collaboration on Cancer Reporting guidelines for oropharyngeal and nasopharyngeal carcinomas is presented, along with discussion of the salient evidence and practical issues.

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Staging of malignancies is critical for prognosis and treatment planning. The head and neck region is one of the most diverse subsites in the body for cancer types and anatomic complexity. In addition, the presence of the oncogenic viruses, human papillomavirus (HPV) and Epstein-Barr virus (EBV), in tumors arising in the oropharynx and nasopharynx increases complexity because of their major prognostic significance. Much has changed since the 7th edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) staging manuals were developed in 2009, particularly for the head and neck region. The biggest changes in the 8th edition involve the pharynx, which is now separated, for staging purposes, into its 3 anatomic components: oropharynx, hypopharynx, and nasopharynx.

The AJCC and UICC staging systems, which have been designed to have almost complete overlap, are based in the United States and Europe, respectively. In order to provide a single, internationally agreed-upon, globally standardized, evidence-based reporting system that goes beyond the various regional groups and across socioeconomic settings, the International Collaboration on Cancer Reporting (ICCR) data sets were developed. The ICCR was established in 2011 through a collaboration between the College of American Pathologists, the Canadian Association of Pathologists–Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer, the Royal

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Table 1. Key Elements for Pathologic Reporting for Oropharyngeal and Nasopharyngeal Carcinomas		
p16 (HPV)–Positive Oropharyngeal SCC	**p16 (HPV)–Negative Oropharyngeal SCC**	**Nasopharyngeal Carcinoma**
Tumor size	Tumor size	Extension of tumor to local structures
T0 category for metastatic p16 (HPV)–positive squamous cell carcinomas of unknown primary	Depth of invasion	T0 category for metastatic EBV-positive carcinoma of unknown primary
HPV status (p16 immunostaining as acceptable surrogate)	Tumor grade/differentiation	EBV status (EBER in situ hybridization)

Abbreviations: EBER, EBV-encoded RNA; EBV, Epstein-Barr virus; HPV, human papillomavirus; SCC, squamous cell carcinoma.

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 Faculty of Pathology at the Royal College of Physicians of Ireland, as sustaining members. Further, members of the data set authoring committee were selected from the additional sponsoring organizations: 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. The ICCR data sets aim to ensure that the data sets produced for different tumor types have a consistent reporting style and content using standardized terminology and elements, and contain all the parameters needed to guide management and prognostication for individual cancers. Because they are intended to be truly global, compromises are sometimes necessary in order to simplify staging or place caveats in the staging systems that could aid physicians in developing countries to provide a useful stage for their patients. This review focuses on the data set for nasopharyngeal and oropharyngeal carcinomas, providing a discussion of the key elements that were included, other elements that were not, and explanations of why and how certain elements are critical to the staging of these malignancies, particularly as it relates to HPV- and EBV-positive tumors.[23]

KEY ELEMENTS

By far, the most significant change in head and neck cancer in the past several decades has been the rise of HPV-positive oropharyngeal squamous cell carcinoma (SCC). These tumors have been increasing at ~5% per year, particularly in higher socioeconomic countries among white men.[1,2] The HPV status of such tumors strongly dictates tumor biology. After the steady accumulation of evidence showing that this was a distinctive cancer type, it became clear that a unique staging system for these patients was needed (Table 1).[3] This distinct system is a key element of AJCC staging of the oropharynx.[4,5]

HPV status is somewhat complicated to determine, given the myriad tests available and the confusing data regarding the presence of DNA versus transcriptionally active high-risk HPV. The latter is critical for prognostication and staging. Overexpression of p16 is a proven prognostic marker in oropharyngeal SCC, because it is a surrogate for transcriptionally active high-risk HPV in tumors.[6–8] For this reason, and because it is widely available across practice settings and is easy to perform and interpret, the AJCC,[5] UICC, College of American Pathologists, and World Health Organization[9] recognize this as a suitable standalone test. The status of p16 must be ascertained for these patients, and the T (and N) staging differs based on the results.[5] It is important to emphasize that the correlation between p16 expression and HPV status and prognosis does not apply to nonoropharyngeal sites. For p16-positive oropharyngeal SCC patients, there is no T in situ, and T4 tumors are no longer divided into T4a or T4b. A separate *Nodal Excisions and Neck Dissection Specimens for Head and Neck Tumours Histopathology Reporting Guide* has been developed by the ICCR, and it should be completed when lymph nodes are submitted.[24] However, it should be noted that the p16 (HPV) status alters how the regional nodes are clinically and pathologically staged. Because oropharyngeal SCC can be treated reasonably with either primary chemoradiation or with surgery (with or without adjuvant therapy), pathologic staging of oropharyngeal SCC is common across US and European practices.[4,5] The ICCR *Carcinomas of the Nasopharynx and Oropharynx Histopathology Reporting Guide* and other reporting systems retain the same T-stage classification for p16 (HPV)–positive oropharyngeal SCCs for both clinical and pathologic staging.

It is recognized that some resource-limited geographic regions may not have access to p16 immunohistochemistry. The morphology of HPV-positive oropharyngeal SCC is usually distinctive and has been termed nonkeratinizing (Figure 1).[10,11] The tumors typically consist of cells with high nuclear to cytoplasmic ratios, forming large nests with pushing borders and little to no stromal reaction. Tumor cells have hyperchromatic, round to oval nuclei with inconspicuous nucleoli and exhibit brisk mitotic activity and apoptosis. Maturing squamous differentiation is usually limited or only partial. Approximately 90% to 95% of all HPV-positive oropharyngeal SCCs have this morphology.[12] Although this distinctive morphologic pattern is characteristic of HPV status, it is not as specific as p16 as a surrogate marker.[10] In resource-limited countries, however, using nonkeratinizing morphology and clinical characteristics, such as younger age of onset, bulky regional nodal disease with small primary tumor, cystification of nodal metastases, origin in the palatine tonsil or base of tongue rather than other oropharyngeal subsites, and/or nonsmoking status, one can reasonably infer positive HPV status without any laboratory testing.[13] These parameters, however, could not formally be included in the ICCR staging system, which follows the World Health Organization guidance, even though it is considered a minimum data set. When p16 testing is not available, for classification purposes, the tumors are regarded as HPV negative, although local discretion may be used where morphology alone is available if there is likely to be a change in prognosis and treatment.

Another key element of the ICCR pharynx data set is the EBV status for nasopharyngeal carcinomas.[14] It is not used for staging, but the panel agreed that the literature shows the prognostic importance of positive EBV status.[15] More importantly, it can and does direct certain treatment

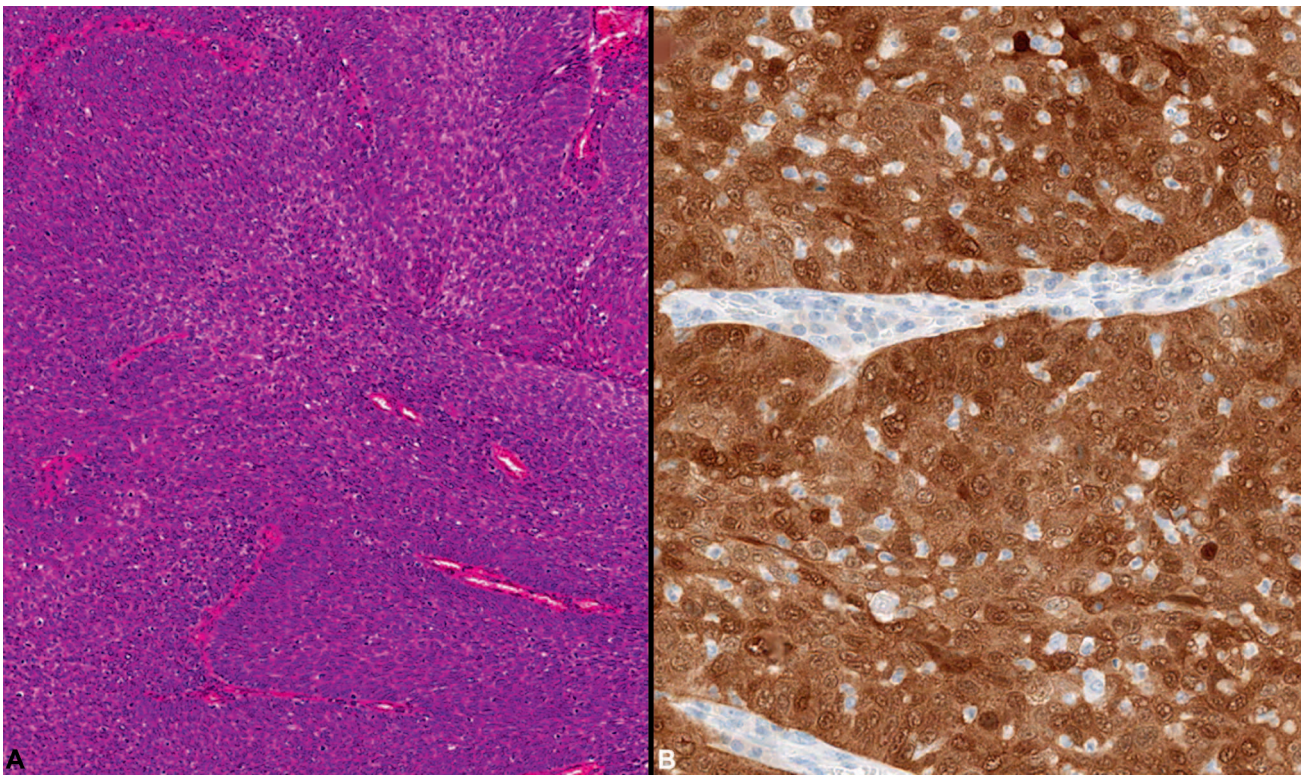

Figure 1. *A, Typical nonkeratinizing squamous cell carcinoma of the oropharynx. B, Strong and diffuse, nuclear and cytoplasmic p16-positive immunohistochemical staining in a human papillomavirus–associated oropharyngeal squamous cell carcinoma (hematoxylin-eosin, original magnification ×200 [A]; p16 immunohistochemistry, original magnification ×400 [B]).*

decisions. Most EBV-positive nasopharyngeal carcinomas are nonkeratinizing, usually with a lymphoepithelial or undifferentiated pattern (Figure 2). Their cells have indistinct cell borders and vesicular, round nuclei with prominent nucleoli.[15,16] Morphology strongly correlates with EBV status, but, particularly in endemic regions such as southeast Asia, even keratinizing type (conventional) SCC of the nasopharynx can be EBV positive.[15] The gold standard test for EBV-encoded RNA is in situ hybridization on tumor tissue.[15] Although EBV plasma DNA can be measured at diagnosis for prognosis and monitoring for residual, persistent, or recurrent disease,[17] this testing is not considered sensitive enough to be used as a primary test in establishing tumor EBV status.

Nasopharyngeal carcinomas have a modified T staging from the 7th-edition TNM, with involvement of pterygoid muscles and prevertebral muscles now being downstaged to T2.[5] This is based on AJCC recommendations from an analysis with current treatment regimens that showed that patients with tumors invading these areas have a more favorable prognosis than previously reported. The terminology for T4 criteria was modified to "soft tissue involvement" rather than "masticator space" and "infratemporal fossa."[4]

ELEMENTS NOT INCLUDED

It is notable that the list of features not recommended is comparable to the list of new recommended features (Table 2). Many of the classically reported pathologic features of SCC "fall away" in HPV- and EBV-positive carcinomas. The primary examples are tumor grade/differentiation, in situ versus invasive carcinoma, and depth of invasion. Most of this derives from the fact that p16 (HPV)–positive oropharyngeal SCCs arise from the reticulated tonsillar crypt epithelium, which has intraepithelial capillaries but does not have a complete basement membrane. It is believed that this predisposes tumors arising here to early metastases and is supported by the finding of primary tumor specimens that look entirely "in situ" along the crypt epithelium but which already have nodal metastases. In addition, this reticulated crypt epithelium is made up of distinctive basaloid/nonkeratinizing squamous cells. It is believed that most p16 (HPV)–positive SCCs show differentiation into these immature-appearing cells (nonkeratinizing SCC), thus explaining why the tumor cells have high nuclear to

Table 2. Summary of Core and Noncore Data Set Reporting Elements for Nasopharyngeal and Oropharyngeal Carcinomas

Core Elements (Required)	Noncore Elements (Recommended)
Neoadjuvant therapy	Depth of invasion
Operative procedure	Coexistent pathology
Specimens submitted	
Tumor site	
Tumor dimensions	
Histologic tumor type	
Histologic tumor grade	
Perineural invasion	
Lymphovascular invasion	
Margin status	
Ancillary studies	
Pathologic staging	

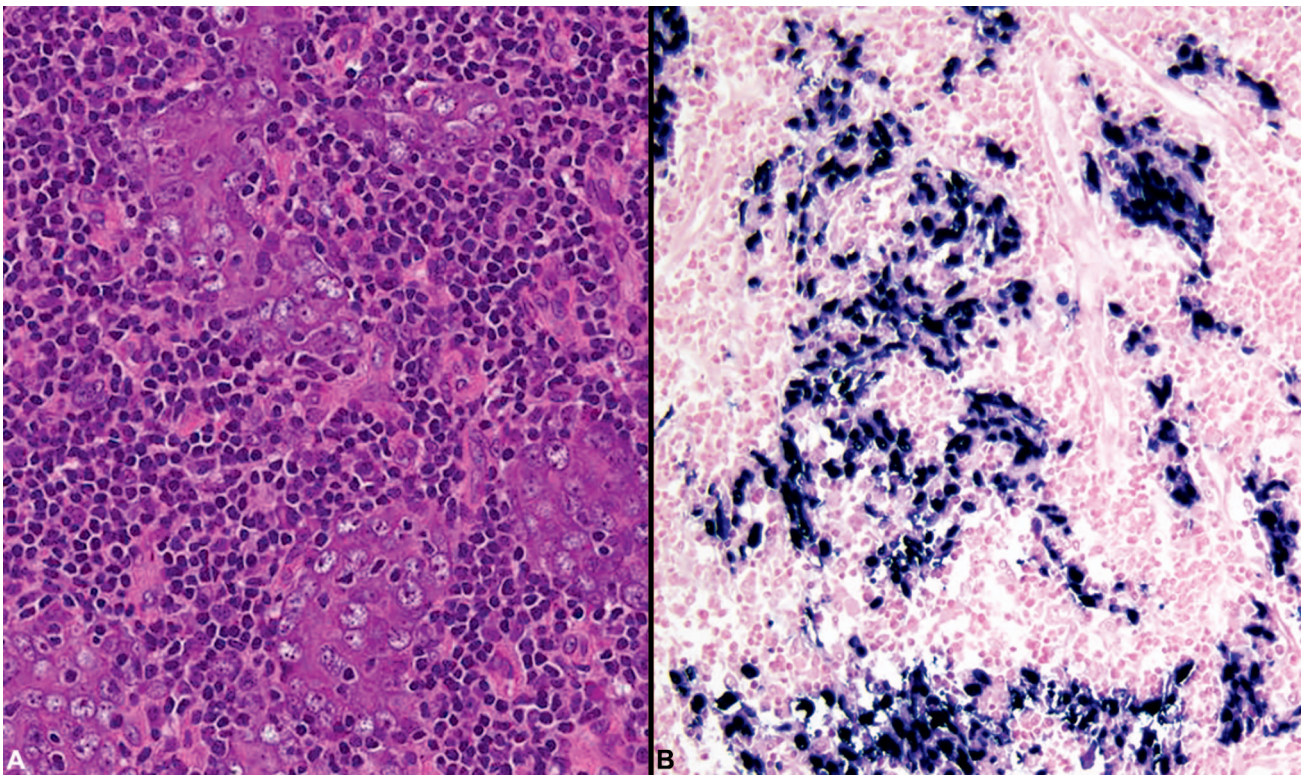

Figure 2. *A, Typical nonkeratinizing (undifferentiated) nasopharyngeal carcinoma with a syncytial appearance. B, Strongly and diffusely positive nuclear staining by Epstein-Barr virus–encoded RNA in situ hybridization (hematoxylin and eosin, original magnification ×400 [A]; original magnification ×350 [B]).*

cytoplasmic ratios, round to ovoid to spindled nuclei, and brisk proliferative activity.[10,18] These tumors are poorly differentiated by traditional grading yet have the best prognosis. Thus, providing grading/differentiation either provides no additional useful information or is potentially confusing to the clinician. As such, grading is not recommended,[8,9] although HPV-negative SCCs are still graded. Similarly, for EBV-positive nasopharyngeal carcinoma, the tumors are histologically subtyped but have never been graded according to a maturing differentiation schema.

Depth of invasion, although critical for oral cavity SCC staging, is not relevant for HPV-positive oropharyngeal SCC, nor is it relevant for nasopharyngeal carcinomas. Oropharyngeal SCCs usually arise in the tonsillar crypts, which are already below the surface, so one cannot find where tumors actually "originate" in order to assess a depth. Thus, no additional information beyond simple tumor size would be obtained if a measurement of depth was attempted. Similarly, the nasopharynx is a thin structure over muscle, bone, and cartilage, where depth of invasion of tumors has never been a prognostic criterion of importance.

SEPARATE CANCER STAGING DATA SETS

TNM staging for cancer has been in place since the 1940s and 1950s, and now the 2 major systems in practice, the AJCC and UICC systems, are largely aligned with each other. Although very helpful, these systems were developed in the United States and Europe and may not always be applicable to best practice worldwide. For the pharynx, the ICCR data set is aligned with the guidelines proposed in the 8th editions of the UICC and AJCC staging manuals.[4,5] Recent studies suggest that staging systems may need to change in the future. Recent validation cohorts of HPV-positive oropharyngeal SCC show a lack of a clear separation of outcomes of patients with stage II cancer from those for patients with stage I and stage III cancers.[19–21] Further, the distribution of patients in the 3 stages is not well balanced, with almost 60% of patients assigned to stage I.[19–22] These findings will be addressed in future editions. For now, however, the systems are a major improvement, and there are not enough data to diverge from them in the current ICCR data set. The improvements in prognostication are in large part due to our increased understanding of these virus-related tumors.

SUMMARY

The staging for nasopharyngeal and oropharyngeal carcinomas is unique among head and neck tumors because of the specialized anatomy and the frequent viral (EBV and HPV) associations of these cancers. The ICCR data set provides staging guidelines that balance the current, cutting-edge knowledge in these fields with providing a workable and practical framework that can be used across all practice settings. Key features are the need for p16 immunohistochemistry as a surrogate marker test for HPV in all new oropharyngeal SCCs,[5,8] the unique staging used for p16-positive (HPV-positive) SCC relative to p16-negative (HPV-negative) SCC,[4,5] and the revised classification for nasopharyngeal carcinomas, which also need to be tested for EBV status in each patient with a new diagnosis. Some traditional features, such as grade/differentiation status, depth of invasion, and in situ versus invasive tumor status, are not to be reported for the virus-positive carcinomas. Widespread use and feedback from users of

these new ICCR head and neck data sets will help to validate the data elements and, when necessary, help to refine and improve them further.

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