Data Set for the Reporting of Mucosal Melanomas of the Head and Neck

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

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• Standardized pathologic reporting for cancers allows for improved communication for patient care and prognostic determination. If used universally, synoptic reporting enhances comparing data globally for scientific leverage. The International Collaboration on Cancer Reporting is a nonprofit organization whose mission is to develop evidence-based, universally available surgical pathology reporting data sets. Multiple different sites within the head and neck may be affected by mucosal melanoma, whose behavior and patient outcome are not equivalent to carcinomas of the corresponding sites. Factors such as Breslow thickness and Clark depth of invasion applied to cutaneous melanomas do not yield any prognostic significance in mucosal sites, and thus are not meaningful. Likewise, margin assessment is unique in head and neck sites. Further, the genetic profile of mucosal melanomas is different from that of most cutaneous tumors. Thus, within the head and neck region, mucosal melanoma is a distinct entity for which a dedicated data set was developed for implementation. The elements that comprise the core (required) and noncore (recommended) elements are discussed.

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Standardized pathologic reporting for cancers is a process that allows for improved communication for patient care and prognostic determination. When the same standardization is expanded beyond a single institution or organization, the impact of structured reporting with common terminology and categorization leads to health data that can be compared globally.[1] The International Collaboration on Cancer Reporting (ICCR) was established in 2011 with the mission to develop standardized, internationally recognized, evidence-based cancer reporting protocols. This nonprofit organization is recognized and receives support from the College of American Pathologists, the Canadian Association of Pathologists-Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer, 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, as well as a growing list of affiliated organizations, of which 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 are specific sponsors of the head and neck data set.

The suite of head and neck data sets (Table 1) was developed by 9 expert authoring panels under the direction of the series champion. Using the standards and framework established by the ICCR, the members of the Dataset Authoring Committee for head and neck mucosal melanoma reviewed worldwide references on the topic, compiling the data for consideration into core and noncore elements, discussed in several teleconferences over a number of months. Core elements represent required, key elements for melanoma reporting, factors used in management and/or staging. Evidentiary support for core elements was at level III-2 or above, but when such data were lacking, expert opinion was provided with reasons documented. Noncore elements represent data set elements that may be used in practice but may not have a direct impact on patient prognosis, are emerging findings requiring further validation, and/or involve testing that is not widely available. Staging from the 8th edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) was included as applicable. The completed data set sustained open public comment, from

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Table 1. International Collaboration on Cancer Reporting Histopathology Reporting Guides Developed for Head and Neck Structured Data Sets
Nasal Cavity and Paranasal Sinuses Carcinomas
Hypopharynx, Larynx, and Tracheal Carcinomas
Oral Cavity Carcinomas
Nasopharyngeal and Oropharyngeal Carcinomas
Metastatic Carcinoma in Lymph Node Resections and Neck Dissections of the Head and Neck
Major Salivary Gland Carcinomas
Malignant Odontogenic Tumors
Ear and Temporal Bone Tumors
Mucosal Melanoma of the Head and Neck

which additional clarification was provided before ICCR publication. This manuscript highlights selected data elements and provides additional explanation and discussion on their inclusion in this surgical pathology ICCR data set for reporting head and neck mucosal melanomas.[2,3,43]

CLINICAL BACKGROUND

Mucosal melanoma is recognized as a distinct histopathologic entity that represents less than 1% of all melanomas. However, about 60% of mucosal melanomas arise in the upper aerodigestive tract, with sinonasal tract accounting for 66%, oral cavity about 25%, and the remaining in the nasopharynx, oropharynx, and larynx; mucosal melanoma represents about 4% of all sinonasal malignancies.[4] Within the sinonasal tract, the nasal cavity was affected twice as often as paranasal sinuses in a series of more than 20 years of data collected through the Surveillance Epidemiology and End Results database in the United States.[5] Presenting sinonasal tract symptoms are most commonly epistaxis or obstructive symptoms,[6,7] whereas oral cavity presentation is as a painless pigmented lesion of the palate or alveolus, although maybe as a raised mucosal colored and/or ulcerated lesion.[8–10] The median age for head and neck mucosal melanoma is 67 to 73 years without a sex predilection (0.8:1.3 male to female ratio).[4,5]

Factors contributing to the development of mucosal melanoma remain largely undefined, although an association with melanosis is possible.[11] Biologically, mucosal melanomas are distinct from cutaneous melanomas. Many histopathologic findings used in cutaneous melanoma for risk stratification are not applicable to mucosal melanoma, and thus are not included in the head and neck mucosal melanoma data set, as will be highlighted below.

The overall outcomes in head and neck mucosal melanoma remain poor regardless of disease extent at presentation.[8] This aggressive disease course is reflected in the TNM classification discussed in the staging section. The overall survival is less than 30% at 5 years.[12]

SCOPE

This data set is to be used for biopsy and resection specimens of primary mucosal melanomas of the upper aerodigestive system; subsites include nasal cavity and paranasal sinuses, nasopharynx, oropharynx, larynx, hypopharynx, and oral cavity. Importantly, tumors arising from cutaneous sites extending to involve the mucosa should not be included in this data set. Similarly, melanoma metastases to the aerodigestive tract are excluded. Challenging cases involving the lips and nares should be clinically correlated in an attempt to distinguish cutaneous melanomas from mucosally derived tumors, recognizing that cutaneous melanomas are significantly more common than mucosal melanomas. When neck lymph node dissections are included, a separate, linked data set for *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours* would be completed.[44]

Table 2. Summary of Core and Noncore Head and Neck Mucosal Melanoma Data Set Elements	
Core Elements (Required)	**Noncore Elements (Recommended)**
Operative procedure	Tumor focality
Specimens submitted	Margin status
Tumor site	Histologic subtypes
Tumor dimensions	Coexistent pathology
Histologic tumor type	Ancillary studies
Pathologic staging	

DATA SET ELEMENTS

The head and neck mucosal melanoma data set is composed of 11 total data elements. Table 2 shows the distribution of these data elements into the 6 core (required) and 5 noncore (recommended) elements. Core elements signify information that should be included in all reports and is used for clinical care. Additional elements that relate to the disease but are not universally available and/or for which the significance is not clearly established are designated as noncore. Although noncore elements are optional, including this information is encouraged for future validation. All elements have predefined, standardized terminology and options listed, with free text available when necessary. These standardized data elements and response terminology have been unified across all ICCR data sets, enhancing communication with clinicians and the comparison of patients' data between institutions.

CORE ELEMENTS

Operative Procedure

Because this data set/template is used for both biopsy and resection specimens, the extent of the surgery is documented in the operative procedure element. Biopsy should be further clarified as an excisional or incisional biopsy, whereas resection specimens are also specifically stated (eg, maxillectomy). If a neck dissection is performed or lymph nodes are removed as part of the surgery, this is recorded in the operative procedure section. However, reporting of the lymph node findings is recorded on a separate, linked data set: *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours*.[44] "Other" is also included if a different procedure has been performed or if another anatomic site was surgically evaluated (eg, distant metastatic site) not captured in the primary resection.

Specimens Submitted

Specimens submitted to pathology associated with the primary tumor resection are recorded. Where this includes multiple separate specimens, each should be listed for completeness. Multiple specimens are a particularly common occurrence for resection of sinonasal primary mucosal melanomas. All specimens related to the primary tumor site should be listed, including both specimens with and without tumor. Submitted lymph node specimens would be

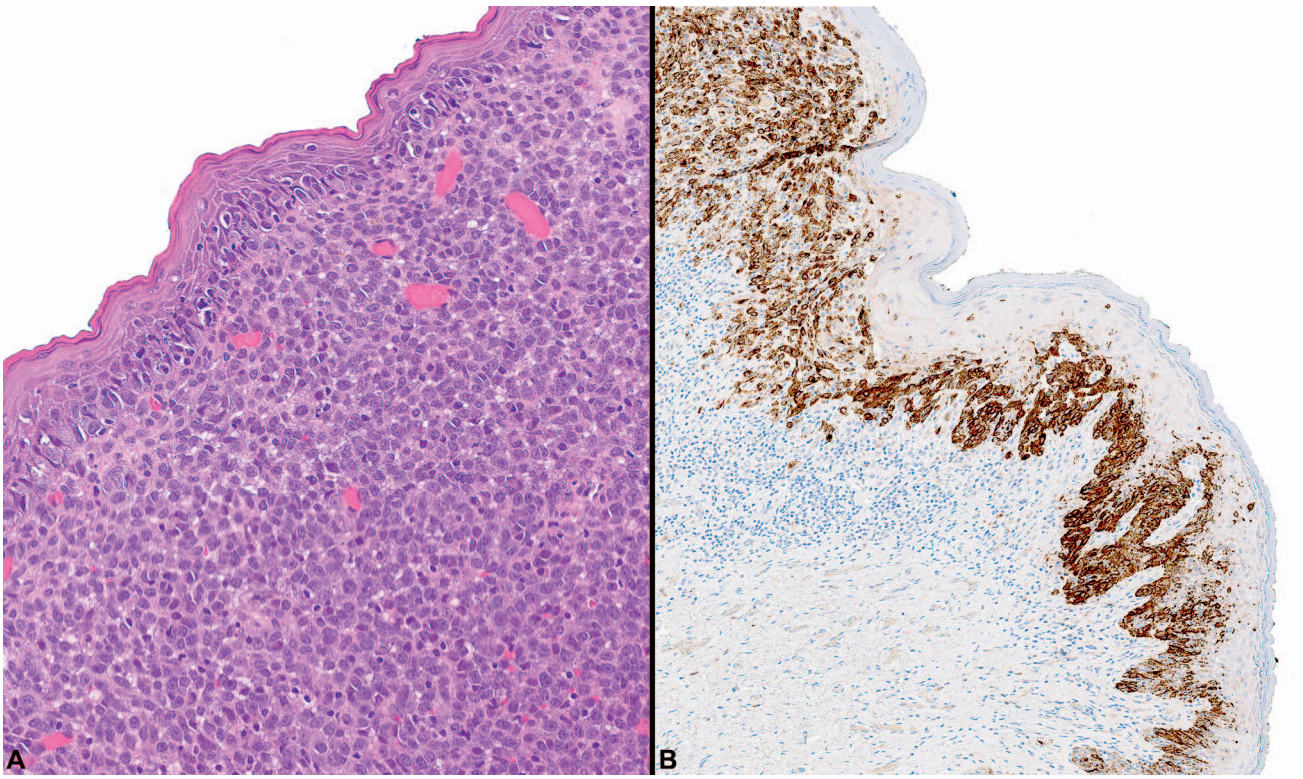

Figure 1. *A, An oral mucosal melanoma shows a junctional/in situ component, although it is difficult to delineate on hematoxylin-eosin. B, An immunohistochemical study for HMB-45 highlights both an in situ and invasive component in other areas of the tumor (original magnifications ×400 [A] and ×200 [B]).*

separately reported on the corresponding neck dissection data set.

Tumor Site

Mucosal melanomas of the upper aerodigestive tract may arise at the following primary tumor sites: sinonasal, oral cavity, larynx, nasopharynx, and other. Multiple sites should be selected if a tumor extends between locations (eg, sinonasal primary with extension into nasopharynx). To further characterize the primary tumor site, laterality of the tumor (right, left, midline, or not specified) aids in the description of the primary tumor location and extent. Additionally, detailing the anatomic subsites involved is encouraged in an open text box by site (eg, septal or turbinate for sinonasal tract; gingiva or hard palate for oral cavity).

There is a predilection of mucosal melanoma to specific sites within the head and neck mucosae. Within the sinonasal cavity, 62% to 66% of primary mucosal melanomas involved only the nasal cavity, septum, and/or turbinate,[6,7] whereas upper gingiva and/or hard palate accounted for most oral cavity tumors.[13,14] The distinction of mucosal lip versus cutaneous lip is highlighted because cutaneous primaries would require a different data set and staging elements.

Tumor Dimensions

Tumor size remains a core data element of pathologic reporting for all tumor types. The recommendation in mucosal melanoma is to report the largest single, linear tumor dimension in the specimen with the largest tumor volume (core element), irrespective of overlying mucosal orientation (additional dimensions of the largest tumor are noncore). This guideline applies even if the tumor is removed in multiple components, as may occur in the sinonasal region. Although the limitation of using only a single specimen is noteworthy, the additive value of combining multiple specimens potentially overestimates the size and has no added value. Mucosal melanomas, particularly of the sinonasal region, are often polypoid and thereby may be removed initially to improve visualization of the remaining nasal cavity for further surgical resection. Unlike cutaneous melanomas where Breslow thickness or Clark level is used, these are not easily determined in mucosal sites.[15] Several studies have correlated larger tumor size (>3 cm) with a worse prognosis.[6,13,16,17] However, tumor size is not included in pT staging categorization.

Histologic Tumor Type

Mucosal melanoma diagnosis is established through histologic review and additional ancillary studies, as needed. Only about 60% of mucosal melanomas will have pigment to aid in the histologic diagnosis.[6,7,9] Therefore, mucosal melanomas should be considered in the differential diagnosis of undifferentiated or small round blue cell tumors, particularly in the sinonasal region. Importantly, the distinction to clearly delineate mucosal melanoma from melanoma of cutaneous origin is critical for staging, prognosis, and tumor biology. Therefore, correlation with clinical history, including the presence of skin involvement and/or prior cutaneous resections, may aid in favoring a primary cutaneous origin over a mucosal origin. Similarly, distinction from metastatic melanomas to a mucosal site is important. In the oral cavity, criteria to establish a primary mucosal melanoma of the oral cavity were first proposed by Greene et al,[18] which required both histologic evaluation for

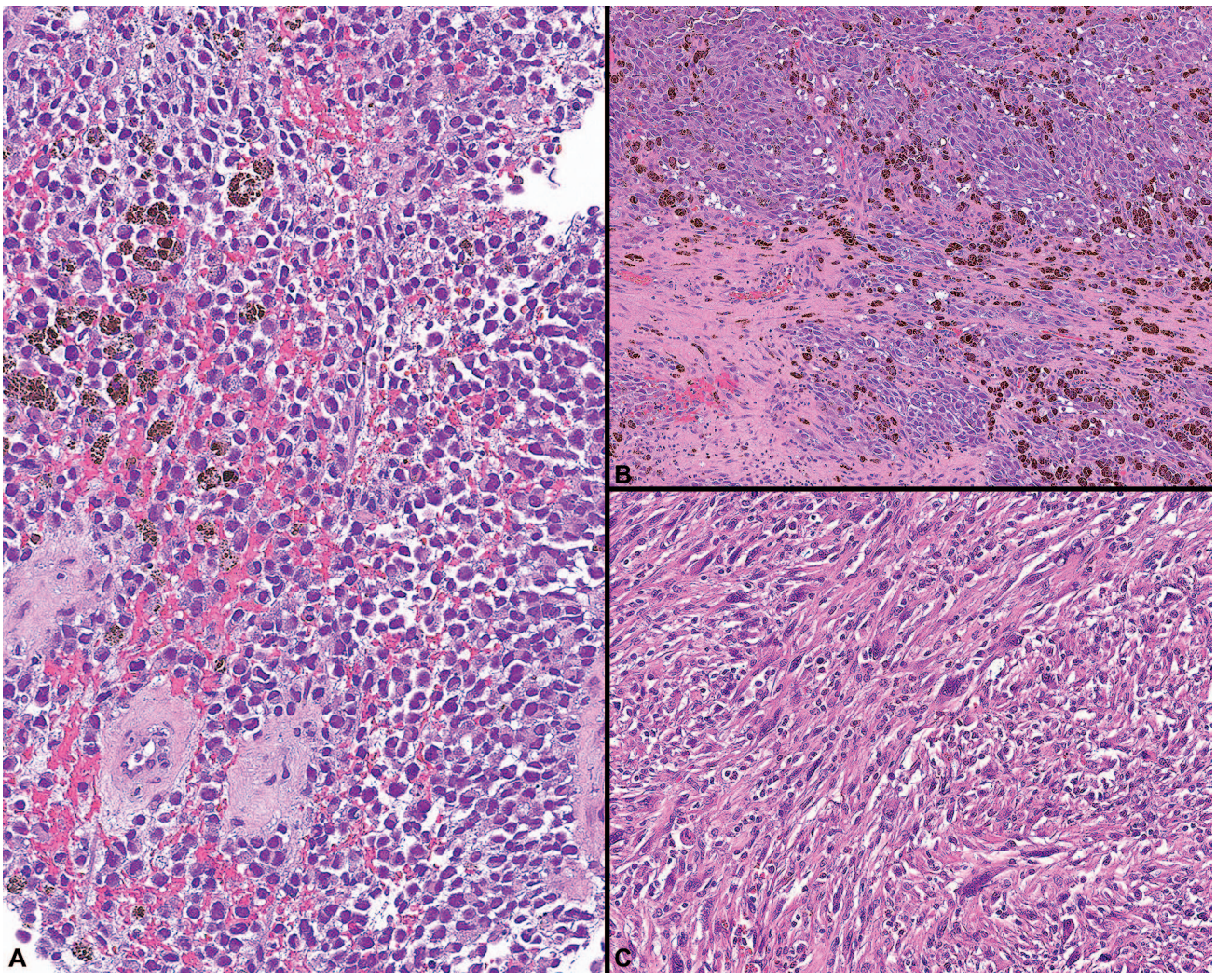

Figure 2. *Mucosal melanomas show a range of cytologic features and are commonly amelanotic or with low levels of pigment identified. A, Small plasmacytoid epithelioid cells. B, Spindled cells with prominent pigmented macrophages in the background. C, Pleomorphic amelanotic spindled cells (hematoxylin-eosin, original magnifications ×400 [A and C] and ×200 [B]).*

an intraepithelial component and clinical exclusion of another primary site (Figure 1). However, in sinonasal tract melanomas, an in situ/junctional component is infrequently encountered (<25%).[6]

NONCORE ELEMENTS

Although there may be limited data to inform clinical management or prognosis at this time, noncore elements still provide meaningful data for further study and evaluation.

Tumor Focality

Mucosal melanomas may be multifocal, and this has been shown in rare case reports of patients with underlying melanosis.[9,11] The added challenge in the sinonasal tract region is determining whether multiple specimens are contiguous or indeed multifocal. If true multifocal tumors exist, the recommendation is to complete separate data sets for each tumor. The guidance for indeterminate cases of possible contiguous versus multifocal tumors is to use 1 template.

Histologic Subtypes

Head and neck mucosal melanomas show great diversity in both cellular morphology and growth patterns. Patterns include peritheliomatous/perivascular, solid, fascicular, storiform, papillary, and alveolar, whereas cytomorphologic features include epithelioid, spindled, plasmacytoid, rhabdoid, meningothelial, pleomorphic, and undifferentiated (Figure 2). The main significance of this marked histologic variability is to consider mucosal melanoma in the broad differential diagnosis of head and neck neoplasms, even though these patterns or cytologic features do not seem to correlate with patient prognosis.[6,16] Importantly, these observations allow for meaningful comparison with potential metastases, which are often amelanotic.[9]

The specific subtypes of melanoma included in this data set are balloon cell melanoma,[19] mixed epithelioid and spindle cell melanoma, epithelioid, spindled, amelanotic, undifferentiated, and other, specify. The specific subtype of melanoma is associated with prognosis in uveal melanoma, but not yet correlated to outcome for mucosal sites.[20–22] Amelanotic melanomas show little to no appreciable

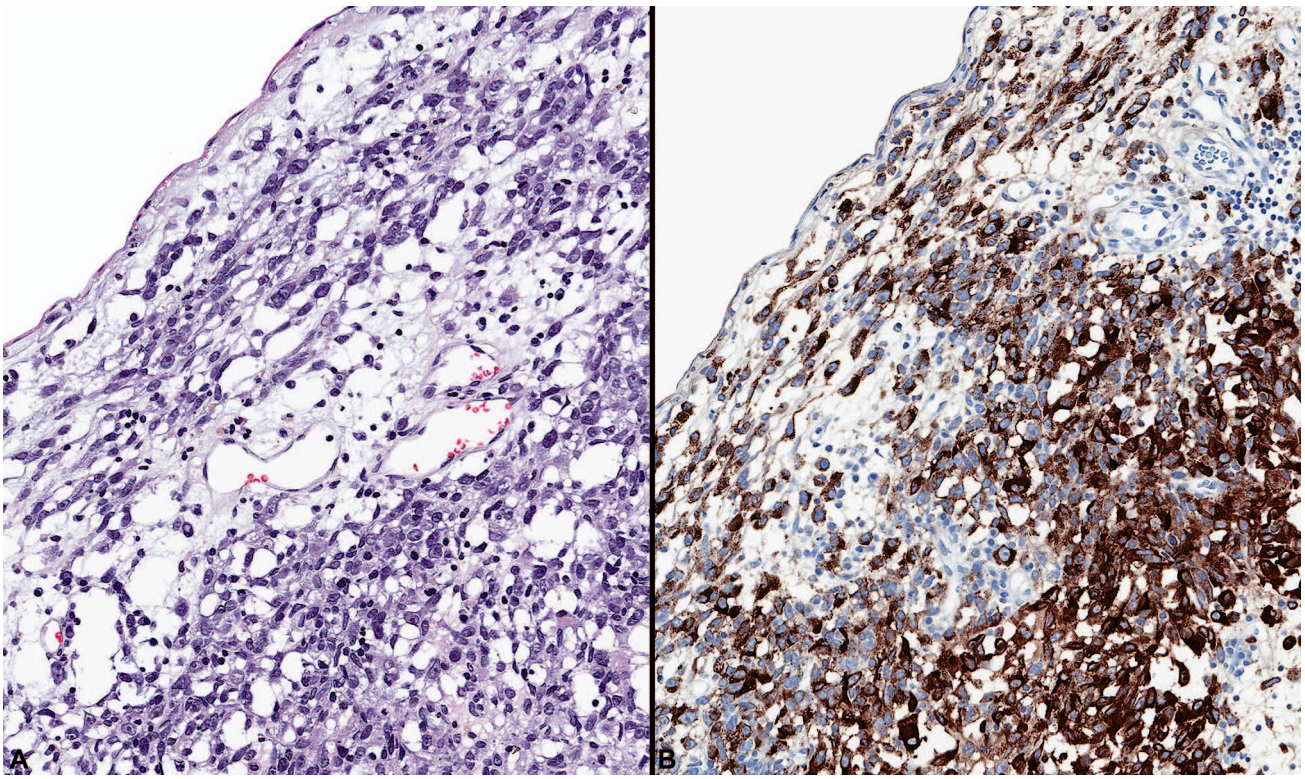

Figure 3. *A, An amelanotic small round blue cell tumor is present beneath denuded surface epithelium. B, Immunohistochemical analysis is required to determine cell lineage. Panmelanoma marker highlights the tumor cells, allowing for the diagnosis of mucosal melanoma (hematoxylin-eosin, original magnification ×400 [A]; Melan-A and tyrosinase immunohistochemistry, original magnification ×400 [B]).*

pigmentation, a finding that makes the diagnosis more challenging, especially in the sinonasal tract (Figures 1 through 3).[6,7,9] Desmoplastic melanoma is characterized by amelanotic invasive spindled cells in a fibrotic stroma and seems to show a high propensity for perineural invasion (up to 83%).[23]

Margin Status

Both pathologists and clinicians use margin status to determine the adequacy of surgery, and in many cancers this correlates with rates of local recurrence and overall outcome. Additionally, in many tumor types, margin status may trigger adjuvant therapy or augmented therapy when surgery was viewed as incomplete. However, in mucosal sites, resections are often performed by obtaining multiple separate specimens, making margin assessment unreliable. Some studies have shown the prognostic value of margin status[7,24]; however, the very high propensity for vascular invasion may contribute to earlier distant metastasis, which contributes to overall mortality in this patient population, irrespective of margin status. Further, even when tumors have limited submucosal disease, outcomes are still poor, and thus margin status is not an independent prognostic factor.[8,25] If margins are evaluable, invasive versus in situ tumor should be reported. Submucosal tumor is considered invasive, whereas atypical melanocytic cells either in increased numbers and/or confluent along the epithelial basement membrane junction or with upward (Pagetoid) mucosal spread would constitute an in situ component.[8,26,27]

Coexistent Pathology

Factors that contribute to mucosal melanoma remain largely unknown; however, recording coexisting pathology may over time provide insight into this disease. Findings such as melanosis may occur with mucosal melanoma, as noted in case reports, and this warrants further study.[11,28–30]

Ancillary Studies

Supplemental studies, most often in the form of immunohistochemistry, are used to confirm the diagnosis of mucosal melanoma, especially if amelanotic, rather than for their prognostic value. The neoplastic cells usually react with S100 protein (about 90% of tumors), SOX10, HMB-45 (about 75% of tumors), Melan-A, and tyrosinase (Figure 3, B), among others, although positivity rates vary[6,22,31] and other tumors may also show immunoreactivity for these markers.

Increasingly, ancillary studies (immunohistochemistry or molecular assessment) may be performed for possible targeted therapies. Importantly, the genetic profile of mucosal melanomas is unique and does not align with that of cutaneous melanomas.[32–34] Mucosal melanomas have shown 18% and 12% rates of *KIT* (CD117) and *NRAS* mutations, respectively, with infrequent *BRAF* alterations.[32–36]

PATHOLOGIC STAGING

The AJCC/UICC 8th edition staging systems, unchanged from the 7th edition, are based on the pathologic extent of disease (TNM), supported by several studies.[16,37,38] However, site-specific staging of sinonasal melanomas also

Table 3. Pathologic Staging Categories for Head and Neck Mucosal Melanoma[a,b]
pT Primary Tumor
pTx Primary tumor cannot be assessed
T3 Tumors limited to the epithelium and/or submucosa (mucosal disease) *[regardless of thickness or greatest dimension]*[c]
T4a Moderately advanced disease Tumor invades deep soft tissue, cartilage, bone, or overlying skin
T4b Very advanced disease Tumor invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

[a] Reproduced with permission from Union for International Cancer Control (UICC) in Brierley et al[3]: Brierley JD, Gospodarowicz MK, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours*. 8th ed. Chichester, UK: Wiley-Blackwell; 2017.
[b] The results of lymph node/neck dissection are derived from a separate data set.
[c] Comment in *[italics]* supplied by panel for emphasis and clarification.

stratified patients into prognostic groups.[39] This data set is applied to all upper aerodigestive tract sites, even though sinonasal tract disease forms the basis for the staging,[2,6] and previous staging proposals have been rendered obsolete.[40–42]

T Categorization

The UICC 8th edition staging is provided in Table 3, also reflecting the current AJCC criteria. Reflecting the poor prognosis and high recurrence rates, the pT categorization is truncated, with no T1 or T2 designations. Specifically, all head and neck mucosal melanomas are classified as either T3 for localized disease limited to the epithelium and/or submucosa, or T4 for advanced tumors. T4 is further divided into T4a for tumors extending into the deep soft tissue, cartilage, bone, or overlying skin, and T4b for extension of tumors into the central nervous system (brain, dura), skull base, lower cranial nerves (IX, X, XI, XII), prevertebral or masticator space, carotid artery, or mediastinal structures.

Because size is not the discriminating factor, a polypoid nasal mass may qualify as a pT3 tumor when the evaluation of the stalk shows limited submucosal involvement (Figure 4), whereas documentation of bone invasion places the tumor in pT4 (Figure 5).

N Categorization

Lymph node metastases are found in 15% of oral cavity and up to one-third of sinonasal mucosal melanomas at initial presentation. Despite an association with worse outcomes in multiple studies, the number or size of lymph nodes does not further stratify patients.[6,8,37,42] Therefore, regional lymph node disease (N category) is defined as either absent (N0) or present (N1). If lymph nodes are present as part of a mucosal melanoma case, reporting of the lymph nodes is captured via the separate but linked *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours* data set.[44] Although the 8th edition of AJCC/UICC has incorporated extranodal extension into many

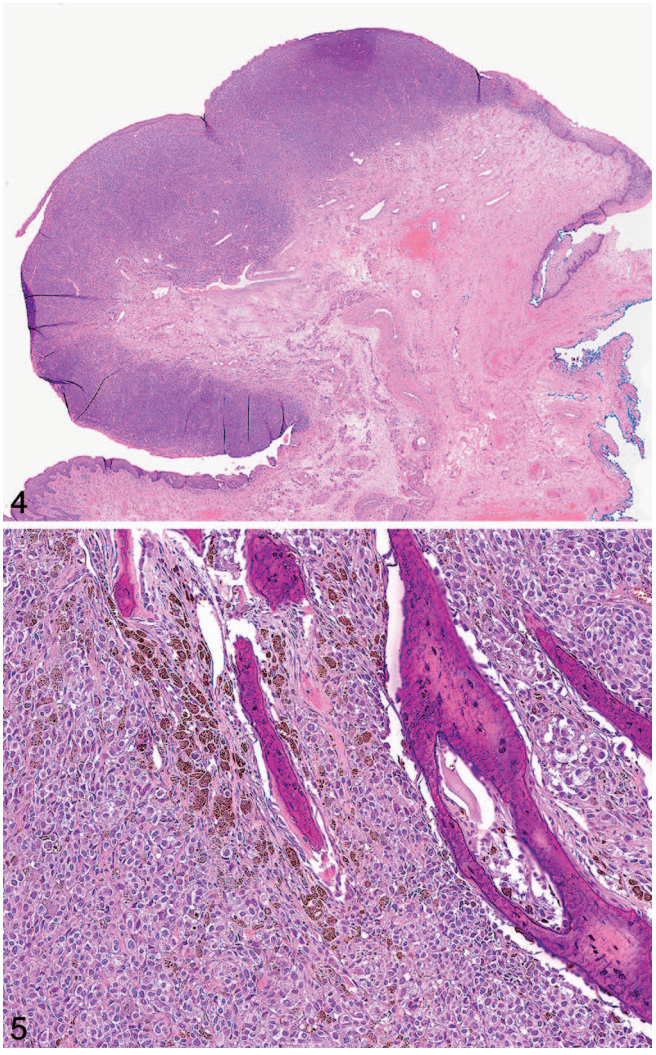

Figure 4. *A polypoid sinonasal mucosal melanoma. The tumor remains superficial within the submucosa, meeting the criteria for a pT3 Union for International Cancer Control tumor. Size of the tumor and a measured depth/thickness are not components of mucosal melanoma T categorization (hematoxylin-eosin, original magnification ×10).*

Figure 5. *A mucosal melanoma of the sinonasal region with bone invasion allowing for characterization of pT4 by the Union for International Cancer Control staging (hematoxylin-eosin, original magnification ×400).*

head and neck tumor types for N determination, the significance of this finding in mucosal melanoma is unknown and does not modify the N category in this disease.

M Categorization

Although distant metastasis (M1) has been identified as the most important factor determining patient outcome, with 100% mortality (death with disease) by 5 years,[6] the 8th edition of AJCC/UICC does *not* designate prognostic stage groupings, even though there is support for such a determination.[2]

CONCLUSIONS

The goal of the ICCR is to allow for the standardization of data elements reported across each tumor site. In rare

diseases, such as head and neck mucosal melanoma, the literature is mixed on what may be prognostic elements in this disease. To date, there are no well-developed prospectively validated prognostic factors in head and neck mucosal melanoma. Thus, the move toward global implementation of standardized data sets would allow for the collection of data that may achieve better identification of frequency, distribution, and prognostic factors, while documenting geographic, genetic, and other underlying global differences. These data could then permit improved communication within and between institutions and allow for harmonized therapeutic approaches and improved outcome for these rare neoplasms when presented and compared based on uniform terminology and standardized criteria.

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