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Mucosal Melanomas of the Head and Neck Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

- ◯ Information not provided
- ◯ Information provided (select all that apply)
  - ☐ Previous therapy
    - ☐ Surgery
    - ☐ Chemotherapy
    - ☐ Radiotherapy
    - ☐ Targeted therapy, *specify if available*
    - ☐ Immunotherapy, *specify if available*
  - ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ◯ Biopsy (excisional, incisional, core needle), *specify*
- ☐ Resection (e.g., maxillectomy, hemiglossectomy, partial laryngectomy), *specify*
- ☐ Neck (lymph node) dissection,[a] *specify*
- ☐ Other, *specify*

[a] *If a neck (lymph node) dissection is submitted, then a separate dataset is used to record the information.*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Anatomic site, *specify (may be multiple separate sites)*
- ☐ Neck (lymph node) dissection,[a] *specify*

TUMOUR SITE (Note 4)

- ◯ Not specified
- ◯ Sinonasal, *specify subsite(s)*
- ◯ Oral cavity, *specify subsite(s)*
- ◯ Larynx, *specify subsite(s)*
- ◯ Pharynx, *specify subsite(s)*
- ◯ Other, *specify site/subsite(s)*

TUMOUR LATERALITY (select all that apply)

- ◯ Not specified
- ☐ Left
- ☐ Right
- ☐ Midline

TUMOUR DIMENSIONS (Note 5)

Maximum tumour dimension (largest tumour) (pathology and/or imaging determination)

mm

Additional dimensions (largest tumour)

mm x mm

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BLOCK IDENTIFICATION KEY (Note 6)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 7)
(Value list based on the World Health Organization Classification of Head and Neck Tumours (2024))

- ◯ Mucosal melanoma
- ◯ Melanoma (uncertain origin), *specify*

Histologic subtypes (select all that apply)

- ☐ Lentiginous
- ☐ Nodular
- ☐ Desmoplastic
- ☐ Other, *specify*

NECROSIS (Note 8)

- ◯ Not identified
- ◯ Present

EXTENT OF INVASION (Note 9)

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Clinical observation and/or imaging
  - ☐ Histologic
    - ◯ Limited to mucosa and/or submucosa

Moderately advanced

- ☐ Deep soft tissues or muscle
- ☐ Cartilage
- ☐ Bone
  - ◯ Superficial cortical bone involvement
  - ◯ Medullary bone involvement
- ☐ Overlying skin

Very advanced invasion

- ☐ Brain
- ☐ Dura
- ☐ Skullbase
- ☐ Any lower cranial nerves (IX, X, XI,XII)
- ☐ Masticator space
- ☐ Carotid artery
- ☐ Prevertebral space
- ☐ Mediastinal structures
- ◯ Cannot be assessed, *specify*

LYMPHOVASCULAR INVASION (Note 10)

- ◯ Not identified
- ◯ Present, *specify if named*

PERINEURAL INVASION (Note 11)

- ◯ Not identified
- ◯ Present, *specify if named*

POST THERAPY CHANGES (Note 12)

- ◯ No response
- ◯ Response

Tumour viability

- ◯ Absent
- ◯ Present

Percentage viable tumour ____ %

MARGIN STATUS (Note 13)

Invasive melanoma

- ◯ Not involved

Distance of invasive melanoma from closest margin ____ mm

Specify closest margin(s), if possible

- ◯ Involved

Specify margin(s), if possible

Melanoma in situ

- ◯ Not involved

Distance of melanoma in situ from closest margin ____ mm

Specify closest margin(s), if possible

- ◯ Involved

Specify margin(s), if possible

COEXISTENT PATHOLOGY (select all that apply) (Note 14)

- ◯ None identified
- ☐ Melanosis
- ☐ Other, *specify*

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ANCILLARY STUDIES (Note 15)

- ◯ Not performed
- ◯ Performed, *record test(s), methodology and results*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[b] (Note 16)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - during or following multimodality therapy

Primary tumour (pT)[c]

- ◯ TX[d] Primary tumour cannot be assessed
- ◯ T3 Tumour limited to the epithelium and/or submucosa (mucosal disease)
- ◯ T4a Moderately advanced disease
  Tumour invades deep soft tissue, cartilage, bone, or overlying skin
- ◯ T4b Very advanced disease
  Tumour 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

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12th July 2024).*

[c] *Note that the results of neck (lymph node) dissection are derived from a separate dataset.*

[d] *TX should be used only if absolutely necessary.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC.

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Scope

The dataset has been developed for the reporting of resection and biopsy specimens of mucosal melanoma arising in the nasal cavity and paranasal sinuses, oral cavity, nasopharynx, oropharynx, larynx and hypopharynx. All other malignancies are dealt with in separate ICCR datasets, specifically cutaneous melanoma is separately reported.

Direct extension of a cutaneous primary into a mucosal site should be excluded and would not be reported in this dataset. Metastatic melanoma to a head and neck mucosal site is also excluded. If there are overlapping sites, clinical centring of the tumour should determine the dataset to be completed. If a primary tumour extends to involve the contralateral side, the tumour is still considered a unifocal tumour, but involving multiple, contiguous sites. It should be noted that for limited biopsies the pathologist may not be able to complete all of the elements in the ICCR dataset.

Neck lymph node dissections and excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.[2]

This dataset is intended for use for primary cancer resections. For resections of recurrent disease, the reporting guide may be used pragmatically although some data elements may be not applicable nor assessable.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Head and Neck Tumours, 5th edition, 2024.[3]

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core)

Documenting if previous therapy has been given for the current neoplastic process is important and considered a core element. The types of previous therapies may include surgery, chemotherapy (conventional agents), radiotherapy (such as external beam radiation), and newer therapies, including targeted therapy often to a molecular alteration and immunotherapy. Previous therapy is included as a prefix in pathologic staging (see **Note 16 – PATHOLOGICAL STAGING**).

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Note 2 – Operative procedure (Core)

Delineating the operative procedure(s) provides the extent of surgery performed and informs what specimens are then received. A biopsy is often the initial procedure for the diagnosis of mucosal melanoma and may be excisional, for a polypoid or small lesion versus incisional, with a portion of the abnormal tissue submitted for diagnosis. Alternatively, record the surgical resection performed for the primary tumour site (e.g., maxillectomy, hemiglossectomy, laryngectomy, etc.), and include any lymph node sampling or dissections.

As not all mucosal melanomas proceed to definitive resection, the ICCR Mucosal melanomas of the head and neck dataset is recommended for use at the time of a first biopsy diagnosis.

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Note 3 – Specimen(s) submitted (Core)

The surgical approach for mucosal melanoma largely depends on the site of the primary tumour. In some locations such as gingiva, a single specimen may be received with/without additional separate margins. This may be a mucosal based resection or a composite resection with underlying tissues including bone. In the sinonasal cavity, while there may be a primary tumour specimen, numerous further specimens are received from contiguous anatomic sites in a three-dimensional approach. The specimens submitted help to delineate

the anatomic extent required for resection and may include bilateral tissues. Lymph node dissections are dealt with in a separate ICCR dataset.[2]

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Note 4 – Tumour site (Core)

Mucosal melanomas of the head and neck show specific sites of predilection, but in general are rare. Approximately 70% of mucosal melanomas arise in the sinonasal tract and 15% occur in the oral cavity with the remainder developing in other mucosal sites of the head and neck.[4]

Sinonasal region: The majority of tumours are identified within the nasal cavity or septum. When the primary arises in the sinuses, the maxillary and ethmoid sinuses were encountered with similar frequency.[4-6]

Oral cavity: Most tumours are found on the palate or gingiva, although any site may be affected.[7-9]

Primary melanoma within the nasopharynx, oropharynx, larynx and hypopharynx are exceedingly uncommon.[10] However, nasopharyngeal primaries have an even worse prognosis than other head and neck sites.[6]

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Note 5 – Tumour dimensions (Non-core)

Unlike melanoma in cutaneous sites, tumour thickness (Breslow) and tumour level (Clark) are not clinically significant as prognostic factors, nor are they easily determined due to anatomic locations and frequent fragmentation. The single largest tumour dimension in any one of the samples submitted may be entered, though is not utilised for staging.[11,12] When reported, do not use aggregate measurements, as trying to combine multiple measurements from different tissue fragments and/or sites does not yield clinically meaningful data.

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Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 7 – Histological tumour type (Core and Non-core)

All mucosal melanoma tumours should be classified based on the most recent edition of the WHO Classification of Head and Neck Tumours, 5th edition, 2024 (Table 1).[3] Making the definitive determination of mucosal melanoma as the tumour type is a core element and should be supported by anatomic site without confounding clinical information. Should the origin as mucosal derived versus cutaneous be indeterminate (i.e., direct extension), melanoma of uncertain origin may alternatively be utilised with a comment supporting such ambiguity. As mucosal melanomas are molecularly distinct from those of cutaneous origin, occasional cases may require further molecular evaluation prior to definitively classifying as being of mucosal origin. The presence of a *BRAF* p.V600E mutation is much more frequent in cutaneous melanomas.

The inclusion of the specific histologic type or pattern of melanoma is primarily for differential diagnostic considerations, while the specific type does not impact patient outcome or management (non-core element).[6] Three subtypes are recognised in the WHO 5th edition, including lentiginous, nodular, and desmoplastic.[3]

Table 1: World Health Organization classification of mucosal melanomas of the head and neck.[3]

Descriptor	ICD-O codes[a]
Mucosal melanoma	**8720/3**
Mucosal lentiginous melanoma	8746/3
Nodular melanoma	**8721/3**
Malignant melanoma, NOS	8720/3
Desmoplastic melanoma	8745/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[13] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour: /2 for carcinoma in situ and grade Ill intraepithelial neoplasia; /3 for malignant tumours, primary site: and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

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Note 8 – Necrosis (Non-core)

Necrosis in biopsy and resection specimens where the patient has not received neoadjuvant treatment should be documented, especially if necrosis is abundant hampering microscopic evaluation of the tumour.

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Note 9 – Extent of invasion (Core)

Pathologic evaluation of mucosal melanomas of the head and neck includes determining the associated tissues and anatomic structures involved which directly relates to staging and prognosis. Those tumours limited to the mucosa and/or submucosa correspond to pT3 classification in Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) the lowest classification for this aggressive tumour.[11,12]

Often invasion into other tissues indicates a moderately advanced tumour (pT4a), including invasion into deep soft tissue or muscle, underlying cartilage, bone or overlying skin.

Similarly, recognition of invasion into surrounding subsites is also recorded as a core element. The following sites indicate a very advanced (pT4b), including brain, dura, skull base, any cranial nerves (IX, X, XI,XII), masticator space, carotid artery, prevertebral space, and/or mediastinal structures.

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Note 10 – Lymphovascular invasion (Non-core)

Identifying the presence of lymphovascular invasion in the primary tumour site, may be reported though is without independent prognosis for mucosal melanomas. Biologically, lymphovascular invasion occurs in approximately 15% of patients presenting with nodal disease at and 12% with distant metastasis. The frequency of regional and distant metastases is higher in oral cavity primaries compared to sinonasal origin.[4]

Cases that are still equivocal after taking additional steps may be reported as 'indeterminate' for lymphovascular invasion, but this designation should be sparingly used and it is useful to provide the reason in a comment in the report.

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Note 11 – Perineural invasion (Non-core)

Perineural invasion is commonly encountered in the rare desmoplastic histologic subtype and may contribute to local recurrence.[14] Include the presence or absence of perineural invasion when performing histologic review (non-core).

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Note 12 – Post therapy changes (Non-core)

In the post neoadjuvant setting only, tumour viability may be recorded as a percentage of viable tumour within the tumour bed. The tumour bed size is estimated based on the area of histologic changes showing fibrosis, inflammation and/or necrosis. Viable tumour can be difficult to distinguish from background macrophages which are more common than tumour necrosis.[15]

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Note 13 – Margin status (Non-core)

In general, tumour margins are reported, but margin status has not been an independent prognostic factor for head and neck mucosal melanomas secondary to systemic recurrences driving the poor prognosis. A 2021 study shows potential early benefit with negative surgical margins,[16] which may prove important as changes in practice, including adjuvant therapies targeting systemic disease may aid in mucosal melanoma

management. Melanoma in situ (if detected) may indicate risk for local recurrence and thus reporting is encouraged but is not a core element.

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Note 14 – Coexistent pathology (Non-core)

Melanosis is considered to be a potential precursor, although with conflicting data based on anatomic site and geographic distribution of the reported patients.[17-19]

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Note 15 – Ancillary studies (Non-core)

The diagnosis of melanoma is supported by the use of melanoma markers, including S100 protein, SOX10, HMB45, Melan A and tyrosinase, among others. CD117 may be aberrantly expressed, but does not correlate to KIT gene mutation status and thus may not be meaningful.[20-22] Further, molecular studies can also be performed in selected cases, either for diagnostic purposes (helping to confirm the diagnosis), or for potential use in targeted therapies based on the results. Molecular findings in mucosal melanoma are different from cutaneous primaries, with *NRAS* mutations (approximately 40%) predominating and alterations in regulators of Ras-MAPK signalling pathway, including in *NF1*, *PTEN*, *PIK3CA, SPRED1*, and others. *BRAF* mutations are rare, identified in only 4% of melanomas of mucosal sites.[9,23-26]

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Note 16 – Pathological staging (Core)

By UICC/AJCC convention,[11,12] the designation 'T' refers to a primary tumour that has not been previously treated. The symbol 'p' refers to the pathologic classification of the stage, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. There is no pathologic M0 category as this designation requires clinical evaluation and imaging. Clinical classification (cTNM) is usually carried out by the evaluating clinician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease, whether or not the primary tumour has been completely removed. If a biopsied tumour is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied even though total removal of the primary cancer was not performed.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the 'm' suffix and 'y' and 'r' prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The ‘m’ suffix indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m)NM.

The ‘y’ prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a ‘y’ prefix. The ycTNM or ypTNM categorises the extent of tumour actually present at the time of that examination. The ‘y’ categorisation is not an estimate of tumour prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The ‘r’ prefix indicates a recurrent tumour when staged after a documented disease-free interval, and is identified by the ‘r’ prefix: rTNM.

The 8th edition of the UICC/AJCC staging of head and neck cancers includes a separate chapter for mucosal melanomas.[11,12] Even small tumours behave aggressively with high rates of recurrence and death.[27] To reflect this aggressive behaviour, primary cancers limited to the mucosa are considered T3 lesions.

Pathologic T3 mucosal melanomas of the head and neck are defined as limited to the mucosa and immediately underlying soft tissue/submucosa. As tumour size and thickness are not considered, polypoid lesions of the nasal cavity often meet these criteria.

Advanced mucosal melanomas are classified as T4a and T4b. The anatomic extent criteria to define moderately advanced (T4a) and very advanced (T4b) disease are given above. Rare examples of in situ mucosal melanomas occur but in situ mucosal melanomas are excluded from staging, as they are extremely rare.[11,12]

For the pN classification of regional lymph nodes, see ICCR Nodal excisions and neck dissection specimens dataset.[2]

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC8,[11,12] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

Pathological staging should not be reported if the submitted specimen is insufficient for definitive staging, especially with biopsy samples (core needle, incisional or excisional). Staging is based on the submitted resection, and even if there is grossly residual disease or there is tumour at the margin, pT staging should only be reported on findings in the resection specimen and/or at operation.[11,12]

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[28]

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