Sponsored by

Carcinomas of the Major Salivary Glands 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, *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
- ☐ Parotid gland
  - ☐ Superficial lobe
  - ☐ Deep lobe
- ☐ Submandibular gland
- ☐ Sublingual gland
- ☐ Neck (lymph node) dissection,[a] *specify*
- ☐ Accompanying specimens, *specify*
- ☐ Other (e.g., partial gland excision), *specify*

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

TUMOUR SITE (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Parotid gland
  - ☐ Superficial lobe
  - ☐ Deep lobe
- ☐ Submandibular gland
- ☐ Sublingual gland
- ☐ Other, *specify*

TUMOUR LATERALITY (Note 3)

- ◯ Not specified
- ◯ Left
- ◯ Right

TUMOUR FOCALITY (Note 4)

- ◯ Unifocal
- ◯ Bilateral
- ◯ Multifocal
  - Specify number of tumours

Version 2.0 Published July 2024 ISBN: 978-1-922324-51-1

TUMOUR DIMENSIONS (Note 5)

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

mm

Additional dimensions (largest tumour)

mm x mm

◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE[b] (select all that apply) (Note 7)

(Value list based on the World Health Organization Classification of Head and Neck Tumours (2024))

- ☐ Mucoepidermoid carcinoma
- ☐ Adenoid cystic carcinoma
  - ◯ Tubular/cribriform pattern predominant
  - ◯ Solid pattern
    - % of solid component %
- ☐ Acinic cell carcinoma
- ☐ Secretory carcinoma
- ☐ Microsecretory adenocarcinoma
- ☐ Polymorphous adenocarcinoma
  - ◯ Classic
  - ◯ Cribriform
- ☐ Hyalinising clear cell carcinoma
- ☐ Basal cell adenocarcinoma
- ☐ Intraductal carcinoma
- ☐ Salivary duct carcinoma, *specify subtype(s)*
- ☐ Myoepithelial carcinoma
- ☐ Epithelial-myoepithelial carcinoma
- ☐ Mucinous adenocarcinoma
- ☐ Sclerosing microcystic adenocarcinoma
- ☐ Carcinoma ex pleomorphic adenoma
  - Carcinoma subtype(s), *specify*
  - ◯ Intracapsular
  - ◯ Minimally invasive ◯ Widely invasive
    - Distance from capsule mm
- ☐ Carcinosarcoma of the salivary glands
- ☐ Sebaceous adenocarcinoma
- ☐ Lymphoepithelial carcinoma
- ☐ Squamous cell carcinoma
- ☐ Sialoblastoma
- ☐ Salivary gland carcinoma NOS
- ☐ Other, *specify*

[b] *Not all listed histological tumour types develop in major salivary glands, but are included for completeness when the list is used for minor salivary gland reporting.*

HISTOLOGICAL TUMOUR GRADE (Note 8)

(Not applicable to all tumours)

- ◯ Not applicable
- ◯ Grade 1, well differentiated, low grade
- ◯ Grade 2, moderately differentiated, intermediate grade
- ◯ Grade 3, poorly differentiated, high grade
- ◯ Undifferentiated
- ◯ High grade transformation

Grading system used, *specify*

◯ Cannot be assessed, *specify*

EXTENT OF INVASION (Note 9)

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Clinical observation and/or imaging
  - ☐ Histologic
    - ☐ Macroscopic extraparenchymal extension
    - ☐ Bone
      - ◯ Superficial cortical involvement
      - ◯ Medullary bone involvement
    - ☐ Skin
    - ☐ Facial nerve
    - ☐ Other, *specify*
    - ◯ Cannot be assessed, *specify*

LYMPHOVASCULAR INVASION (Note 10)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate, *specify reason*

PERINEURAL INVASION (Note 11)

- ◯ Not identified
- ◯ Present
  - Nerve size, if known mm
  - Location
    - ◯ Intratumoural ◯ Extratumoural
  - Degree of extent
    - ◯ Focal ◯ Extensive
- ◯ Indeterminate, *specify reason*

MARGIN STATUS (Note 12)

- ◯ Not involved by invasive carcinoma
  - Distance of tumour from closest margin ____ mm
  - ◯ Distance not assessable
  - Specify closest margin(s), if possible
- ◯ Involved by invasive carcinoma
  - Specify margin(s), if possible
- ◯ Cannot be assessed, *specify*

COEXISTENT PATHOLOGY (select all that apply) (Note 13)

- ◯ None identified
- ☐ Oncocytic metaplasia
- ☐ Tumour-associated lymphoid proliferation (TALP)
- ☐ Intercalated duct hyperplasia/adenoma
- ☐ Concurrent benign tumour(s), *specify*
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 14)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry biomarkers, *specify test(s) and result(s)*
  - ☐ Molecular biomarkers, *specify test(s) and result(s)*
  - ☐ Other, *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)[c] (Note 15)

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

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

Primary tumour (pT)[d]

- ◯ TX[e] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ
- ◯ T1 Tumour 2 cm or less in greatest dimension without extraparenchymal extension[f]
- ◯ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension[f]
- ◯ T3 Tumour more than 4 cm and/or tumour with extraparenchymal extension[f]
- ◯ T4a Moderately advanced local disease
  Tumour invades skin, mandible, ear canal, and/or facial nerve
- ◯ T4b Very advanced local disease
  Tumour invades base of skull and/or pterygoid plates, and/or encases carotid artery

[c] *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).*

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

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

[f] *Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.*

Version 2.0 Published July 2024 ISBN: 978-1-922324-51-1

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.

⬆ Back

Scope

The dataset has been developed for the reporting of primary cancer resection and biopsy specimens of malignancies arising from the major salivary glands (parotid, submandibular and sublingual glands). For resections of recurrent disease, the reporting guide may be used pragmatically although some data elements may be not applicable nor assessable. Melanomas, lymphomas, and sarcomas are dealt with in separate ICCR datasets.[2] Minor salivary gland malignancies arising in the oral cavity, nasal cavity and paranasal sinuses, larynx, hypopharynx, trachea, nasopharynx, oropharynx, gnathic bones, and ear-temporal bone specimens are staged according to their anatomical sub-site and are dealt with in separate ICCR datasets.[3] Minor salivary gland tumours are rare with insufficient quality evidence currently to support a separate dataset, recognising this is a limitation. Further, the ICCR follows Union for International Cancer Control (UICC) guidance for staging,[4] and the major salivary gland system is not applicable to minor salivary glands. The notes on histological typing and grading in this dataset may be used to inform reporting of minor salivary gland malignancies. In addition, neck dissections and nodal excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.[5]

This dataset is based on histology, but if cytology is the only material available, we recommend using the 'other' box in the operative procedure section to record appropriate information.[6-8]

For bilateral tumours, a separate dataset should be completed for each tumour.

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.[9]

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

The authors of this dataset can be accessed here.

Back

Note 1 – Clinical information (Core and Non-core)

In general adjuvant or neoadjuvant therapy are not employed for salivary gland tumours, but as this field develops, it would be wise to include any previous surgery, chemotherapy, radiotherapy, targeted or immunotherapy which may have been used to manage the patient prior to the biopsy/resection.

Back

Note 2 – Operative procedure (Core)

The wide distribution of subsites that are involved by salivary gland malignancies results in a significant complexity of procedural types and necessitates open communication between the operating surgeon and the pathologist. The exact type of procedure (i.e., excisional biopsy versus resection) will be interpreted in discussion with the multidisciplinary team, especially since procedural nomenclature is constantly evolving.[10-13] In the context of recurrent disease, there may be nodules of recurrent carcinoma without any surrounding salivary gland tissue, and the best procedure designation would require discussion between pathologist and surgeon.[12,14]

Back

Note 3 – Specimen(s) submitted (Core), Tumour site (Core) and Tumour laterality (Core)

The salivary sites, particularly the parotid have a nuanced, oncologically relevant compartmentalisation that should be represented appropriately under specimen submitted and tumour site.[10] Tissue types and microanatomic structures encountered histologically are dependent on this specimen type and site. Thus, as with operative procedure, open communication is necessary to maximise accuracy. An attempt should be made at tumour centring within the submitted sample to document the true site of the primary neoplasm (such as superficial or deep parotid lobes). Accompanying specimens would include skin, bone (mandible or maxilla), and other localised tissues which aid in final staging and thus should be included.

Laterality is a standard identifying parameter for specimens submitted, with ‘not specified’ sparingly selected and only after best efforts have been made to obtain the requisite information. Reporting of

laterality provides supporting information to ensure that the correct site is recorded and is a common quality assurance metric.[12,15-17]

Back

Note 4 – Tumour focality (Non-core)

Multifocality is defined as separate foci of tumour in the same salivary gland, while multicentric is defined as multiple tumours in separate organs/sites (e.g., bilateral parotid glands). These designations apply to primary tumours, not metastases, and require histologic confirmation that tumour is present. Truly multifocal salivary carcinomas are rare.[18-20] The most common multifocal malignancy is acinic cell carcinoma.[21] Rarely multifocality in basal cell adenocarcinoma may raise the possibility of Brooke-Spiegler syndrome (*CYLD* cutaneous syndrome).[22] If bilateral or multifocal tumours are identified, an additional dataset is completed for each additional tumour(s).

Back

Note 5 – Tumour dimensions (Core and Non-core)

Tumour size, specifically the largest dimension is a key staging element for UICC and American Joint Committee on Cancer (AJCC) and is prognostically critical.[4,12,23,24] Tumour measurement should ideally be performed macroscopically on the fresh specimen if possible, since formalin fixation may cause tumour shrinkage.[25] Occasionally, the microscopic extent of tumour should be used to record tumour size, for example, when the size significantly exceeds macroscopic estimates. When sample fragmentation or disruption precludes accurate measurement, reliance of imaging or intraoperative dimensions may be necessary.

Back

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.

Back

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

All salivary gland tumours should be classified based on the most recent edition of the WHO Classification of Head and Neck Tumours, 5th edition, 2024 (Table 1).[9] Histologic type informs biologic behaviour and thus influences prognosis, patterns of recurrence and clinical management.[26,27] Carcinoma biology is quite different (i.e., basal cell adenocarcinoma is indolent with locoregional recurrence and low nodal metastatic rates[28] versus salivary duct carcinoma with high rates of nodal metastasis[29-31]), and thus accurate classification is important.

Carcinoma ex pleomorphic adenoma is further subclassified by carcinoma subtype and extent of invasion. The histologic type of the malignant component should be reported (most commonly salivary duct carcinoma, myoepithelial carcinoma, and epithelial-myoepithelial carcinoma).[32-34] Extent of invasion beyond the pleomorphic adenoma borders is separately into: 1) intracapsular: when the carcinoma is confined within the polymorphous adenoma capsule; 2) minimally invasive: when the carcinoma invades <6 millimetres (mm) beyond the pleomorphic adenoma capsule; and 3) invasive: when the invasion beyond the pleomorphic adenoma capsule measures ≥6 mm. Prior to diagnosing an in situ/intracapsular carcinoma ex pleomorphic adenoma, sectioning of the entire lesion for histologic evaluation is recommended in order to exclude the presence of invasive growth. Prognosis has been linked to degree of invasion with non-invasive and minimally invasive cancers having a better prognosis than invasive cancers.[35-37] The presence of a solid component in adenoid cystic carcinoma has been shown to be an independent prognostic factor,[38] and thus is a core element. However, the percentage of solid pattern is not yet standardised without cutoffs determined, and as such, the percentage of solid pattern is non-core at this time.

Metastasising pleomorphic adenoma, despite metastatic development is not included here since it is technically considered benign under the recent WHO classification of tumours.[39]

Primary salivary gland neuroendocrine carcinomas (small cell and large cell) are not specifically included in the salivary gland classification in the WHO 5th edition,[9] but should be included under 'other' in this reporting guide. Harmonisation resulted in a single chapter within the WHO classification devoted to neuroendocrine neoplasms.

The diagnosis of primary squamous cell carcinoma of the salivary gland should be used sparingly as it is typically a metastasis from another site, unless sialodochodysplasia is histologically identified or primary skin or mucosal squamous cell carcinoma can be definitively excluded.

Table 1: World Health Organization classification of epithelial tumours of the salivary glands.[9]

Descriptor	ICD-O coding[a]
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Secretory carcinoma	8502/3
Microsecretory carcinoma	8502/3
Polymorphous carcinoma	8525/3
Hyalinising clear cell carcinoma	8310/3
Basal cell adenocarcinoma	8147/3
Intraductal carcinoma	8500/2
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Epithelial-myoepithelial carcinoma	8562/3
Mucinous adenocarcinoma	8480/3
Sclerosing microcystic adenocarcinoma	8407/3
Carcinoma ex pleomorphic adenoma	8941/3
Carcinosarcoma of the salivary glands	8980/3
Sebaceous adenocarcinoma	8410/3
Lymphoepithelial carcinoma	8082/3
Squamous cell carcinoma	8070/3
Sialoblastoma	8974/1
Salivary gland carcinoma NOS and emerging entities	8140/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[40] 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.

Back

Note 8 – Histological tumour grade (Core)

The histologic (microscopic) grading of salivary gland carcinomas has been shown to be an independent predictor of behaviour and plays a role in optimising therapy. Further, there is often a positive correlation between histologic grade and clinical stage.[35] However, most salivary gland carcinoma types have an intrinsic biologic behaviour, such as basal cell adenocarcinoma (low grade) compared to salivary duct carcinoma (high grade) and attempted application of a universal grading scheme is not recommended.[35] Thus by assigning a histologic type, the tumour grade itself is often implied. Still, several grading systems for each tumour type are available, with differing merits, and as such, recording which system has been applied is more clinically meaningfully (use 'specify' to state the system used), with the ICCR deferring to the WHO Classification current edition for grading guidance and preference.[9] As a general guide, histologic grade is not applied for

acinic cell carcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, hyalinising clear cell carcinoma, myoepithelial carcinoma, sebaceous adenocarcinoma, lymphoepithelial carcinoma, salivary duct carcinoma, microsecretory adenocarcinoma, sclerosing microcystic adenocarcinoma, and sialoblastoma (refer to Table 1).

High grade transformation has evolved into an important concept of tumour progression in salivary gland carcinomas. Historically designated as 'dedifferentiation', it describes progression of a typically monomorphic carcinoma into a pleomorphic high grade carcinoma, showing sheet-like growth, tumour necrosis, mitotic index, and profound nuclear pleomorphism.[41,42] The importance of this phenomenon is that tumours demonstrating high grade transformation show an aggressive clinical course that deviates drastically from the usual behaviour for a given tumour type, thus alerting to the potential need for more aggressive clinical management. Tumours for which this phenomenon is well characterised include acinic cell carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma, while secretory carcinoma and polymorphous adenocarcinoma also rarely undergo high grade transformation.[43,44] High grade and high grade transformation may sound similar, but the latter generally implies there is a low grade component concurrently present with the high grade transformation.

Back

Note 9 – Extent of invasion (Core)

Macroscopic extraparenchymal extension is the parameter required to upstage a tumour to pT3 or higher and is thus more important than microscopic extraparenchymal extension. Extraparenchymal extension can be difficult to clarify in minor salivary gland sites, but extension into adjacent structures informs stage determination. Bone, skin, and facial nerve involvement are parameters that define stage T4a.[23] While microscopic extraparenchymal extension is not a stage defining parameter, in certain instances it may yield useful information for postoperative clinical management. Direct extension into lymph nodes is not considered lymph node involvement. However, if lymph node(s) are included within the samples submitted, a separate reporting guide for neck lymph nodes should be completed,[5] as intra- and peri-parotid or submandibular gland lymph nodes are commonly present, and are known to predict cervical lymph node metastases.[45-48]

Back

Note 10 – Lymphovascular invasion (Core)

Lymphovascular invasion is diagnostic of malignancy in salivary gland tumours (except for benign metastasising pleomorphic adenoma). Existing data are limited but support its prognostic value although this varies by tumour type and study.[49-57] As with many other organ sites, the significance of the distinction between vascular and lymphatic invasion as well as the extent of vascular invasion is not known.

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.

Back

Note 11 – Perineural invasion (Core and Non-core)

Perineural invasion is diagnostically useful since it often confirms a malignant classification (although there are benign exceptions). Perineural, circumferential, or intraneural invasion is defined as the presence of carcinoma juxtaposed intimately along, around, or within a nerve. Specifically, it includes the potential space between the bundles of axons and the perineurium; thus, carcinoma external to the perineurium is not perineural invasion. Further, some distinguish between intratumoural versus extratumoural affected nerves, although robust data supporting such a distinction is not yet available for salivary gland tumours.[49,58-61] The value of perineural invasion as a prognosticator varies depending on tumour type and literature.[55,62-67] Selected named nerve (i.e., facial nerve) involvement is incorporated into staging and assigned a more advanced stage,[23] but nerve involvement should be recorded regardless the size of the nerve(s). A more granular documentation to include extent of perineural invasion, localisation and size of involved nerves (measured in millimetre diameter of the largest nerve[68]) may be prognostically relevant, though not well studied, hence their inclusion as non-core elements.

⬆ Back

Note 12 – Margin status (Core)

Complete surgical excision to include cancer-free surgical margins is the primary mode of therapy for salivary gland cancers, as retrospective studies have shown an increased risk for recurrence and decreased survival with positive surgical margins.[69-72] Still, when controlling for stage, histologic risk group, and use of radiation, margin status is not an independent risk factor.[73] Unlike mucosal sites, there are no data to indicate a specified critical distance of tumour from margin indicative of a prognostic difference.[52,54,61,73,74] Indeed this may be dependent on tumour type, major salivary gland involved, and border.[73,75] Based on current level of evidence, reporting of distances to margins constitute a non-core element, giving these distance may aid in decisions about therapeutic intervention (postoperative radiation or chemotherapy).[64,76,77]

⬆ Back

Note 13 – Coexistent pathology (Non-core)

For salivary epithelial malignancies, non-neoplastic salivary pathology is of interest but not currently oncologically relevant overall. For some tumours however, a tumour-associated lymphoid proliferation (TALP)[78] may be mistaken for a lymph node and this distinction is important for staging. For acinic cell carcinomas, those with a prominent TALP may actually be more indolent.[79] Data suggests lesions such as intercalated duct hyperplasia/adenoma may be a precursor lesion,[80] while benign tumours (pleomorphic adenoma, sclerosing polycystic adenoma) may have carcinoma develop within them.[81-83] Distinguishing between oncocytic metaplasia, hyperplasia and oncocytoma may be challenging, but as none of these are considered precursor lesions, require no formal documentation.

⬆ Back

Note 14 – Ancillary studies (Non-core)

Ancillary studies encompass immunohistochemistry as well as molecular analysis. The main use of ancillary testing in salivary gland is to refine diagnosis. While there may be prognostic and therapeutic applications, they are not required as standard of care. There is growing evidence that androgen receptor (AR) results may aid in prognosis and treatment of salivary duct carcinoma, while data regarding human epidermal growth factor receptor 2 (HER2) have thus far not been associated with a worse overall survival.[84-87] HER2 is identified in a small fraction (about 5-10%) of mucoepidermoid carcinoma,[88-91] although positivity versus overexpression can be misleading (up to 84%[86]). HER2 overexpression is seen in salivary duct carcinoma (about 40%), but has not been shown to be associated with a worse overall survival.[84,87,90,91] However, amplification is seen in only about 20% of the cases that have HER2 immunohistochemistry (two thirds of positive cases). If the tumours are metastatic, co-expression of HER2 and AR seems to provide augmented response to trastuzumab therapies than just androgen deprivation therapy.[92]

Canonical genomic alterations have aided in refining salivary gland classification, testable by many methodologies.[93-98] A detailed review of each relevant pathogenic variant for each salivary gland cancer type is beyond the scope of this dataset.[99-102] Alterations in benign tumours such as pleomorphic adenoma and basal cell adenoma may be retained in their malignant counterparts.

Back

Note 15 – Pathological staging (Core)

By UICC/AJCC convention,[4,103] the designation 'T' refers to a primary tumour that has not been previously treated. The symbol 'p' refers to the pathologic classification of the TNM, as opposed to the clinical classification, and based on clinical stage information supplemented/ modified by operative findings and gross and microscopic evaluation of the resected specimens.[4,103] pT entails a resection of the primary tumour or biopsy 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. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumour. Pathologic staging depends on pathologic 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 without total removal of the primary cancer.

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.

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 AJCC TNM8,[4,103] 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.[4,103]

For the pN classification of regional lymph nodes, see ICCR Nodal excisions and neck dissection specimens dataset.[5]

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[104]

Back

References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 International Collaboration on Cancer Reporting (2024). *ICCR Datasets*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/ (Accessed 15th January 2024).

3 International Collaboration on Cancer Reporting (2024). *Head & Neck datasets*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/ (Accessed 31st July 2024).

4 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

5 International Collaboration on Cancer Reporting (2024). *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/nodal-excisions/ (Accessed 31st July 2024).

6 Tochtermann G, Nowack M, Hagen C, Rupp NJ, Ikenberg K, Broglie MA, Saro F, Lenggenhager D and Bode PK (2023). The Milan system for reporting salivary gland cytopathology-A single-center study of 2156 cases. *Cancer Med* 12(11):12198-12207.

7 Pusztaszeri M, Deschler D and Faquin Md Ph DW (2023). The 2021 ASCO guideline on the management of salivary gland malignancy endorses FNA biopsy and the risk stratification scheme proposed by the Milan System for Reporting Salivary Gland Cytopathology. *Cancer Cytopathol* 131(2):83-89.

8 Jo VY and Krane JF (2018). Ancillary testing in salivary gland cytology: A practical guide. *Cancer Cytopathol* 126 Suppl 8:627-642.

9 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.

10 Quer M, Guntinas-Lichius O, Marchal F, Vander Poorten V, Chevalier D, Leon X, Eisele D and Dulguerov P (2016). Classification of parotidectomies: a proposal of the European Salivary Gland Society. *Eur Arch Otorhinolaryngol* 273(10):3307-3312.

11 Holmes JD (2008). Neck dissection: nomenclature, classification, and technique. *Oral Maxillofac Surg Clin North Am* 20(3):459-475.

12 van Herpen C, Vander Poorten V, Skalova A, Terhaard C, Maroldi R, van Engen A, Baujat B, Locati LD, Jensen AD, Smeele L, Hardillo J, Martineau VC, Trama A, Kinloch E, Even C and Machiels JP (2022). Salivary gland cancer: ESMO-European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. *ESMO Open* 7(6):100602.

13 Geiger JL, Ismaila N, Beadle B, Caudell JJ, Chau N, Deschler D, Glastonbury C, Kaufman M, Lamarre E, Lau HY, Licitra L, Moore MG, Rodriguez C, Roshal A, Seethala R, Swiecicki P and Ha P (2021). Management of Salivary Gland Malignancy: ASCO Guideline. *J Clin Oncol* 39(17):1909-1941.

14 Chen AM, Garcia J, Bucci MK, Chan AS, Kaplan MJ, Singer MI and Phillips TL (2008). Recurrent salivary gland carcinomas treated by surgery with or without intraoperative radiation therapy. *Head Neck* 30(1):2-9.

15 Nakhleh RE, Idowu MO, Souers RJ, Meier FA and Bekeris LG (2011). Mislabeling of cases, specimens, blocks, and slides: a college of american pathologists study of 136 institutions. *Arch Pathol Lab Med* 135(8):969-974.

16 Hanna MG and Pantanowitz L (2015). Bar Coding and Tracking in Pathology. *Surg Pathol Clin* 8(2):123-135.

17 Lippi G, Blanckaert N, Bonini P, Green S, Kitchen S, Palicka V, Vassault AJ, Mattiuzzi C and Plebani M (2009). Causes, consequences, detection, and prevention of identification errors in laboratory diagnostics. *Clin Chem Lab Med* 47(2):143-153.

18 Kaleem A, Patel N, Alzahrani S, Hatoum H and Tursun R (2020). Concurrent presence of secretory carcinoma and Warthin's tumor in ipsilateral parotid gland. *Oral Oncol* 109:104691.

19 Seifert G and Donath K (1996). Multiple tumours of the salivary glands--terminology and nomenclature. *Eur J Cancer B Oral Oncol* 32b(1):3-7.

20 van Tongeren J, Creytens DH, Meulemans EV, de Bondt RB, de Jong J and Manni JJ (2009). Synchronous bilateral epithelial-myoepithelial carcinoma of the parotid gland: case report and review of the literature. *Eur Arch Otorhinolaryngol* 266(9):1495-1500.

21 Gnepp DR, Schroeder W and Heffner D (1989). Synchronous tumors arising in a single major salivary gland. *Cancer* 63(6):1219-1224.

22 Kazakov DV (2016). Brooke-Spiegler Syndrome and Phenotypic Variants: An Update. *Head Neck Pathol* 10(2):125-130.

23 Lydiatt WM, Mukherji SK, O'Sullivan B, Patel SG and Shah JP (2017). Major Salivary Glands. In: *AJCC Cancer Staging Manual 8th ed.*, Amin MB et al (eds), Springer, New York.

24 Bhattacharyya N and Fried MP (2005). Determinants of survival in parotid gland carcinoma: a population-based study. *Am J Otolaryngol* 26(1):39-44.

25 Chen CH, Hsu MY, Jiang RS, Wu SH, Chen FJ and Liu SA (2012). Shrinkage of head and neck cancer specimens after formalin fixation. *J Chin Med Assoc* 75(3):109-113.

26 Baddour HM, Jr., Fedewa SA and Chen AY (2016). Five- and 10-Year Cause-Specific Survival Rates in Carcinoma of the Minor Salivary Gland. *JAMA Otolaryngol Head Neck Surg* 142(1):67-73.

27 Olarte LS and Megwalu UC (2014). The Impact of Demographic and Socioeconomic Factors on Major Salivary Gland Cancer Survival. *Otolaryngol Head Neck Surg* 150(6):991-998.

28 Seethala RR (2009). An update on grading of salivary gland carcinomas. *Head Neck Pathol* 3(1):69-77.

29 Griffith CC, Thompson LD, Assaad A, Purgina BM, Lai C, Bauman JE, Weinreb I, Seethala RR and Chiosea SI (2014). Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma. *Histopathology* 65(6):854-860.

30 Schmitt NC, Sharma A, Gilbert MR and Kim S (2015). Early T Stage Salivary Duct Carcinoma: Outcomes and Implications for Patient Counseling. *Otolaryngol Head Neck Surg* 153(5):795-798.

31 Robinson RA (2021). Basal Cell Adenoma and Basal Cell Adenocarcinoma. *Surg Pathol Clin* 14(1):25-42.

32 Avdagic E, Farber N, Katabi N and Shinder R (2017). Carcinoma Ex Pleomorphic Adenoma of the Lacrimal Gland with Epithelial-Myoepithelial Carcinoma Histologic Type. *Ophthalmic Plast Reconstr Surg* 33(3S Suppl 1):S136-s138.

33 El Hallani S, Udager AM, Bell D, Fonseca I, Thompson LDR, Assaad A, Agaimy A, Luvison AM, Miller C, Seethala RR and Chiosea S (2018). Epithelial-Myoepithelial Carcinoma: Frequent Morphologic and Molecular Evidence of Preexisting Pleomorphic Adenoma, Common HRAS Mutations in PLAG1-intact and HMGA2-intact Cases, and Occasional TP53, FBXW7, and SMARCB1 Alterations in High-grade Cases. *Am J Surg Pathol* 42(1):18-27.

34 Kusafuka K, Yamashita M, Muramatsu A, Arai K and Suzuki M (2021). Epithelial-myoepithelial carcinoma ex-pleomorphic adenoma of the parotid gland: report of a rare case with immunohistochemical and genetic analyses. *Med Mol Morphol* 54(2):173-180.

35 Seethala RR (2011). Histologic grading and prognostic biomarkers in salivary gland carcinomas. *Adv Anat Pathol* 18(1):29-45.

36 Brandwein M, Huvos AG, Dardick I, Thomas MJ and Theise ND (1996). Noninvasive and minimally invasive carcinoma ex mixed tumor: a clinicopathologic and ploidy study of 12 patients with major salivary tumors of low (or no?) malignant potential. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81(6):655-664.

37 Suzuki M, Matsuzuka T, Saijo S, Takahara M, Harabuchi Y, Okuni T, Himi T, Kakizaki T, Fukuda S, Yamada K, Nagahashi T, Abe T, Shinkawa H, Katagiri K, Sato H, Fukui N, Ishikawa K, Suzuki T, Kobayashi T, Saito D, Saijo S, Tateda M, Hashimoto S, Ishida A, Kakehata S, Suzuki O, Hashimoto Y and Omori K (2016). Carcinoma ex pleomorphic adenoma of the parotid gland: a multi-institutional retrospective analysis in the Northern Japan Head and Neck Cancer Society. *Acta Otolaryngol* 136(11):1154-1158.

38 van Weert S, van der Waal I, Witte BI, Leemans CR and Bloemena E (2015). Histopathological grading of adenoid cystic carcinoma of the head and neck: analysis of currently used grading systems and proposal for a simplified grading scheme. *Oral Oncol* 51(1):71-76.

39 Bell D, Bullerdiek J, Gnepp DR, Schwartz MR, Stenman G and Triantafyllou A (2017). Pleomorphic adenoma. In: *WHO Classification of Tumours of the Head and Neck*, El-Naggar AK, Chan JK, Grandis JR, Ohgaki H and Slootweg P (eds), IARC, Lyon, France, 185-186.

40 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th March 2024).

41 Costa AF, Altemani A and Hermsen M (2011). Current concepts on dedifferentiation/high-grade transformation in salivary gland tumors. *Patholog Res Int* 2011:325965.

42 Skalova A, Leivo I, Hellquist H, Agaimy A, Simpson RHW, Stenman G, Vander Poorten V, Bishop JA, Franchi A, Hernandez-Prera JC, Slouka D, Willems SM, Olsen KD and Ferlito A (2021). High-grade Transformation/Dedifferentiation in Salivary Gland Carcinomas: Occurrence Across Subtypes and Clinical Significance. *Adv Anat Pathol* 28(3):107-118.

43 Skalova A, Vanecek T, Majewska H, Laco J, Grossmann P, Simpson RH, Hauer L, Andrle P, Hosticka L, Branzovsky J and Michal M (2014). Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, beta-catenin, EGFR, and CCND1 genes. *Am J Surg Pathol* 38(1):23-33.

44 Simpson RH, Pereira EM, Ribeiro AC, Abdulkadir A and Reis-Filho JS (2002). Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. *Histopathology* 41(3):250-259.

45 Terada T and Kawata R (2022). Role of Intra-Parotid Lymph Node Metastasis in Primary Parotid Carcinoma. *Life (Basel)* 12(12):2053.

46 Yuan J, Meng F, Xu C, Li W, Wu S and Li H (2022). Occult neck metastases risk factors and the role of elective neck dissection in cT3-4N0 adenoid cystic carcinoma of the parotid gland. *Front Oncol* 12:935110.

47 Kouka M, Koehler B, Buentzel J, Kaftan H, Boeger D, Mueller AH, Wittig A, Schultze-Mosgau S, Ernst T, Schlattmann P and Guntinas-Lichius O (2022). Role of Intraparotid and Neck Lymph Node Metastasis in Primary Parotid Cancer Surgery: A Population-Based Analysis. *Cancers (Basel)* 14(12):2822.

48 Guntinas-Lichius O, Thielker J, Robbins KT, Olsen KD, Shaha AR, Mäkitie AA, de Bree R, Vander Poorten V, Quer M, Rinaldo A, Kowalski LP, Rodrigo JP, Hamoir M and Ferlito A (2021). Prognostic role of intraparotid lymph node metastasis in primary parotid cancer: Systematic review. *Head Neck* 43(3):997-1008.

49 Erovic BM, Shah MD, Bruch G, Johnston M, Kim J, O'Sullivan B, Perez-Ordonez B, Weinreb I, Atenafu EG, de Almeida JR, Gullane PJ, Brown D, Gilbert RW, Irish JC and Goldstein DP (2015). Outcome analysis of 215 patients with parotid gland tumors: a retrospective cohort analysis. *J Otolaryngol Head Neck Surg* 44:43.

50 Hosni A, Huang SH, Goldstein D, Xu W, Chan B, Hansen A, Weinreb I, Bratman SV, Cho J, Giuliani M, Hope A, Kim J, O'Sullivan B, Waldron J and Ringash J (2016). Outcomes and prognostic factors for major salivary gland carcinoma following postoperative radiotherapy. *Oral Oncol* 54:75-80.

51 Mifsud MJ, Tanvetyanon T, McCaffrey JC, Otto KJ, Padhya TA, Kish J, Trotti AM, Harrison LB and Caudell JJ (2016). Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. *Head Neck* 38(11):1628-1633.

52 Baněčková M, Thompson LDR, Hyrcza MD, Vaněček T, Agaimy A, Laco J, Simpson RHW, Di Palma S, Stevens TM, Brcic L, Etebarian A, Dimnik K, Majewska H, Stárek I, O'Regan E, Salviato T, Helliwell T, Horáková M, Biernat W, Onyuma T, Michal M, Leivo I and Skalova A (2023). Salivary Gland Secretory Carcinoma: Clinicopathologic and Genetic Characteristics of 215 Cases and Proposal for a Grading System. *Am J Surg Pathol* 47(6):661-677.

53 Alsarraj M, Alshehri SM, Qattan A, Mofti A, Wazqer L, Bukhari S, Shamsaldin A and Rajab R (2022). Lymph Node Involvement and the Clinical Stage as Predictors of the Survival of Patients With Adenoid Cystic Carcinoma of the Head and Neck: A Systematic Review and Meta-Analysis. *Cureus* 14(10):e30780.

54 Xu B, Viswanathan K, Umrau K, Al-Ameri TAD, Dogan S, Magliocca K, Ghossein RA, Cipriani NA and Katabi N (2022). Secretory carcinoma of the salivary gland: a multi-institutional clinicopathologic study of 90 cases with emphasis on grading and prognostic factors. *Histopathology* 81(5):670-679.

55 Reny DC, Ranasinghe VJ, Magana LC, Kaufman AC, Chalian AA, O'Malley BW, Jr., Weinstein GS and Brody RM (2020). Predictors of Nodal Metastasis in Mucoepidermoid Carcinoma of the Oral Cavity and Oropharynx. *ORL J Otorhinolaryngol Relat Spec* 82(6):327-334.

56 Park YM, AlHashim MA, Yoon SO, Koh YW, Kim SH, Lim JY and Choi EC (2020). Prognostic significance of lymphovascular invasion in patients with salivary duct cell carcinoma of the head and neck. *Int J Oral Maxillofac Surg* 49(6):693-699.

57 Martins-Andrade B, Dos Santos Costa SF, Sant'ana MSP, Altemani A, Vargas PA, Fregnani ER, Abreu LG, Batista AC and Fonseca FP (2019). Prognostic importance of the lymphovascular invasion in head and neck adenoid cystic carcinoma: A systematic review and meta-analysis. *Oral Oncol* 93:52-58.

58 Frankenthaler RA, Luna MA, Lee SS, Ang KK, Byers RM, Guillamondegui OM, Wolf P and Goepfert H (1991). Prognostic variables in parotid gland cancer. *Arch Otolaryngol Head Neck Surg* 117(11):1251-1256.

59 Smith BD (2009). Prognostic factors in patients with head and neck cancer. In: *Head and neck cancer: A multidisciplinary approach*, Harrison LB, Sessions RB and Hong WK (eds), Lippincott Williams and Wilkins, Philadelphia.

60 Terhaard CH, Lubsen H, Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA, Tjho-Heslinga RE, de Jong JM, Roodenburg JL and Dutch Head and Neck Oncology Cooperative Group (2004). Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck* 26(8):681-692; discussion 692-693.

61 Carta F, Bontempi M, De Seta D, Corrias S, Tatti M, Marrosu V, Mariani C, Gerosa C, Shetty SA, Atzeni M, Buckley C, Figus A and Puxeddu R (2023). Survival in Patients with Primary Parotid Gland Carcinoma after Surgery-Results of a Single-Centre Study. *Curr Oncol* 30(3):2702-2714.

62 Speight PM and Barrett AW (2009). Prognostic factors in malignant tumours of the salivary glands. *Br J Oral Maxillofac Surg* 47(8):587-593.

63 Coca-Pelaz A, Rodrigo JP, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, Strojan P, Rinaldo A, Haigentz M, Jr., Takes RP, Mondin V, Teymoortash A, Thompson LD and Ferlito A (2015). Adenoid cystic carcinoma of the head and neck--An update. *Oral Oncol* 51(7):652-661.

64 Huang BS, Chen WY, Hsieh CE, Lin CY, Lee LY, Fang KH, Tsang NM, Kang CJ, Wang HM and Chang JT (2016). Outcomes and prognostic factors for surgery followed by modern radiation therapy in parotid gland carcinomas. *Jpn J Clin Oncol* 46(9):832-838.

65 Israel Y, Rachmiel A, Gourevich K and Nagler R (2019). Kaplan-Meier analysis of salivary gland tumors: prognosis and long-term survival. *J Cancer Res Clin Oncol* 145(8):2123-2130.

66 de Melo GM, de Medeiros GS, Gatti AP, Guilherme LH, das Neves MC, Rosano M, Callegari FM, Russell J, Abrahao M and Cervantes O (2022). Perineural Invasion as Worsening Criterion for Salivary Gland Mucoepidermoid Carcinoma. *Indian J Otolaryngol Head Neck Surg* 74(Suppl 3):6225-6235.

67 Zupancic M, Näsman A, Berglund A, Dalianis T and Friesland S (2023). Adenoid Cystic Carcinoma (AdCC): A Clinical Survey of a Large Patient Cohort. *Cancers (Basel)* 15(5):1499.

68 Barrett AW and Speight PM (2009). Perineural invasion in adenoid cystic carcinoma of the salivary glands: a valid prognostic indicator? *Oral Oncol* 45(11):936-940.

69 Tran L, Sadeghi A, Hanson D, Juillard G, Mackintosh R, Calcaterra TC and Parker RG (1986). Major salivary gland tumors: treatment results and prognostic factors. *Laryngoscope* 96(10):1139-1144.

70 Vander Poorten VL, Balm AJ, Hilgers FJ, Tan IB, Loftus-Coll BM, Keus RB, van Leeuwen FE and Hart AA (1999). The development of a prognostic score for patients with parotid carcinoma. *Cancer* 85(9):2057-2067.

71 Amini A, Waxweiler TV, Brower JV, Jones BL, McDermott JD, Raben D, Ghosh D, Bowles DW and Karam SD (2016). Association of Adjuvant Chemoradiotherapy vs Radiotherapy Alone With Survival in Patients With Resected Major Salivary Gland Carcinoma: Data From the National Cancer Data Base. *JAMA Otolaryngol Head Neck Surg* 142(11):1100-1110.

72 Sideris A, Rao A, Maher N, Parker A, Crawford J, Smee R, Jacobson I and Gallagher R (2021). Acinic cell carcinoma of the salivary gland in the adult and paediatric population: a survival analysis. *ANZ J Surg* 91(6):1233-1239.

73 Hanson M, McGill M, Mimica X, Eagan A, Hay A, Wu J, Cohen MA, Patel SG and Ganly I (2022). Evaluation of Surgical Margin Status in Patients With Salivary Gland Cancer. *JAMA Otolaryngol Head Neck Surg* 148(2):128-138.

74 Ord RA and Ghazali N (2017). Margin Analysis: Malignant Salivary Gland Neoplasms of the Head and Neck. *Oral Maxillofac Surg Clin North Am* 29(3):315-324.

75 Llerena P, Wang K, Puram SV, Pipkorn PJ, Jackson RS and Bollig CA (2022). National analysis of positive surgical margins in oropharyngeal salivary gland malignancies. *Am J Otolaryngol* 43(5):103527.

76 Ali S, Palmer FL, Katabi N, Lee N, Shah JP, Patel SG and Ganly I (2017). Long-term local control rates of patients with adenoid cystic carcinoma of the head and neck managed by surgery and postoperative radiation. *Laryngoscope* 127(10):2265-2269.

77 Wu WJ, Shao X, Huang MW, Lv XM, Zhang XN and Zhang JG (2017). Postoperative iodine-125 interstitial brachytherapy for the early stages of minor salivary gland carcinomas of the lip and buccal mucosa with positive or close margins. *Head Neck* 39(3):572-577.

78 Auclair PL (1994). Tumor-associated lymphoid proliferation in the parotid gland. A potential diagnostic pitfall. *Oral Surg Oral Med Oral Pathol* 77(1):19-26.

79 Michal M, Skalova A, Simpson RH, Leivo I, Ryska A and Starek I (1997). Well-differentiated acinic cell carcinoma of salivary glands associated with lymphoid stroma. *Hum Pathol* 28(5):595-600.

80 McLean AC, Rooper LM, Gagan J, Thompson LDR and Bishop JA (2023). A Subset of Salivary Intercalated Duct Lesions Harbors Recurrent CTNNB1 and HRAS Mutations: A Molecular Link to Basal Cell Adenoma and Epithelial-Myoepithelial Carcinoma? *Head Neck Pathol* 17(2):393-400.

81 Skálová A, Baněčková M, Laco J, Di Palma S, Agaimy A, Ptáková N, Costes-Martineau V, Petersson BF, van den Hout M, de Rezende G, Klubíčková N, Koblížek M, Koshyk O, Vaneček T and Leivo I (2022). Sclerosing Polycystic Adenoma of Salivary Glands: A Novel Neoplasm Characterized by PI3K-AKT Pathway Alterations-New Insights Into a Challenging Entity. *Am J Surg Pathol* 46(2):268-280.

82 Di Palma S (2013). Carcinoma ex pleomorphic adenoma, with particular emphasis on early lesions. *Head Neck Pathol* 7 Suppl 1(Suppl 1):S68-76.

83 Antony J, Gopalan V, Smith RA and Lam AK (2012). Carcinoma ex pleomorphic adenoma: a comprehensive review of clinical, pathological and molecular data. *Head Neck Pathol* 6(1):1-9.

84 Williams CYK, Townson AT, Terry N, Schmitt NC and Sharma A (2023). Role of HER2 in Prognosis of Salivary Duct Carcinoma: A Systematic Review and Meta-Analysis. *Laryngoscope* 133(3):476-484.

85 Yoshimura T, Higashi S, Yamada S, Noguchi H, Nomoto M, Suzuki H, Ishida T, Takayama H, Hirano Y, Yamashita M, Tanimoto A and Nakamura N (2021). PCP4/PEP19 and HER2 Are Novel Prognostic Markers in Mucoepidermoid Carcinoma of the Salivary Gland. *Cancers (Basel)* 14(1):54.

86 Javaheripour A, Saatloo MV, Vahed N, Gavgani LF and Kouhsoltani M (2022). Evaluation of HER2/neu expression in different types of salivary gland tumors: a systematic review and meta-analysis. *J Med Life* 15(5):595-600.

87 Ferguson DC, Momeni Boroujeni A, Zheng T, Mohanty AS, Ho AL, Arcila ME, Ross DS and Dogan S (2022). ERBB2 amplification status in 67 salivary duct carcinomas assessed by immunohistochemistry, fluorescence in situ hybridization, and targeted exome sequencing. *Mod Pathol* 35(7):895-902.

88 Shang J, Shui Y, Sheng L, Wang K, Hu Q and Wei Q (2008). Epidermal growth factor receptor and human epidermal growth receptor 2 expression in parotid mucoepidermoid carcinoma: possible implications for targeted therapy. *Oncol Rep* 19(2):435-440.

89 Nakano T, Yamamoto H, Hashimoto K, Tamiya S, Shiratsuchi H, Nakashima T, Nishiyama K, Higaki Y, Komune S and Oda Y (2013). HER2 and EGFR gene copy number alterations are predominant in high-grade salivary mucoepidermoid carcinoma irrespective of MAML2 fusion status. *Histopathology* 63(3):378-392.

90 Clauditz TS, Reiff M, Gravert L, Gnoss A, Tsourlakis MC, Münscher A, Sauter G, Bokemeyer C, Knecht R and Wilczak W (2011). Human epidermal growth factor receptor 2 (HER2) in salivary gland carcinomas. *Pathology* 43(5):459-464.

91 Egebjerg K, Harwood CD, Woller NC, Kristensen CA and Mau-Sørensen M (2021). HER2 Positivity in Histological Subtypes of Salivary Gland Carcinoma: A Systematic Review and Meta-Analysis. *Front Oncol* 11:693394.

92 De Block K, Vander Poorten V, Dormaar T, Nuyts S, Hauben E, Floris G, Deroose CM, Schöffski P and Clement PM (2016). Metastatic HER-2-positive salivary gland carcinoma treated with trastuzumab and a taxane: a series of six patients. *Acta Clin Belg* 71(6):383-388.

93 Bishop JA, Weinreb I, Swanson D, Westra WH, Qureshi HS, Sciubba J, MacMillan C, Rooper LM and Dickson BC (2019). Microsecretory Adenocarcinoma: A Novel Salivary Gland Tumor Characterized by a Recurrent MEF2C-SS18 Fusion. *Am J Surg Pathol* 43(8):1023-1032.

94 Antonescu CR, Katabi N, Zhang L, Sung YS, Seethala RR, Jordan RC, Perez-Ordoñez B, Have C, Asa SL, Leong IT, Bradley G, Klieb H and Weinreb I (2011). EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. *Genes Chromosomes Cancer* 50(7):559-570.

95 Rooper LM, Argyris PP, Thompson LDR, Gagan J, Westra WH, Jordan RC, Koutlas IG and Bishop JA (2021). Salivary Mucinous Adenocarcinoma Is a Histologically Diverse Single Entity With Recurrent AKT1 E17K Mutations: Clinicopathologic and Molecular Characterization With Proposal for a Unified Classification. *Am J Surg Pathol* 45(10):1337-1347.

96 Seethala RR, Dacic S, Cieply K, Kelly LM and Nikiforova MN (2010). A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. *Am J Surg Pathol* 34(8):1106-1121.

97 Skálová A, Vanecek T, Sima R, Laco J, Weinreb I, Perez-Ordonez B, Starek I, Geierova M, Simpson RH, Passador-Santos F, Ryska A, Leivo I, Kinkor Z and Michal M (2010). Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol* 34(5):599-608.

98 Persson M, Andrén Y, Mark J, Horlings HM, Persson F and Stenman G (2009). Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. *Proc Natl Acad Sci U S A* 106(44):18740-18744.

99 Seethala RR and Stenman G (2017). Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. *Head Neck Pathol* 11(1):55-67.

100 Skálová A, Hyrcza MD and Leivo I (2022). Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. *Head Neck Pathol* 16(1):40-53.

101 Skálová A, Hyrcza MD, Vaneček T, Baněčková M and Leivo I (2022). Fusion-positive salivary gland carcinomas. *Genes Chromosomes Cancer* 61(5):228-243.

102 Karpinets TV, Mitani Y, Liu B, Zhang J, Pytynia KB, Sellen LD, Karagiannis DT, Ferrarotto R, Futreal AP and El-Naggar AK (2021). Whole-Genome Sequencing of Common Salivary Gland Carcinomas: Subtype-Restricted and Shared Genetic Alterations. *Clin Cancer Res* 27(14):3960-3969.

103 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

104 Wittekind C, Brierley JD, van Eycken AL and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition*, Wiley, USA.

 ISBN: 978-1-922324-51-1