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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.

SCOPE OF THIS DATASET

OPERATIVE PROCEDURE (select all that apply) (Note 1)

- ○ Not specified
- ☐ Biopsy (excisional, incisional), *specify*
- ☐ Resection, *specify*
- ☐ Neck (lymph node) dissection*, *specify*
- ☐ Other, *specify*

* *If a neck dissection is submitted, then a separate dataset is used to record the information.*

SPECIMENS SUBMITTED (select all that apply) (Note 2)

- ○ Not specified
- ☐ Parotid gland
  - ☐ Superficial lobe only
  - ☐ Deep lobe only
  - ☐ Total parotid (superficial and deep lobe)
- ☐ Submandibular gland
- ☐ Sublingual gland
- ☐ Other *(e.g. partial gland excision), specify*

TUMOUR SITE (select all that apply) (Note 2)

- ○ Cannot be assesed
- ☐ Parotid gland
  - ☐ Left ☐ Right ○ Laterality not specified
  - ☐ Superficial lobe only
    - ☐ Left ☐ Right ○ Laterality not specified
  - ☐ Deep lobe only
    - ☐ Left ☐ Right ○ Laterality not specified
  - ☐ Total parotid (superficial and deep lobe)
    - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Submandibular gland
  - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Sublingual gland
  - ☐ Left ☐ Right ○ Laterality not specified
- ☐ Other, *specify including laterality*

TUMOUR FOCALITY (Note 3)

- ○ Unifocal
- ○ Multifocal
  - *Specify number of tumours in specimen*
- ○ Cannot be assessed, *specify*

TUMOUR DIMENSIONS (Note 4)

Maximum tumour dimension (largest tumour) mm

Additional dimensions (largest tumour) mm x mm

- ○ Cannot be assessed, *specify*

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 5)

(Value list from the World Health Organization Classification of Head and Neck Tumours (2017))

- ☐ Acinic cell carcinoma
- ☐ Secretory carcinoma
- ☐ Mucoepidermoid carcinoma
  - ○ Low grade ○ Intermediate grade
  - ○ High grade
- ☐ Adenoid cystic carcinoma
  - ○ Tubular/cribriform pattern predominant
    - % of solid component, if any %
  - ○ Solid pattern
    - % of solid component, if any %
- ☐ Polymorphous adenocarcinoma
  - ○ Classic ○ Cribriform
  - ⇩ Grade, *specify*

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- [ ] Epithelial-myoepithelial carcinoma
- [ ] (Hyalinizing) Clear cell carcinoma
- [ ] Basal cell adenocarcinoma
- [ ] Sebaceous adenocarcinoma
- [ ] Myoepithelial carcinoma
- [ ] Intraductal carcinoma
  - ◯ Low grade ◯ High grade
- [ ] Cystadenocarcinoma
  - ◯ Low grade ◯ High grade
- [ ] Adenocarcinoma, not otherwise specified (NOS)
  - ◯ Low grade ◯ Intermediate grade ◯ High grade
- [ ] Salivary duct carcinoma
  - Variant(s), *specify*
- [ ] Carcinoma ex pleomorphic adenoma
  - Tumour type(s), *specify*
  - ◯ Intracapsular ◯ Minimally invasive
  - ◯ Widely invasive
  - Distance from capsule ____ mm
- [ ] Carcinosarcoma
- [ ] Poorly differentiated carcinoma: Neuroendocrine and non-neuroendocrine
  - ◯ Undifferentiated carcinoma
  - ◯ Large cell neuroendocrine carcinoma
  - ◯ Small cell neuroendocrine carcinoma
- [ ] Lymphoepithelial carcinoma
- [ ] Squamous cell carcinoma
- [ ] Oncocytic carcinoma
- [ ] Other, *specify*
- ◯ Cannot be assessed, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 6)

- ◯ Not applicable
- ◯ High grade transformation
- ◯ Cannot be assessed, *specify*

EXTENT OF INVASION (select all that apply) (Note 7)

- ◯ Not identified
- [ ] Macroscopic extraparenchymal extension
- [ ] Bone
- [ ] Skin
- [ ] Facial nerve
- [ ] Other, *specify*
- ◯ Cannot be assessed, *specify*

PERINEURAL INVASION (Note 8)

◯ Not identified ◯ Present

Nerve size, if known ____ mm

Location

◯ Intratumoural ◯ Extratumoural

Degree of extent

◯ Focal ◯ Extensive

◯ Cannot be assessed, *specify*

LYMPHOVASCULAR INVASION (Note 9)

◯ Not identified ◯ Present

◯ Cannot be assessed, *specify*

MARGIN STATUS (Note 10)

◯ Involved by carcinoma

Specify margin(s), if possible

◯ Not involved by carcinoma

Distance of tumour from closest margin ____ mm

◯ Distance not assessable

Specify closest margin, if possible

◯ Cannot be assessed, *specify*

COEXISTENT PATHOLOGY (select all that apply) (Note 11)

- ◯ None identified
- [ ] Sialadenitis
- [ ] Tumour associated lymphoid proliferation (TALP)
- [ ] Benign tumour(s), *specify*
- [ ] Other, *specify*

ANCILLARY STUDIES (Note 12)

- ○ Not performed
- ○ Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition)## (Note 13)

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

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)**

- ○ TX 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^
- ○ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension^
- ○ T3 Tumour more than 4 cm and/or tumour with extraparenchymal extension^
- ○ 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

^ *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.*

** *Note that the results of lymph node/neck dissection are derived from a separate dataset.*

Scope

The dataset has been developed for the reporting of resection and biopsy specimens of malignant neoplasms and associated carcinoma in situ arising from the major salivary glands. The protocol applies to all carcinomas of the parotid, submandibular and sublingual glands. Melanomas, lymphomas, and sarcomas are dealt with in separate datasets. Minor salivary gland malignancies arising in the oral cavity, nasal cavity and paranasal sinuses, trachea, nasopharynx, oropharynx and hypopharynx and odontogenic specimens are staged according to their anatomical sub-site and are dealt with in separate datasets. In addition, neck dissections and nodal excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.

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

Note 1 – Operative procedure (Core)

Reason/Evidentiary Support

The wide distribution of subsites that are involved by salivary gland carcinomas results in a wide 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.[1,2] 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 dialog between pathologist and surgeon.[3]

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Note 2 – Specimens submitted (Core) and Tumour site (Core)

Reason/Evidentiary Support

The salivary sites, particularly the parotid have a nuanced, oncologically relevant compartmentalization that should be represented appropriately under specimen type and tumour type.[1] Tissue types and microanatomic structures encountered histologically are dependent on this specimen type and site. Thus as with procedure type, open communication is necessary to maximize accuracy.

Laterality is a standard identifying parameter for specimen types that should rarely be left not specified. Reporting of laterality provides supporting information to ensure that the correct site is recorded, and is a common quality assurance metric.[4] Not specified should be used rarely and only after best efforts have been made to obtain the requisite information.

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Note 3 – Tumour focality (Core and Non-core)

Reason/Evidentiary Support

Truly multifocal salivary carcinomas are rare. The most common multifocal malignancy is acinic cell carcinoma.[5] Rarely multifocality in basal cell adenocarcinoma may raise the possibility of a *CYLD* associated syndrome (i.e. Brooke Spiegler syndrome).[6]

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Note 4 – Tumour dimensions (Core and Non-core)

Reason/Evidentiary Support

Tumour size, specifically the largest dimension is a key staging element for American Joint Committee on Cancer (AJCC) and is prognostically critical.[7,8] Tumour measurement should ideally be performed macroscopically on the fresh specimen if possible, since formalin fixation may cause tumour shrinkage.[9] Occasionally, the microscopic extent of tumour should be used to record tumour size, for example, when the size significantly exceeds macroscopic estimates.

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Note 5 –Histological tumour type (Core and Non-core)

Reason/Evidentiary Support

Salivary carcinoma histologic type essentially defines its biologic behaviour and thus influences prognosis, patterns of recurrence and thus clinical management.[10,11] Some carcinoma types (i.e. basal cell adenocarcinoma, conventional acinic cell carcinoma) are more indolent with locoregional recurrence but low nodal and distant metastatic rates.[12] Other tumour types are aggressive even at early T stage, aggressive lesions (such as conventional salivary duct carcinoma) show high rates of nodal metastasis and worse 5-year overall survival.[13,14]

Carcinoma ex pleomorphic adenoma is subclassifed by type and extent of invasion. Non-invasive cancers are completely confined within the capsule of the adenoma. The definition for minimally invasive carcinomas varies, ranging from 1.5 mm to 6 mm (this distance should be specified when possible). Invasive carcinomas extend beyond 6 mm; non-invasive cancers are completely confined to within the capsule without evidence of penetration into extracapsular tissue. Prior to diagnosing a non-invasive 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 apparently having a better prognosis than invasive cancers.[15,16] For salivary duct carcinoma arising from pleomorphic adenoma, intracapsular lesions behave indolently. But once invasive, the concept of minimal

invasion may be less relevant since cases with extracapsular invasion ≤2 mm have still been reported to be clinically aggressive.[13]

Metastasizing pleomorphic adenoma, despite its aggressive behaviour is not included here since it is technically considered benign under the recent World Health Organization (WHO) classification of tumours.[17]

In the 2017 WHO classification of tumours, cribriform adenocarcinoma of (minor) salivary gland origin is a subcategory of polymorphous adenocarcinoma.[18] This is a controversial area and the recommendation is to separate classical and cribriform pattern polymorphous adenocarcinomas in the dataset to allow acquisition of prognostic information. Unlike classic polymorphous adenocarcinoma, cribriform adenocarcinomas of minor salivary gland are more frequently extrapalatal, commonly at base of tongue, and have a higher propensity for nodal metastasis. Histologically they have more pronounced vescicular nuclei and tend to have a papillary glomeruloid and cribriform growth rather than a targetoid fascicular pattern seen in classic polymorphous adenocarcinoma.[19] They tend to demonstrate translocations involving the *PRKD* family of genes,[20] rather than the *PRKD1* point mutations[21] seen in classic polymorphous adenocarcinoma. For the purposes of reporting, differentiating between these entities may be helpful given the noticeably different behavioural profile.

Note: The diagnosis of primary squamous cell carcinoma of the salivary gland should be used sparingly as it is typically a metastasis from another site.

WHO classification of tumours of the salivary glands[a][22]

Descriptor	ICD-O codes
Malignant tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Polymorphous adenocarcinoma	8525/3
Clear cell carcinoma	8310/3
Basal cell adenocarcinoma	8147/3
Intraductal carcinoma	8500/2
Adenocarcinoma, NOS	8140/3
Salivary gland carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Epithelial-myoepithelial carcinoma	8562/3
Carcinoma ex pleomorphic adenoma	8941/3
Secretory carcinoma	8502/3
Sebaceous adenocarcinoma	8410/3
Carcinosarcoma	8980/3
Poorly differentiated carcinoma	
Undifferentiated carcinoma	8020/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3

Descriptor	ICD-O codes
Lymphoepithelial carcinoma	8082/3
Squamous cell carcinoma	8070/3
Oncocytic cell carcinoma	8290/3
Uncertain malignant potential	
Sialoblastoma	8974/1

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

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Note 6 – Histological tumour grade (Core)

Reason/Evidentiary Support

The histologic (microscopic) grading of salivary gland carcinomas has been shown to be an independent predictor of behaviour and plays a role in optimizing therapy. Further, there is often a positive correlation between histologic grade and clinical stage.[15,23-25] However, as alluded to above, most salivary gland carcinoma types have an intrinsic biologic behaviour and attempted application of a universal grading scheme is not recommended.[15] Thus by assigning a histologic type the tumour grade itself is often implied. Thus a generic grading scheme is no longer recommended for salivary gland carcinomas.[7]

Carcinoma types for which grading systems exist and are relevant are incorporated into histologic type. The major categories that are amenable to grading include adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma, not otherwise specified.[15,24,26] Additionally, with the new WHO classification, polymorphous adenocarcinoma is another tumour type that is to be graded,[18] with the understanding that a validated grading scheme has not yet been established.

In adenoid cystic carcinoma histologic grading is based on growth pattern.[26] Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high grade carcinomas. However, recent studies suggest that any solid component may still be of prognostic relevance.[27] The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (e.g. cystic, solid, neurotropism) and cytomorphologic findings (e.g. anaplasia, mitoses, necrosis).[28-30] Adenocarcinomas, not otherwise specified, do not have a formalized grading scheme and are graded intuitively based on cytomorphologic features.[15] Similarly, as the concept of grading polymorphous adenocarcinomas will be a new one,[18] as these also lack a formalized grading scheme. Currently, the recommendation is to grade these intuitively based on cytomorphologic features, acknowledging that the majority will be low grade.

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.[31] 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 characterized include acinic cell carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma. Mammary analogue secretory carcinoma and polymorphous adenocarcinoma also rarely undergo high grade transformation.[32,33]

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Note 7 – Extent of invasion (Core)

Reason/Evidentiary Support

Macroscopic extraparenchymal extension is the parameter required to upstage a tumour to T3 and is thus more important than microscopic extraparenchymal extension. Bone, skin and facial nerve involvement are parameters that define stage T4a.[7] While microscopic extraparenchymal extension is not a stage defining parameter, in certain instances it may yield useful information for post operative clinical management.

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Note 8 – Perineural invasion (Core and Non-core)

Reason/Evidentiary Support

Perineural invasion is diagnostically useful since it establishes a malignant categorization. The value of perineural invasion as a prognosticator varies depending on tumour type and literature.[34] While this has not been as well studied for salivary gland as for head and neck squamous cell carcinoma, much of the literature supports the importance of recording this feature as a data element.[35-38] Select named nerve (i.e. facial nerve) involvement is incorporated into staging and assigned a more advanced stage.[7] But even beyond this, a more granular documentation, extent of perineural invasion, localization and size of involved nerves may be prognostically relevant as well, though not well studied, hence their inclusion as non-core elements.

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Note 9 – Lymphovascular invasion (Core)

Reason/Evidentiary Support

Lymphovascular invasion is diagnostic of malignancy in salivary gland tumours. Existing data are limited but support its prognostic value although this varies by tumour type and study.[37,39,40] As with

other organ sites, the significance of the distinction between vascular and lymphatic invasion as well as the extent of vascular invasion is not known.

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Note 10 – Margin status (Core and Non-core)

Reason/Evidentiary Support

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.[41-43] Unlike mucosal sites, there are no data to indicate a specified critical distance of tumour from margin indicative of a prognostic difference. Indeed this may be dependent on tumour type, major salivary gland involved, and border as well. Based on current level of evidence, reporting of distances to margins constitute a non-core element.

For illustration, adenoid cystic carcinoma has an infiltrative border and high propensity for local recurrence. The "safe distance" for this tumour will be intuitively greater than for a more indolent carcinoma such as epithelial myoepithelial carcinoma, for instance. Limited data suggest that even with >5 mm clearance, approximately 20% of adenoid cystic carcinomas recur, which is still less than the recurrence rate for close (<5 mm) and positive margins.[44] In contrast, almost all epithelial-myoepithelial carcinomas are cured if margins are negative, even without a stipulation in distance to margin.[45]

Occasionally, even salivary carcinomas may show encapsulation similar to that of pleomorphic adenoma. In superficial parotid gland tumours, this tumour capsule rests on the facial nerve and may thus be resected conservatively (i.e. via extracapsular dissection) in order to spare and minimize injury to the facial nerve. Thus it is not uncommon for such tumours to be "close" with the tumour capsule forming the deep margin. It is not clear whether this scenario indicates an increased risk of local recurrence. Limited data on extracapsular dissection for salivary carcinomas suggest a favourable outcome even with close margins, though this may be influenced by tumour type, since most carcinomas with this configuration are slow growing and low grade.[46]

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Note 11 – Coexistent pathology (Non-core)

Reason/Evidentiary Support

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)[47] 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.[48]

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Note 12 – Ancillary studies (Non-core)

Reason/Evidentiary Support

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 some prognostic and therapeutic applications, they are not yet strongly validated as standard of care, and thus no ancillary study is currently required as a data element in salivary cancers.

Understanding of salivary gland cancer biology has increased tremendously and is largely characterized by a preponderance of chromosomal translocations that frequently define certain tumour types. These are testable by many methodologies. A detailed review of each relevant marker in each salivary gland cancer type is beyond the scope of this dataset.[49] Alterations in benign tumours such as pleomorphic adenoma and basal cell adenoma may be retained in their malignant counterparts.

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Note 13 – Pathological staging (Core)

Reason/Evidentiary Support

By AJCC/Union for International Cancer Control (UICC) convention, 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.[50] 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 categorizes the extent of tumour actually present at the time of that examination. The “y” categorization 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.

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References

1 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.

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

3 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.

4 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.

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

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

7 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.

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

9 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.

10 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.

11 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.

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

13 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.

14 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.

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

16 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.

17 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.

18 Fonseca I, Assaad A, Katabi N, Seethala RR, Simpson RHW, Skalova A, Weinreb I and Wenig BM (2017). Polymorphous Adenocarcinoma. 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, 167-168.

19 Skalova A, Sima R, Kaspirkova-Nemcova J, Simpson RH, Elmberger G, Leivo I, Di Palma S, Jirasek T, Gnepp DR, Weinreb I, Perez-Ordonez B, Mukensnabl P, Rychly B, Hrabal P and Michal M (2011). Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. *Am J Surg Pathol* 35(8):1168-1176.

20 Weinreb I, Zhang L, Tirunagari LM, Sung YS, Chen CL, Perez-Ordonez B, Clarke BA, Skalova A, Chiosea SI, Seethala RR, Waggott D, Boutros PC, How C, Liu FF, Irish JC, Goldstein DP, Gilbert R, Ud Din N, Assaad A, Hornick JL, Thompson LD and Antonescu CR (2014). Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. *Genes Chromosomes Cancer* 53(10):845-856.

21 Weinreb I, Piscuoglio S, Martelotto LG, Waggott D, Ng CK, Perez-Ordonez B, Harding NJ, Alfaro J, Chu KC, Viale A, Fusco N, da Cruz Paula A, Marchio C, Sakr RA, Lim R, Thompson LD, Chiosea SI, Seethala RR, Skalova A, Stelow EB, Fonseca I, Assaad A, How C, Wang J, de Borja R, Chan-Seng-Yue M, Howlett CJ, Nichols AC, Wen YH, Katabi N, Buchner N, Mullen L, Kislinger T, Wouters BG, Liu FF, Norton L, McPherson JD, Rubin BP, Clarke BA, Weigelt B, Boutros PC and Reis-Filho JS (2014). Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. *Nat Genet* 46(11):1166-1169.

22 El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ Eds. (2017). *WHO Classification of Head and Neck Tumours (4th Edition)*. IARC, Lyon, France.

23 Spiro RH, Thaler HT, Hicks WF, Kher UA, Huvos AH and Strong EW (1991). The importance of clinical staging of minor salivary gland carcinoma. *Am J Surg* 162(4):330-336.

24 Spiro RH, Huvos AG and Strong EW (1982). Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients. *Am J Surg* 144(4):423-431.

25 Kane WJ, McCaffrey TV, Olsen KD and Lewis JE (1991). Primary parotid malignancies. A clinical and pathologic review. *Arch Otolaryngol Head Neck Surg* 117(3):307-315.

26 Szanto PA, Luna MA, Tortoledo ME and White RA (1984). Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer* 54(6):1062-1069.

27 Xu B, Drill E, Ho A, Ho A, Dunn L, Prieto-Granada CN, Chan T, Ganly I, Ghossein R and Katabi N (2017). Predictors of Outcome in Adenoid Cystic Carcinoma of Salivary Glands: A Clinicopathologic Study With Correlation Between MYB Fusion and Protein Expression. *Am J Surg Pathol* 41(10):1422-1432.

28 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.

29 Brandwein MS, Ivanov K, Wallace DI, Hille JJ, Wang B, Fahmy A, Bodian C, Urken ML, Gnepp DR, Huvos A, Lumerman H and Mills SE (2001). Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading. *Am J Surg Pathol* 25(7):835-845.

30 Auclair PL, Goode RK and Ellis GL (1992). Mucoepidermoid carcinoma of intraoral salivary glands. Evaluation and application of grading criteria in 143 cases. *Cancer* 69(8):2021-2030.

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

32 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.

33 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.

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

35 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.

36 Smith BD (2009). Prognostic factoris in patients with head and neck cancer. In: *Head and neck cancer: A multidisciplinary approach*, Harrison LB, Sessions RB, Hong WK (eds), Lippincott Williams and Wilkins, Philadelphia, 51-75.

37 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.

38 Terhaard CH, Lubsen H, Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA, Tjho-Heslinga RE, de Jong JM, Roodenburg JL, Dutch H and Neck Oncology Cooperative G (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 692-683.

39 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.

40 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.

41 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.

42 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.

43 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.

44 Bjorndal K, Krogdahl A, Therkildsen MH, Charabi B, Kristensen CA, Andersen E, Schytte S, Primdahl H, Johansen J, Pedersen HB, Andersen LJ and Godballe C (2015). Salivary adenoid cystic carcinoma in Denmark 1990-2005: Outcome and independent prognostic factors including the benefit of radiotherapy. Results of the Danish Head and Neck Cancer Group (DAHANCA). *Oral Oncol* 51(12):1138-1142.

45 Seethala RR, Barnes EL and Hunt JL (2007). Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. *Am J Surg Pathol* 31(1):44-57.

46 Mantsopoulos K, Velegrakis S and Iro H (2015). Unexpected Detection of Parotid Gland Malignancy during Primary Extracapsular Dissection. *Otolaryngol Head Neck Surg* 152(6):1042-1047.

47 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.

48 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.

49 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.

50 Gress DM, Edge SB, Greene FL, Washington MK, Asare EA, Brierley JD, Byrd DR, Compton CC, Jessup JM, Winchester DP, Amin MB and Gershenwald JE (2017). Principles of cancer staging. In: *AJCC Cancer Staging Manual 8th ed*, Amin MB et al (eds), Springer, New York.