# Data Set for the Reporting of Carcinomas of the Major Salivary Glands

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

*Raja R. Seethala, MD; Albina Altemani, MD, PhD; Robert L. Ferris, MD, PhD; Isabel Fonseca, MD; Douglas R. Gnepp, MD; Patrick Ha, MD; Toshitaka Nagao, MD; Alena Skalova, MD, PhD, CSc; Göran Stenman, DMD, PhD; Lester D. R. Thompson, MD*

**• The International Collaboration on Cancer Reporting is a nonprofit organization whose goal is to develop evidence-based, internationally agreed-upon standardized data sets for each anatomic site, to be used throughout the world. Providing global standardization of pathology tumor classification, staging, and other reporting elements will lead to achieving the objective of improved patient management and enhanced epidemiologic research. Salivary gland carcinomas are relatively uncommon, and as such, meaningful data about the many histologic types are not easily compared. Morphologic overlap between tumor types makes accurate classification challenging, but there are often significant differences in patient outcomes. Therefore, issues related to tumor type, tumor grading, high-grade transformation, extent of invasion, number and size of nerves affected, and types of ancillary studies are discussed in the context of daily application to specimens from these organs. This review focuses on the data set developed for salivary gland carcinomas with discussion of the key core and noncore elements developed for inclusion by an international expert panel of head and neck and oral-maxillofacial pathologists and surgeons.**

**(*Arch Pathol Lab Med*. 2019;143:578–586; doi: 10.5858/arpa.2018-0422-SA)**

With the aim of standardizing evidence-based pathology reports for use throughout the world, the International Collaboration on Cancer Reporting (ICCR) since 2011 has developed data sets for various organ systems. The ICCR is an alliance formed by major pathology organizations, including the Royal College of Pathologists of Australasia, the United Kingdom and Ireland; the College of American Pathologists; the Canadian Association of Pathologists-Association Canadienne des Pathologists, in association with the Canadian Partnership Against Cancer; and the American Society of Clinical Pathologists, and recently joined by the European Society of Pathology. Each Dataset Authoring Committee is composed of an expert panel with international experience, which is particularly important in salivary gland cancers, where there are worldwide geographic differences in the presentation and prevalence of different tumor types.

The ICCR has stated guidelines for the development of the data sets (http://www.iccr-cancer.org/datasets/dataset-development). An elected series champion for a suite of related anatomic sites (ie, head and neck) oversees the selection of a chair and domain experts for an organ or anatomic site who serve as the Dataset Authoring Committee. The major salivary glands Dataset Authoring Committee was composed of 8 pathologists from 6 countries, partly selected from the additional sponsoring organizations: North American Society of Head and Neck Pathology; American Academy of Oral and Maxillofacial Pathology; the British Society for Oral and Maxillofacial Pathology; and the International Association of Oral and Maxillofacial Pathologists. Further, several members had previous experience in national data set development. Because treatment and outcome data are more challenging to parse, 2 head and neck surgeons completed the panel.

Accepted for publication October 1, 2018.
Published online November 30, 2018.

From the Department of Pathology and Laboratory Medicine (Dr Seethala) and Division of Head and Neck Surgery, Department of Otolaryngology (Dr Ferris), University of Pittsburgh, Pittsburgh, Pennsylvania; the Department of Anatomic Pathology, Faculty of Medical Sciences, University of Campinas, São Paulo, Brazil (Dr Altemani); the Pathological Anatomy Institute, Faculdade de Medicina, Universidade de Lisboa & Serviço de Anatomia Patológica, Instituto Português de Oncologia Francisco Gentil, Lisbon, Portugal (Dr Fonseca); Head and Neck Pathology, Rye Brook, New York (Dr Gnepp); the Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco (Dr Ha); the Department of Anatomic Pathology, Tokyo Medical University, Tokyo, Japan (Dr Nagao); the Department of Pathology, Faculty of Medicine in Plzen, Charles University, Plzen, Czech Republic (Dr Skalova); the Department of Pathology and Genetics, Sahlgrenska Cancer Center, University of Gothenburg, Gothenburg, Sweden (Dr Stenman); and the Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills (Dr Thompson).

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Lester D. R. Thompson, MD, Southern California Permanente Medical Group, Woodland Hills Medical Center, Department of Pathology, 5601 De Soto Avenue, Woodland Hills, CA 91365 (email: Lester.D.Thompson@kp.org).

The ICCR salivary glands cancer data set is specific to resection specimens and some biopsies of malignant neoplasms and associated carcinoma in situ arising from the major salivary glands.[52] Melanomas, lymphomas, and sarcomas are dealt with in separate data sets. Minor salivary gland malignancies arising in the oral cavity, nasal cavity, and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx and trachea, and odontogenic specimens are dealt with in their respective separate anatomic site data sets, specifically to match stage reporting. In addition, neck nodal dissections/excisions are dealt with in a separate, linked data set for *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours*, and this data set should be used in conjunction, where applicable.[53] When developing the data set, the expert panel distinguished between reporting of core elements and noncore elements. Core elements are considered essential for clinical management, staging, or prognosis, and thus are required reporting items. Reporting of core elements is supported by the National Health and Medical Research Council evidence level III-2 (based on prognostic factors among patients in a single arm of a randomized control trial) and above.[1] Although not considered required, noncore elements are agreed-upon reporting elements that may be clinically important and recommended as good clinical practice. This review will summarize the ICCR major salivary gland carcinoma data set reporting guidelines, with a discussion of the key elements developed for inclusion.

## DATA SET ELEMENTS

### Core (Required) Elements

**Operative Procedure.**—The wide distribution of subsites that are involved by salivary gland carcinomas results in a wide complexity of procedural types, and it necessitates open communication between the operating surgeon and the pathologist. The exact type of procedure (ie, excisional biopsy versus resection) must be interpreted in discussion with a multidisciplinary team, especially because procedural nomenclature is constantly evolving.[2,3] 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 discourse between pathologist and surgeon.[4]

**Specimens Submitted and Tumor Site.**—The salivary sites, particularly the parotid (Figure 1), have a nuanced, oncologically relevant compartmentalization that should be represented appropriately under specimen type and tumor type.[2] 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 categorized as *not specified*. Reporting of laterality provides supporting information to ensure that the correct site is recorded, and is a common quality assurance metric.[5] *Not specified* should be used rarely and only after best efforts have been made to obtain the requisite information.

**Tumor Focality.**—Truly multifocal salivary gland carcinomas are rare. The most common multifocal malignancy is acinic cell carcinoma.[6] Rarely, multifocality in basal cell adenocarcinoma may raise the possibility of a *CYLD*-associated syndrome (such as Brooke-Spiegler syndrome).[7]

**World Health Organization Classification of Tumors of the Salivary Glands**[a]

| Descriptor | ICD-O Codes[b] |
|---|---|
| Malignant tumors | |
| 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 duct 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 |
| Lymphoepithelial carcinoma | 8082/3 |
| Squamous cell carcinoma | 8070/3 |
| Oncocytic carcinoma | 8290/3 |
| Uncertain malignant potential | |
| Sialoblastoma | 8974/1 |

Abbreviation: NOS, not otherwise specified.

[a] Reproduced with permission from the World Health Organization/International Agency for Research on Cancer.[11]

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

**Tumor Dimensions.**—Tumor size, specifically the single largest dimension, is a key staging element for the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), and it is prognostically critical.[8,9] Tumor measurement should be performed macroscopically on the fresh specimen because formalin fixation may cause tumor shrinkage.[10] Occasionally, the microscopic extent of tumor should be used to record tumor size, for example, when the size significantly exceeds macroscopic estimates.

**Histologic Tumor Type.**—Generally, salivary gland carcinomas should be classified according to the World Health Organization (WHO) *Classification of Head and Neck Tumours* (Table).[11] Salivary gland carcinoma histologic type essentially defines its biologic behavior, and this in turn influences prognosis and patterns of recurrence, and thus clinical management.[12,13] Some carcinoma types (such as basal cell adenocarcinoma and conventional acinic cell carcinoma) are more indolent, with locoregional recurrence but low nodal and distant metastatic rates.[14] Other tumor types are aggressive even at early T stage (eg, salivary duct carcinoma), showing high rates of nodal metastasis and a poor 5-year overall survival.[15,16]

Carcinoma ex pleomorphic adenoma is subclassified by type and extent of invasion. Noninvasive cancers are

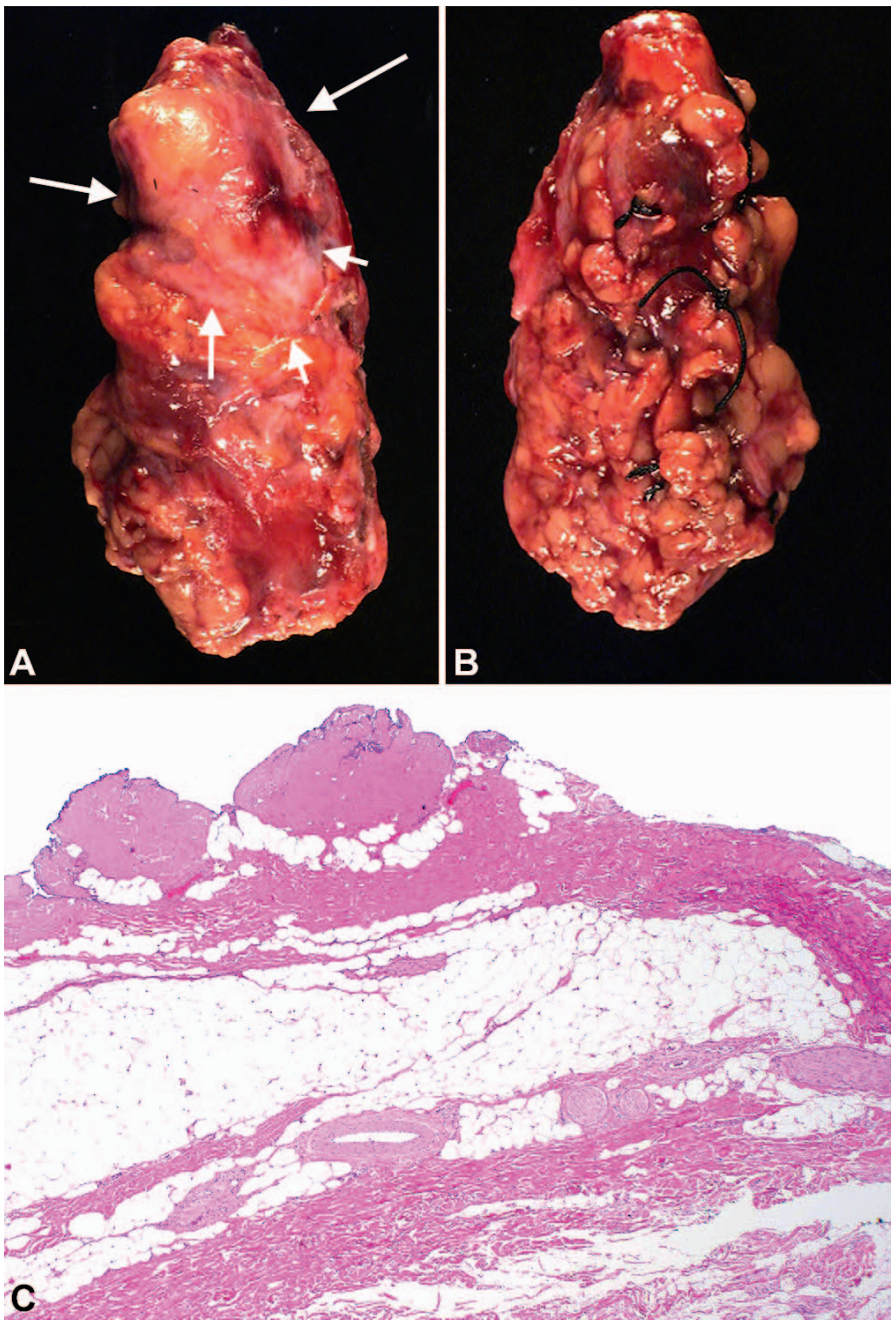


**Figure 1.** *The nuanced gross anatomy and microanatomy of a superficial parotid. A, The lateral (superficial) surface of the superficial parotid is invested by the parotid fascia (arrows), which is contiguous with the masseter fascia and forms an oncologic barrier. B, The medial (deep) surface sits on the branch point of the facial nerve, necessitating meticulous dissection because superficial parotid tumors routinely abut this surface. C, The microanatomic appearance of the parotid fascia demonstrating a bilayer of fibroconnective tissue. In between is fibroadipose tissue and neurovascular bundles. Occasionally lobules of salivary tissue may be noted in between these layers as well (hematoxylin-eosin, original magnification ×20).*

completely confined within the capsule of the adenoma, lacking any penetration of the capsule. The definition for minimally invasive carcinomas varies, ranging from 1.5 to 6 mm (Figure 2, A), but this distance should be specified when possible. Invasive carcinomas extend beyond 6 mm (Figure 2, B). Prior to diagnosing a noninvasive 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 noninvasive and minimally invasive cancers apparently having a better prognosis than invasive cancers.[17,18] For salivary duct carcinoma arising from pleomorphic adenoma, intracapsular tumors behave indolently. However, once invasive, the concept of minimal invasion may be less relevant because cases with extracapsular invasion 2 mm or less have still been reported to be clinically aggressive.[15] The metastasizing pleomorphic adenoma, despite its aggressive behavior, is not included in the data set reporting because it is a benign tumor.[19]

In the 2017 WHO *Classification of Head and Neck Tumours*, cribriform adenocarcinoma of (minor) salivary gland origin is a subcategory of polymorphous adenocarcinoma.[20] Because of continued controversy, separate reporting of classical (Figure 3, A) and cribriform pattern (Figure 3, B) polymorphous adenocarcinomas in the data set will allow for the acquisition of prognostic information. The cribriform adenocarcinomas of minor salivary gland (Figure 3, B) are more frequently extrapalatal, commonly at the base of the tongue, and have a higher propensity for nodal metastasis. Histologically, they have more pronounced vesicular nuclei and tend to have a papillary glomeruloid and cribriform

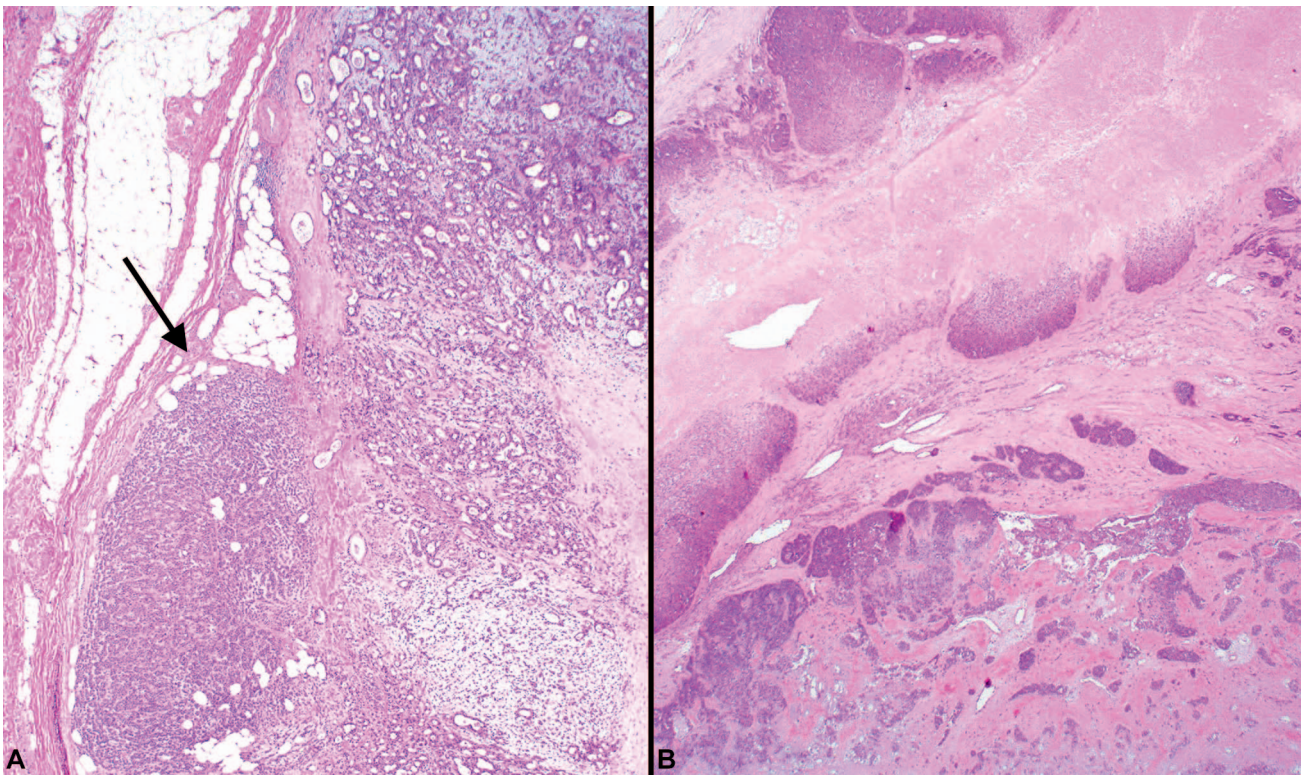


**Figure 2.** *Carcinoma ex pleomorphic adenoma subtypes by extent of invasion. A, Minimally invasive myoepithelial carcinoma ex pleomorphic adenoma of parotid demonstrates focal (<2 mm) extension (arrow) beyond the pleomorphic adenoma capsule. B, This (widely or frankly) invasive carcinoma ex pleomorphic adenoma of parotid with comedonecrosis demonstrates more extensive invasion beyond the pleomorphic adenoma (bottom) component (hematoxylin-eosin, original magnifications ×40 [A] and ×20 [B]).*

growth rather than a targetoid fascicular pattern seen in classic polymorphous adenocarcinoma.[21] Cribriform tumors tend to demonstrate translocations involving the *PRKD* family of genes[22] rather than the *PRKD1* point mutations[23] seen in classic polymorphous adenocarcinoma. For the purposes of reporting, differentiating between these entities may be helpful given the noticeably different behavioral profile.

Primary squamous cell carcinoma of the salivary gland should only be employed in strict circumstances, because it is typically a metastasis from another site (most often a cutaneous primary).

**Histologic Tumor Grade.**—The histologic (microscopic) grading of salivary gland carcinomas has been shown to be an independent predictor of behavior and plays a role in optimizing therapy. Further, there is often a positive correlation between histologic grade and clinical stage.[17,24–26] However, as alluded to above, most salivary gland carcinoma types have an intrinsic biologic behavior, and attempted application of a universal grading scheme is not recommended.[17] Thus, by assigning a histologic type, the tumor grade itself is often implied. As such, a generic grading scheme is no longer recommended for salivary gland carcinomas.[8]

Carcinoma types for which grading systems exist and are relevant are incorporated into histologic type. The major diagnostic categories amenable to grading include adenoid cystic carcinoma (Figure 4), mucoepidermoid carcinoma (Figure 5), and adenocarcinoma, not otherwise specified.[17,25,27–30] Additionally, with the new WHO classification, polymorphous adenocarcinoma is another tumor type that is to be graded.[20]

High-grade transformation has evolved into an important concept of tumor progression in salivary gland carcinomas. Historically designated as "dedifferentiation," it describes progression of a typically monomorphic carcinoma into a pleomorphic, high-grade carcinoma (Figure 6).[31] The importance of this phenomenon is that tumors demonstrating high-grade transformation show an aggressive clinical course that deviates drastically from the usual behavior for a given tumor type, thus alerting the treating team to the potential need for more aggressive treatment. Tumors for which this phenomenon is well characterized include acinic cell carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma. Secretory carcinoma and polymorphous adenocarcinoma also rarely undergo high-grade transformation.[32,33]

**Perineural Invasion.**—Perineural invasion is diagnostically useful because it establishes a malignant categorization. The value of perineural invasion as a prognosticator varies depending on tumor type and literature.[34] Although this has not been as well studied for salivary gland as it has for head and neck squamous cell carcinoma, much of the literature supports the importance of recording this feature as a data set element.[35–38] Involvement of a specifically named nerve (ie, facial nerve) is incorporated into staging and is assigned a more advanced stage.[8] A thorough documentation, to include the extent of perineural invasion, localization, and size of involved nerves, may be prognostically relevant, albeit not well studied, and hence included at this time as a noncore element.

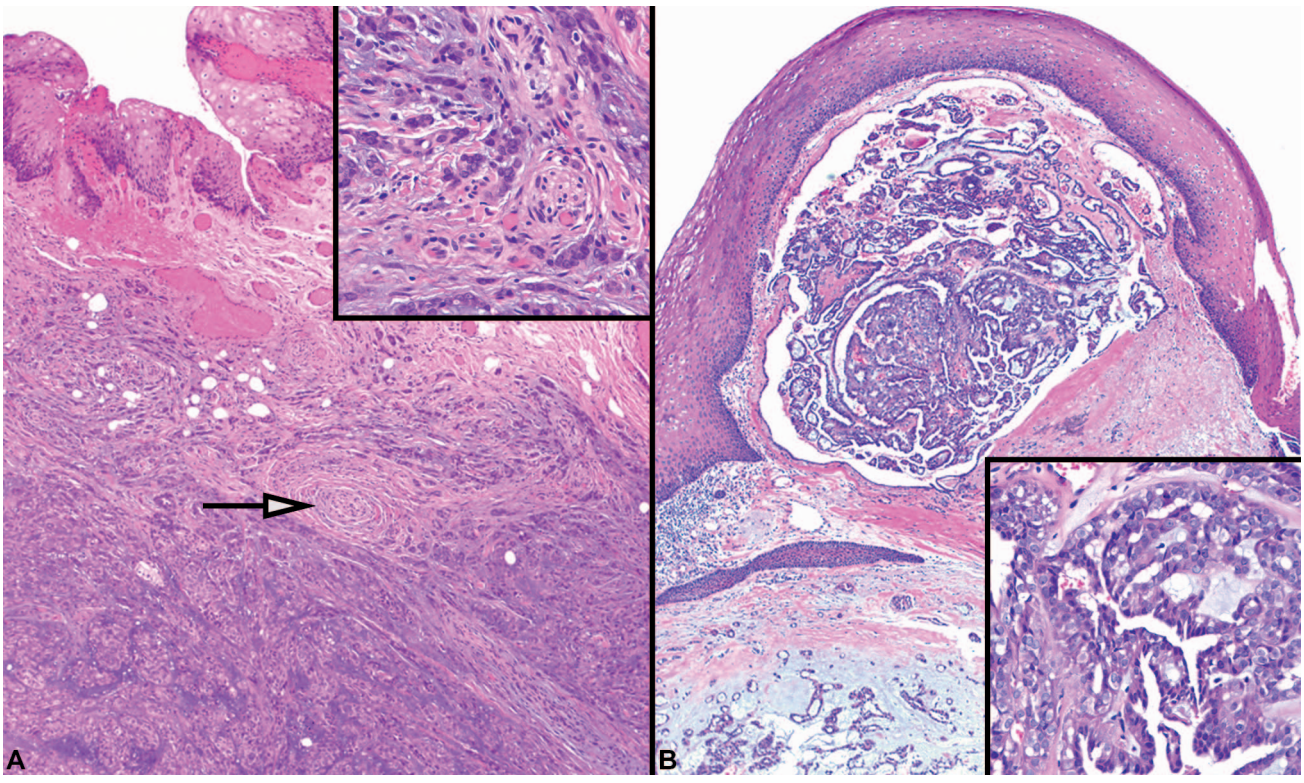


**Figure 3.** *Polymorphous adenocarcinoma family of tumors. A, This classic-appearing polymorphous adenocarcinoma, low grade, of the hard/soft palate junction demonstrates an infiltrative targetoid fascicular growth pattern with neurotropism (arrow). Inset: Nuclei are monomorphic, ovoid, and vesicular in this focus of perineural invasion. B, This cribriform adenocarcinoma of (minor) salivary origin is a base of tongue tumor with a papillary, glomeruloid, and cribriform growth. Inset: Nuclei are somewhat more elongated, with more pronounced clearing than its classic counterpart (hematoxylin-eosin, original magnifications ×20 [A and B] and ×200 [insets]).*

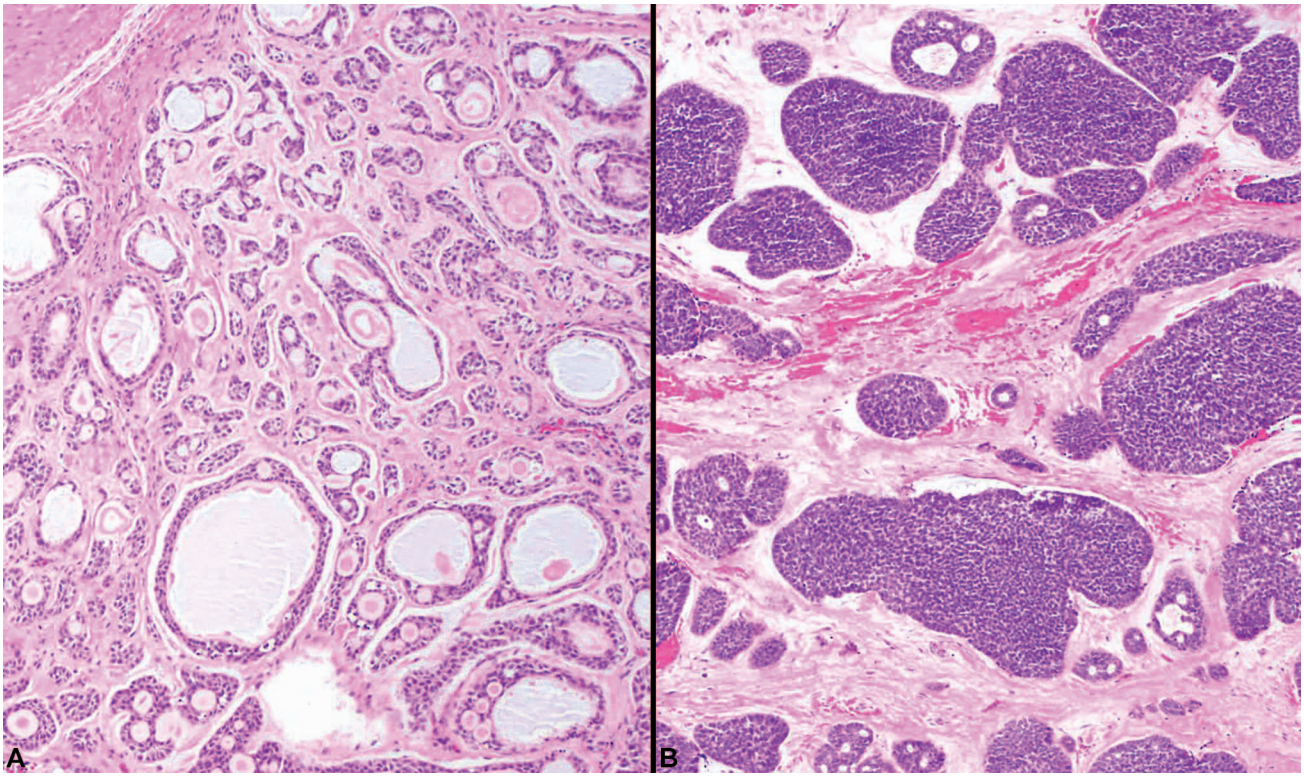


**Figure 4.** *Pattern-based grading in adenoid cystic carcinoma. A, Tubular and cribriform growth pattern. B, The more aggressive solid growth pattern (hematoxylin-eosin, original magnification ×40).*

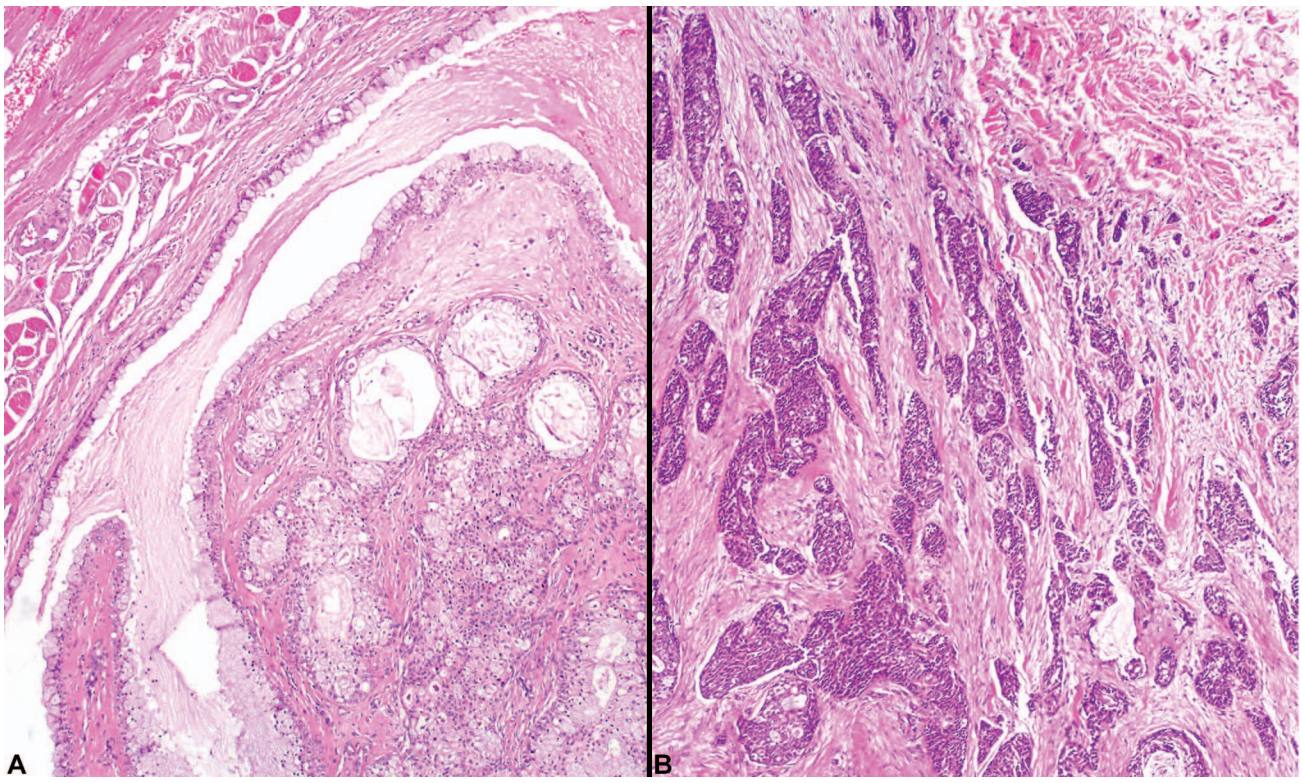


**Figure 5.** *Grade in mucoepidermoid carcinoma. A, Despite the variability in grading systems, this example from the palate would likely be designated universally as low grade, with the well-circumscribed cystic appearance of this tumor and mucous cell–rich areas. B, On the other hand, this tumor (a lethal parotid tumor) would generally be considered high grade because it is solid, highly infiltrative, and composed mainly of intermediate and epidermoid-type cells. Both examples harbored a* MAML2 *rearrangement (data not shown) (hematoxylin-eosin, original magnification ×40).*

**Lymphovascular Invasion.**—Lymphovascular invasion is nearly always diagnostic of malignancy in salivary gland tumors (metastasizing pleomorphic adenoma being the obvious exception). Existing data are limited but support its prognostic value, although this varies by tumor 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.

**Extent of Invasion.**—Macroscopic extraparenchymal extension is the parameter required to upstage a tumor to T3 and is thus more important than microscopic extraparenchymal extension. Bone, skin (Figure 7), and facial nerve involvement are parameters that define stage T4a.[8]

**Margin Status.**—Complete surgical excision to include cancer-free surgical margins is the primary mode of therapy for salivary gland cancers, because retrospective studies have shown an increased risk for recurrence and decreased survival with positive surgical margins.[41–44] Unlike mucosal sites, there are no data to indicate a specified critical distance of tumor from margin that yields a prognostic difference. Indeed, this also may be dependent on tumor type, major salivary gland involved, and border. Based on the current level of evidence, reporting of distances to margins constitutes a noncore element.

For illustration, adenoid cystic carcinoma has an infiltrative border and a high propensity for local recurrence. The "safe distance" for this tumor will be intuitively greater than for a more indolent carcinoma, such as epithelial myoepithelial carcinoma. Limited data suggest that even with more than 5 mm of clearance, approximately 20% of adenoid cystic carcinomas recur, which is still less than the recurrence rate for close (<5 mm) and positive margins.[45] In contrast, almost all epithelial-myoepithelial carcinomas are cured if margins are negative, even without a stipulation in distance to margin.[46]

Occasionally, even salivary carcinomas may show encapsulation similar to that of pleomorphic adenoma. In superficial parotid gland tumors, this tumor capsule rests on the facial nerve and may thus be resected conservatively (ie, via extracapsular dissection) in order to spare and minimize injury to the facial nerve. Thus, it is not uncommon for such tumors to be "close," with the tumor 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 favorable outcome even with close margins, although this may be influenced by tumor type, because most carcinomas with this configuration are slow growing and low grade.[47]

**Pathologic Staging.**—By AJCC/UICC convention, the designation "pT" refers to pathologic classification of a primary tumor that has not been previously treated, based on clinical stage information supplemented/modified by operative findings and gross and microscopic evaluation of the resected specimens.[48] pT entails a resection of the primary tumor 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

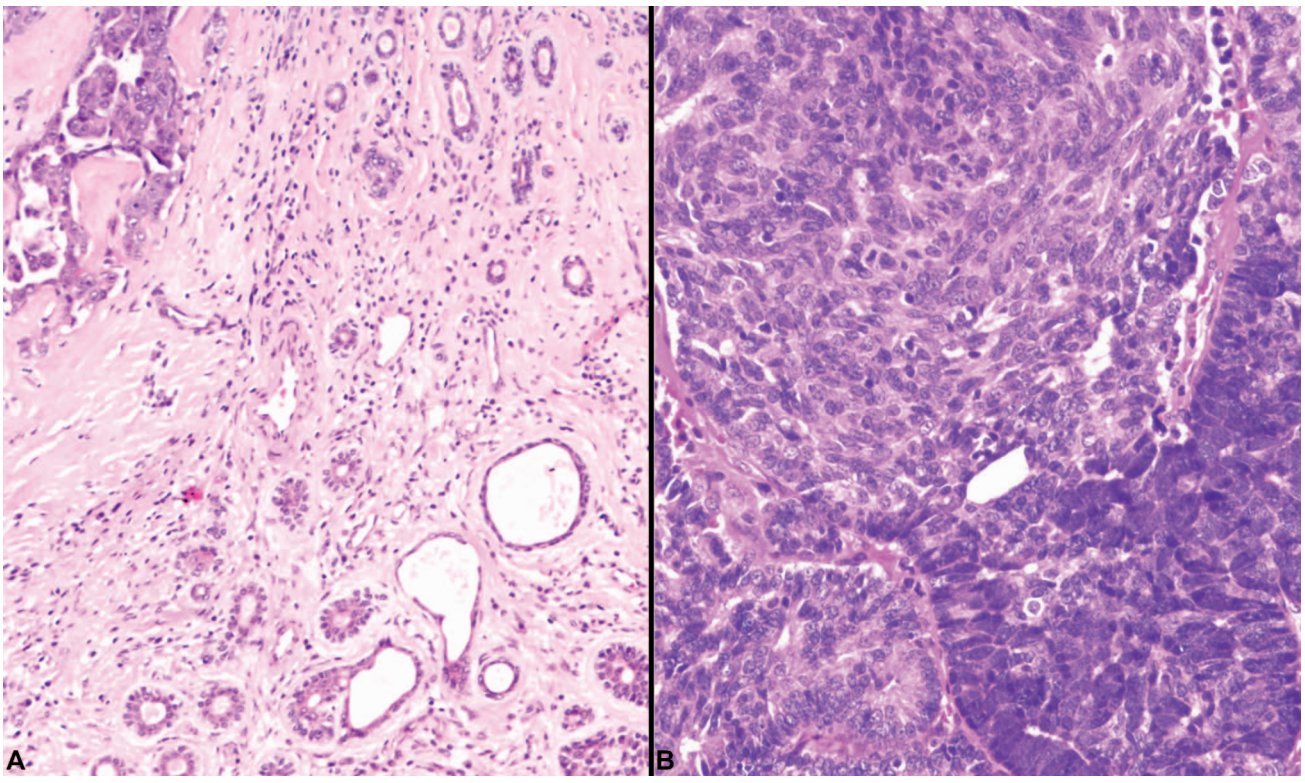


**Figure 6.** *High-grade transformation in salivary gland carcinomas. A, This tubular-patterned adenoid cystic carcinoma shows an abrupt transition to a pleomorphic adenocarcinoma, deviating profoundly from the monomorphic appearance of all patterns of conventional adenoid cystic carcinoma (upper left). B, This acinic cell carcinoma demonstrates high-grade transformation to a high-grade adenocarcinoma with streaming of nuclei. Residual acinar differentiation is noted at the bottom right (hematoxylin and eosin, original magnifications ×100 [A] and ×200 [B]).*

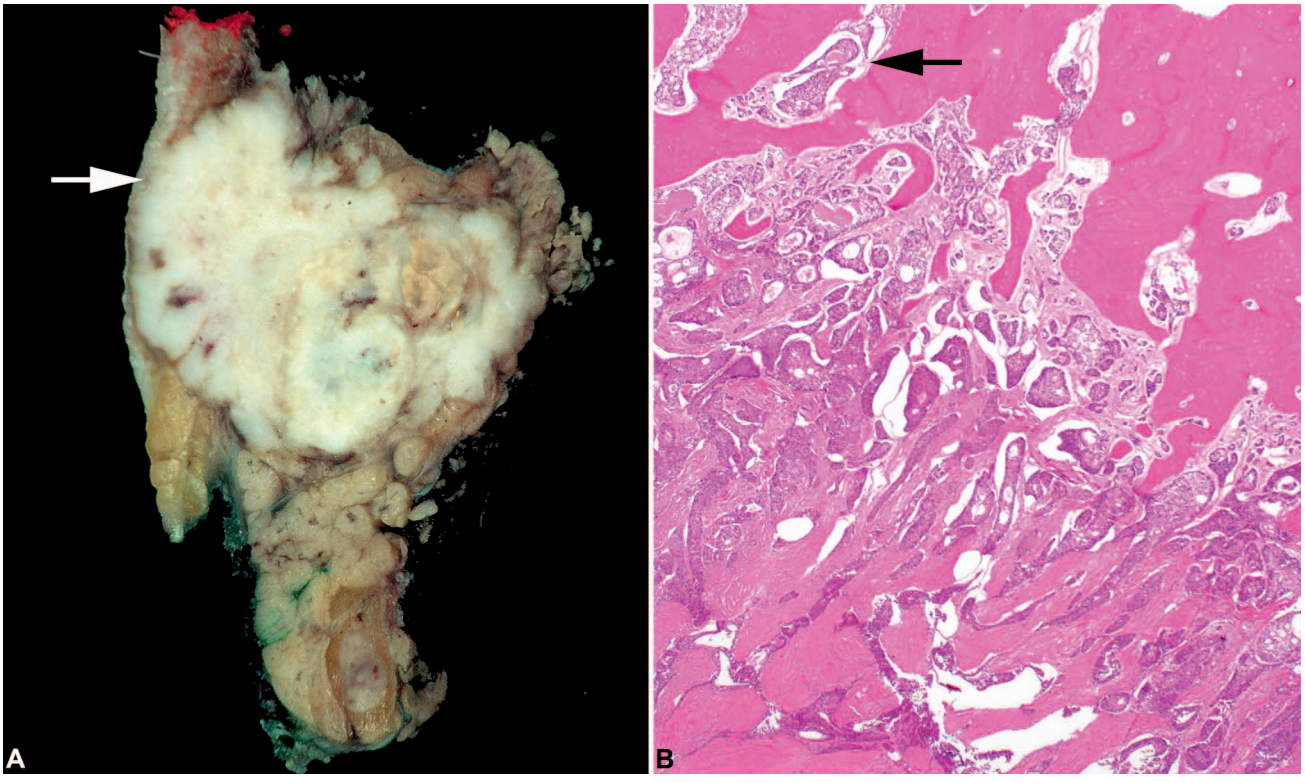


**Figure 7.** *Extent of invasion. A, This parotid salivary duct carcinoma shows dermal involvement (white arrow), and is thus considered pT4a, highlighting the importance of macroscopic examination for the documentation of staging parameters. B, This minor oral salivary gland high-grade (*MAML2 *translocated) mucoepidermoid carcinoma demonstrates mandibular bone invasion (black arrow), also warranting pT4a designation (hematoxylin-eosin, original magnification ×20).*

treatment during the initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (such as if it is technically impractical) and if the highest T and N categories or the M category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

### Noncore (Recommended) Elements

**Noncore Elements Derived From Core Elements.**—Certain core elements may benefit from a more detailed reporting, but this additional documentation is not adequately supported to justify core element status. These elements are discussed above and include: specifying the number of tumors in cases with multifocality; additional tumor dimensions aside from largest tumor dimension; salivary duct carcinoma variant documentation; distance of carcinoma component from tumor capsule in carcinoma ex pleomorphic adenoma; characterization of location (intratumoral versus extratumoral), degree (focal versus extensive), and size of nerves involved in perineural invasion; and specification of margins involved, closest margins, and distance from closest margins.

**Coexistent Pathology.**—For salivary gland carcinomas, nonneoplastic salivary gland pathology is of interest but not currently oncologically relevant. For some tumors, however, a tumor-associated lymphoid proliferation[49] may be mistaken for a lymph node, and this distinction is important for staging. For acinic cell carcinomas, those with a prominent tumor-associated lymphoid proliferation may actually be more indolent.[50]

**Ancillary Studies.**—Ancillary studies encompass histochemistry, immunohistochemistry, and molecular analysis. The main use of ancillary testing in salivary gland tumors is to refine diagnosis. Although there may be some prognostic and therapeutic applications, they are not yet strongly validated as a standard of care, and thus no ancillary study is currently required as a data element in salivary gland cancers.

Understanding of salivary gland cancer biology has increased tremendously and is largely characterized by a preponderance of chromosomal translocations that frequently define certain tumor 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 data set.[51] Alterations in benign tumors, such as pleomorphic adenoma and basal cell adenoma, may be retained in their malignant counterparts.

## CONCLUSIONS

Resection specimens from salivary gland cancers are usually straightforward, although the parotid microanatomy may be more nuanced, which in turn affects staging parameters. The major challenge, however, is the histologic diversity and, for some tumor types, grading and capturing the phenomenon of high-grade transformation. Carcinoma ex pleomorphic adenoma should be qualified by carcinoma type and extent. Developing internationally standardized data sets should simplify and unify the examination and reporting of these specimens. The ICCR Dataset Authoring Committee, composed of an international panel of experts, agreed on 12 core and 2 distinct noncore reporting elements as well as several noncore elements that derive from the core elements that are considered essential for the reporting of salivary gland cancers. With the goal of limiting recommended (core) reporting elements to those that are evidence based and agreed upon by the committee, the resulting data set remains a concise minimum data set. Ancillary testing is gaining prominence but is not yet part of core assessment. Consistency is improved by using a checklist, but comments are encouraged, particularly when there are unusual findings. Harmonization of existing data sets to develop a generic, evidence-based structured cancer reporting data set is the goal of the ICCR to facilitate comparison of data between countries, and this will be important for future research and benchmarking, especially in this arena of head and neck sites. Finally, there is a commitment to regularly review the ICCR data sets in line with revisions to the WHO classifications of tumors and updates to staging manuals.

The authors would like to express their appreciation for the sponsoring societies and organizations and give special thanks to Fleur Webster and Hannah B. Canlas for their exceptional organizational and editing contributions. The views expressed are those of the authors solely.

### References

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

2. Quer M, Guntinas-Lichius O, Marchal F, et al. Classification of parotidectomies: a proposal of the European Salivary Gland Society. *Eur Arch Otorhinolaryngol*. 2016;273(10):3307–3312.

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

4. Chen AM, Garcia J, Bucci MK, et al. Recurrent salivary gland carcinomas treated by surgery with or without intraoperative radiation therapy. *Head Neck*. 2008;30(1):2–9.

5. Nakhleh RE, Idowu MO, Souers RJ, Meier FA, Bekeris LG. Mislabeling of cases, specimens, blocks, and slides: a College of American Pathologists study of 136 institutions. *Arch Pathol Lab Med*. 2011;135(8):969–974.

6. Gnepp DR, Schroeder W, Heffner D. Synchronous tumours arising in a single major salivary gland. *Cancer*. 1989;63(6):1219–1224.

7. Kazakov DV. Brooke-Spiegler syndrome and phenotypic variants: an update. *Head Neck Pathol*. 2016;10(2):125–130.

8. Lydiatt WM, Mukherji SK, O'Sullivan B, Patel SG, Shah JP. Major salivary glands. In: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Chicago, IL: Springer; 2017:95–101.

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

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

11. El Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC; 2017.

12. Baddour HM Jr, Fedewa SA, Chen AY. Five- and 10-year cause-specific survival rates in carcinoma of the minor salivary gland. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):67–73.

13. Olarte LS, Megwalu UC. The impact of demographic and socioeconomic factors on major salivary gland cancer survival. *Otolaryngol Head Neck Surg*. 2014;150(6):991–998.

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

15. Griffith CC, Thompson LD, Assaad A, et al. Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma. *Histopathology*. 2014;65(6):854–860.

16. Schmitt NC, Sharma A, Gilbert MR, Kim S. Early T stage salivary duct carcinoma: outcomes and implications for patient counseling. *Otolaryngol Head Neck Surg*. 2015;153(5):795–798.

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

18. Brandwein M, Huvos AG, Dardick I, Thomas MJ, Theise ND. 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*. 1996;81(6):655–664.

19. Bell D, Bullerdiek J, Gnepp DR, Schwartz MR, Stenman G, Triantafyllou A. Pleomorphic adenoma. In: El-Naggar AK, Chan JK, Grandis JR, Ohgaki H, Slootweg P, eds. *WHO Classification of Tumours of the Head and Neck*. 4th ed. Lyon, France: IARC; 2017:185–186.

20. Fonseca I, Assaad A, Katabi N, et al. Polymorphous adenocarcinoma. In: El-Naggar AK, Chan JK, Grandis JR, Ohgaki H, Slootweg P, eds. *WHO Classification of Tumours of the Head and Neck*. 4th ed. Lyon, France: IARC; 2017:167–168.

21. Skalova A, Sima R, Kaspirkova-Nemcova J, et al. Cribriform adenocarcinoma of minor salivary gland origin principally affecting the tongue: characterization of new entity. *Am J Surg Pathol*. 2011;35(8):1168–1176.

22. Weinreb I, Zhang L, Tirunagari LM, et al. Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. *Genes Chromosomes Cancer*. 2014;53(10):845–856.

23. Weinreb I, Piscuoglio S, Martelotto LG, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. *Nat Genet*. 2014;46(11):1166–1169.

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

25. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary origin: clinicopathologic study of 204 patients. *Am J Surg*. 1982;144(4):423–431.

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

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

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

29. Brandwein MS, Ivanov K, Wallace DI, et al. Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading. *Am J Surg Pathol*. 2001;25(7):835–845.

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

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

32. Skalova A, Vanecek T, Majewska H, et al. 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*. 2014;38(1):23–33.

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

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

35. Frankenthaler RA, Luna MA, Lee SS, et al. Prognostic variables in parotid gland cancer. *Arch Otolaryngol Head Neck Surg*. 1991;117(11):1251–1256.

36. Smith BD, Haffty BG. Prognostic factors in patients with head and neck cancer. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. Philadelphia, PA: Lippincott Williams and Wilkins; 2009:51–75.

37. Erovic BM, Shah MD, Bruch G, et al. Outcome analysis of 215 patients with parotid gland tumors: a retrospective cohort analysis. *J Otolaryngol Head Neck Surg*. 2015;44:43.

38. Terhaard CH, Lubsen H, Van der Tweel I, et al. 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*. 2004;26(8):681–692; discussion 92–93.

39. Hosni A, Huang SH, Goldstein D, et al. Outcomes and prognostic factors for major salivary gland carcinoma following postoperative radiotherapy. *Oral Oncol*. 2016;54:75–80.

40. Mifsud MJ, Tanvetyanon T, McCaffrey JC, et al. Adjuvant radiotherapy versus concurrent chemoradiotherapy for the management of high-risk salivary gland carcinomas. *Head Neck*. 2016;38(11):1628–1633.

41. Tran L, Sadeghi A, Hanson D, et al. Major salivary gland tumors: treatment results and prognostic factors. *Laryngoscope*. 1986;96(10):1139–1144.

42. Vander Poorten VL, Balm AJ, Hilgers FJ, et al. The development of a prognostic score for patients with parotid carcinoma. *Cancer*. 1999;85(9):2057–2067.

43. Amini A, Waxweiler TV, Brower JV, et al. 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*. 2016;142(11):1100–1110.

44. Friedrich RE, Bleckmann V. Adenoid cystic carcinoma of salivary and lacrimal gland origin: localization, classification, clinical pathological correlation, treatment results and long-term follow-up control in 84 patients. *Anticancer Res*. 2003;23(2A):931–940.

45. Bjorndal K, Krogdahl A, Therkildsen MH, et al. 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*. 2015;51(12):1138–1142.

46. Seethala RR, Barnes EL, Hunt JL. 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*. 2007;31(1):44–57.

47. Mantsopoulos K, Velegrakis S, Iro H. Unexpected detection of parotid gland malignancy during primary extracapsular dissection. *Otolaryngol Head Neck Surg*. 2015;152(6):1042–1047.

48. Gress DM, Edge SB, Greene FL, et al. Principles of cancer staging. In: Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Chicago, IL: Springer; 2017:3–30.

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

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

51. Seethala RR, Stenman G. Update from the 4th edition of the World Health Organization Classification of Head and Neck Tumours: tumors of the salivary gland. *Head Neck Pathol*. 2017;11(1):55–67.

52. Seethala RR, Altemani A, Ferris RL, et al. *Carcinomas of the Major Salivary Glands, Histopathology Reporting Guide*. 1st ed. Sydney, Australia: International Collaboration on Cancer Reporting; 2018.

53. Bullock M, Beitler JJ, Carlson DL, et al. *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours, Histopathology Reporting Guide*. 1st ed. Sydney, Australia: International Collaboration on Cancer Reporting; 2018.