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

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• 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.

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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 Pathologistes, 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{2,5} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6} Rarely, multifocality in basal cell adenocarcinoma may raise the possibility of a *CYLD*-associated syndrome (such as Brooke-Spiegler syndrome).\textsuperscript{7}

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### World Health Organization Classification of Tumors of the Salivary Glands\textsuperscript{a}

| Descriptor | ICD-O Codes\textsuperscript{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 | 8020/3                          |
| Undifferentiated carcinoma | 8013/3                          |
| Large cell neuroendocrine carcinoma | 8041/3                          |
| Small cell neuroendocrine carcinoma | 8013/3                          |
| Lymphoepithelial carcinoma | 8082/3                          |
| Squamous cell carcinoma | 8070/3                          |
| Oncocytic carcinoma | 8290/3                          |
| Uncertain malignant potential |                               |
| Sialoblastoma | 8974/1                          |

**Abbreviation:** NOS, not otherwise specified.

\textsuperscript{a} Reproduced with permission from the World Health Organization/International Agency for Research on Cancer.\textsuperscript{11}

\textsuperscript{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.\textsuperscript{8,9} Tumor measurement should be performed macroscopically on the fresh specimen because formalin fixation may cause tumor shrinkage.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{12} 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.\textsuperscript{13,16}

Carcinoma ex pleomorphic adenoma is subclassified by type and extent of invasion. Noninvasive cancers are
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. 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. The metastasizing pleomorphic adenoma, despite its aggressive behavior, is not included in the data set reporting because it is a benign tumor.

In the 2017 WHO Classification of Head and Neck Tumours, cribriform adenocarcinoma of (minor) salivary gland origin is a subcategory of polymorphous adenocarcinoma. 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...
growth rather than a targetoid fascicular pattern seen in classic polymorphous adenocarcinoma.21 Cribriform tumors tend to demonstrate translocations involving the \textit{PRKD} family of genes22 rather than the \textit{PRKD1} point mutations23 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 (i.e., 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).
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 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 X40).
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 (intra-tumoral 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 may be misinterpreted as benign lymphoid proliferation. For acinic cell cancers, those with a prominent tumor-associated lymphoid proliferation may actually be more indolent.

Ancillary Studies.—Ancillary studies encompass histology, 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. 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.

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