Salivary gland neoplasms: diagnostic approach with focus on patterns of recognition and useful ancillary tools☆

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Abstract

Salivary gland neoplasms are rare, yet histologically diverse, posing a diagnostic challenge to many practicing pathologists. The current World Health Organization (WHO) 4th edition of head and neck tumors recognizes 31 types of unique salivary gland epithelial neoplasms, including 20 malignant and 11 benign entities. Adopting a systematic diagnostic approach with a focus on patterns of recognition is the key to accurately diagnosing these tumors. Immunohistochemistry and molecular tools can assist in making the correct diagnosis, especially when faced with overlapping morphology. In this review, we explore the utility of various immunohistochemistry and molecular diagnostic tools and outline helpful approaches in diagnosing salivary gland neoplasms.

Keywords immunohistochemistry; pleomorphic adenoma; salivary gland neoplasm

The 4th edition of World Health Organization (WHO) classification recognizes 31 unique types of salivary gland epithelial neoplasms,[1] many of which share certain morphologic and immunophenotypic similarities. A systematic diagnostic approach encompassing patterns of recognition and utilization of common immunohistochemistry (IHC) and molecular ancillary tests may assist in reaching the correct diagnosis of these tumors.

Histologic features of salivary gland neoplasms: a general approach

Salivary glands are composed of acini and ducts that include intercalated, striated and excretory ducts. While the acini and intercalated ducts are surrounded by myoepithelial cells, the striated and excretory ducts are outlined by basal cells. Immunophenotypically, myoepithelial cells are positive for basaloid markers (p63 and p40) as well as myoepithelial markers such as smooth muscle actin (SMA), S100 and calponin. Basal cells are positive for high molecular weight cytokeratins, p63 and p40, but lack immunoexpression of myoepithelial-specific markers (SMA and calponin).

Overall, there are some morphologic and immunophenotypic similarities between salivary gland neoplasms and normal salivary gland structures and such correlation can be helpful to understand the morphologic classifications of these tumors. Therefore, analyzing tumor cell types and architectural patterns in a salivary gland tumor can be helpful to reach the correct diagnosis. Generally, salivary gland neoplasms can be divided into five broad morphologic categories[1]: tumors with specialized acinar differentiation recapitulating acini, i.e. acinic cell carcinoma (AciCC)[2]; tumors with biphasic ductal and myoepithelial differentiation recapitulating intercalated ducts, including pleomorphic adenoma (PA), basal cell adenoma (BCA), intercalated duct adenoma, carcinoma ex-PA (CA ex-PA), epithelia-myoepithelial carcinoma (EMA), adenoid cystic carcinoma (ACC) and basal cell adenocarcinoma (BCAC)[3]; tumors with oncocytic features mimicking striated ducts, including oncocytoma and Warthin tumor[4]; tumors with epidermoid and glandular features similar to the excretory ducts, including salivary duct carcinoma (SDC), clear cell carcinoma (CCC), adenocarcinoma not otherwise specified (NOS) and mucoepidermoid carcinoma (MEC); and[5] tumors with predominantly myoepithelial (abluminal cell) or modified myoepithelial differentiation, such as polymorphous adenocarcinoma (PAC), myoepithelioma and myoepithelial carcinoma.

When evaluating malignancy in a salivary gland tumor, the first step is to assess the tumor borders for invasion (Figure 1). With a few exceptions, most benign neoplasms are well-circumscribed or encapsulated and lack invasion into the surrounding tissue. Carcinomas, on the other hand, typically exhibit clear evidence of invasion, either as infiltrative islands or as expansile lobules with pushing borders, sometimes associated with lymphovascular and perineural spread. The exceptions to the above assessment are PA and nodular oncocytic hyperplasia as benign conditions with infiltrative borders, and intracapsular CA ex-PA as a malignant tumor with well-circumscribed contour.

PA is probably the only benign salivary gland neoplasm that may exhibit irregular peripheral borders with lobulated protrusions (also called pseudopods) or focal infiltration into the adjacent normal salivary gland tissue. Moreover, recurrent pleomorphic adenoma often presents with numerous miliary nodules in the surgical bed (Figure 2). Nodular oncocytic hyperplasia, also called oncocytosis or nodular oncocytosis, is a non-neoplastic condition that occurs exclusively in the parotid gland. It is characterized by multifocal and often bilateral nodular growth of oncocytic proliferation scattered within the normal parotid gland.[1] Carcinoma ex-pleomorphic carcinoma (CA ex-PA), defined as a carcinoma that arises in association with a PA, is subclassified into intracapsular, minimally invasive or invasive based on the extent of invasion of the malignant component beyond the capsule of the pre-existent PA.[1] By definition, the malignant component in intracapsular CA ex-PA is confined within the pre-existing PA showing no invasion outside the tumor capsule. Rarely, malignant low grade salivary gland neoplasms such as AciCC and MEC exhibit well defined tumor borders; nevertheless, the diagnosis is usually straight forward in

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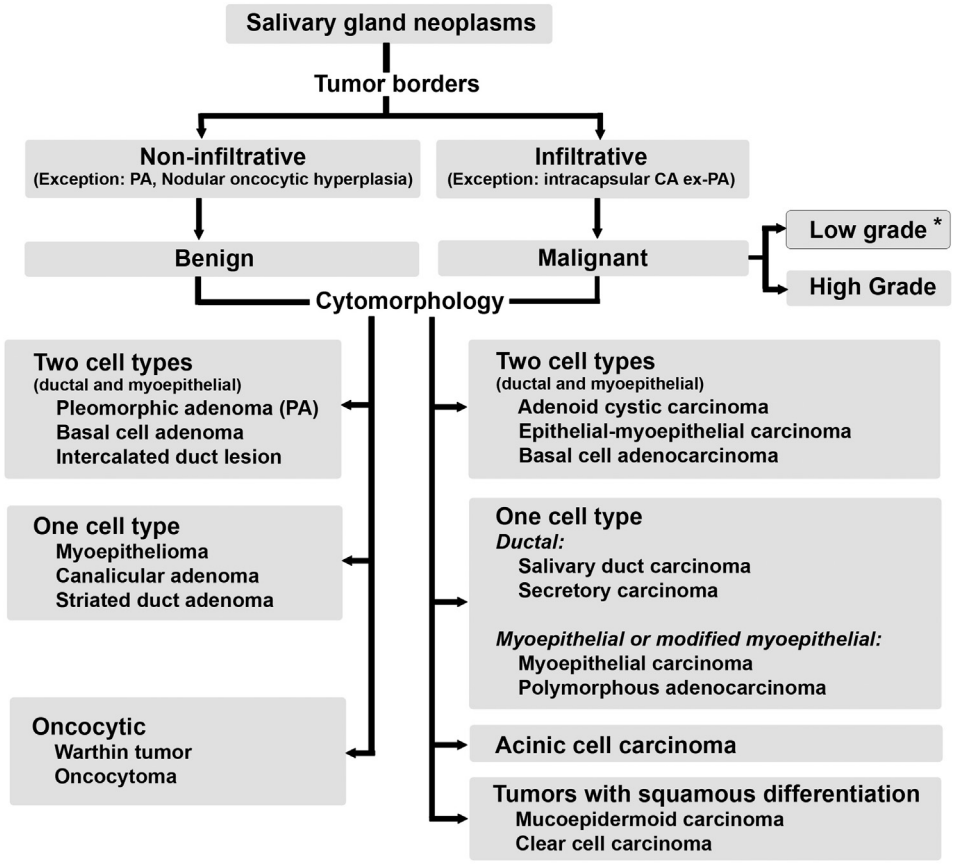

Figure 1 General diagnostic approach for salivary gland neoplasms based on tumor infiltration and cellular distribution. PA: pleomorphic adenoma; CA ex-PA: carcinoma ex-pleomorphic adenoma. *Mucoepidermoid carcinoma has a three-tiered grading scheme (i.e. low, intermediate and high grades).

these cases, as the tumor morphology is commonly typical and diagnostic of the specific tumor type.

After tumor assessment for invasion, the next step is to classify the salivary gland tumor based on its cellular composition, as stated above, in order to pinpoint the differential diagnosis (Figure 1). For example, benign tumors may contain two cell types (e.g. PA, BCA and intercalated duct adenoma), one cell type (e.g. myoepithelioma, canalicular adenoma and striated duct adenoma), or predominantly oncocytic cells (e.g. Warthin tumor and oncocytoma). Similarly, carcinomas may also be divided into several broad categories, including 1) biphasic tumors e.g. ACC, EMC and BCAC; 2) carcinoma with predominantly one cell type, either ductal (e.g. SDC and secretory carcinoma (SC)) or myoepithelial (e.g. myoepithelial carcinoma and PAC); 3) tumor with acinar differentiation, i.e. AciCC; and 4) carcinoma with squamous differentiation, e.g. CCC and MEC (Figure 1). When a malignant tumor is unclassifiable, bares glandular features and does not exhibit features of any specific tumor type, one can classify it as "adenocarcinoma NOS". In the WHO of 2017, adenocarcinoma NOS includes intestinal type adenocarcinoma and adenocarcinoma with various cystic formations (i.e. cystadenocarcinoma).

Moreover, when possible, a histologic grade should be assigned to the salivary gland carcinoma. Malignant tumors are typically graded based on their architectural and cytomorphologic features. Histologic grading is a significant predictor for outcome in salivary gland tumors. Furthermore, tumors are treated differently depending on their grade, with low grade tumors typically treated by surgery with appropriate margins, whereas additional treatments, e.g. neck lymph node dissection, adjuvant chemotherapy and adjuvant radiation therapy, may be considered for high grade carcinomas.[1] In some cases, the specific carcinoma type designates the histologic grade. For example, SDC is by default high grade and is typically associated with high grade histologic features including tumor necrosis, increased mitoses and an aggressive clinical behavior with a 5-year survival of less than 50%.[2–5] In contrast, EMC, SC and AciCC are generally considered to be low grade carcinomas as they usually exhibit bland cytologic features, infrequent mitoses, absence of necrosis and an overall indolent clinical course.[1,6–8] Rare cases of high grade transformation (HGT) have been documented in various types of (low grade) salivary gland carcinoma. The histologic features and clinical implication of HGT will be discussed in the companion review.

The two most commonly graded salivary gland carcinomas are MEC and ACC. MEC has its designated three-tiered grading system. Different grading systems have been reported including Armed Forces Institute of Pathology (AFIP), Brandwein, and Memorial Sloan Kettering Cancer Center (MSKCC) systems; nevertheless, the tumor is generally graded into low, intermediate and high grade which encompasses a combination of cytomorphologic features. While low-grade MEC is well-

