Salivary Gland Tumors
Current Concepts and Controversies

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KEYWORDS

• Salivary gland • Translocations • Molecular • Correlative • Neoplasia • Classification

Key points

- Biphasic salivary gland tumors are a common category of tumors with morphologic overlap between entities; combined morphologic and immunohistochemical approaches are often needed to resolve diagnostic considerations.
- Mammary analogue secretory carcinoma is a new and distinctive entity characterized by an ETV6-NTRK3 translocation; differential diagnosis is varied but includes acinic cell carcinoma and low-grade intraductal carcinoma.
- Polymorphous low-grade adenocarcinoma and cribriform adenocarcinoma of (minor) salivary gland origin are related entities with differing clinicopathologic profiles despite overlap; they are the subject of an ongoing taxonomic debate.

ABSTRACT

This current review focuses on current concepts and controversies for select key salivary gland epithelial neoplasms. Rather than the traditional organization of benign and malignant tumors, this review is structured around select key topics: biphasic tumors, mammary analogue secretory carcinoma, and the controversy surrounding polymorphous low-grade adenocarcinoma and cribriform adenocarcinoma of (minor) salivary gland origin.

OVERVIEW

Despite their diversity, salivary gland tumors are rare, with fewer than 15 cases per 100,000 individuals annually.[1] Most (75%–85%)[2–4] are benign; salivary carcinomas comprise less than 0.5% of all cancers, and only ~6% of head and neck cancers. Each salivary gland entity has distinctive clinical, morphologic, and immunophenotypic characteristics necessitating accurate classification. The histologic overlap between many entities, including both benign and malignant neoplasms, adds considerably to the diagnostic challenge for surgical pathologists. However, morphologic characterization of both old and novel salivary gland tumors has been refined over the past several years. In addition, immunohistochemical markers, which have the historical reputation of adding more confusion to salivary tumor diagnosis, have evolved into highly useful supplementary aides to visualization of cell compartments and cell populations, thus benefitting salivary gland tumor taxonomy. Immunohistochemistry also has an expanding role as a surrogate marker of molecular alterations. Still evolving is the role of molecular diagnostics and theranostics in salivary gland tumors. Many monomorphic salivary gland tumors are now known to harbor defining balanced translocations, some of which are readily testable on paraffin-embedded materials either by fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or next-generation sequencing. In contrast, pleomorphic salivary gland tumors often show complex molecular alterations that are now beginning to have therapeutic implications. The advent

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of molecular testing in salivary gland tumors has not only improved classification overall but has enabled refinements of morphologic criteria used to ensure purity in a given category. However, it has been a source of controversy for some tumor types. The basic and comprehensive clinicopathologic characteristics of salivary gland tumors have been well detailed in the prior iteration of this issue.[5,6] This article focuses on key diagnostic issues.

BIPHASIC SALIVARY GLAND TUMORS

Biphasic salivary gland tumors are tumors composed of luminal ductal cells and abluminal basal/myoepithelial cells. Integral to these tumors is a bilayered arrangement of these components, although they may vary in proportion. This bilayered appearance is readily noticeable on light microscopy, and can be accentuated by immunostains (summarized in **Table 1**). Low-molecular-weight keratin immunostains highlight luminal ductal cells intensely and show variable to negative staining in the abluminal myoepithelial components. High-molecular-weight keratins show an opposite profile with preferential staining of myoepithelial components. p63 and ΔNp63 (p40) highlight basal/myoepithelial cells. Muscle markers are restricted to purely to myoepithelial cell types. Markers of intercalated/terminal duct phenotype, such as S100 and SOX10, highlight both ductal and myoepithelial cell types to varying degrees. DOG1 is more variable but may stain both cell types as well. The prototypical biphasic tumors include pleomorphic adenoma, basal cell adenoma/adenocarcinoma, epithelial-myoepithelial carcinoma (EMCA), adenoid cystic carcinoma, and Warthin tumor, which are not discussed here.

PLEOMORPHIC ADENOMA (BENIGN MIXED TUMOR)

INTRODUCTION

Pleomorphic adenoma (PA) remains the most common salivary gland epithelial tumor, in both adults and children, and comprises one-half to two-thirds of all benign salivary gland tumors.[2,4] It predominates in the parotid (~80%), but can be seen at any salivary site. Tumors usually occur in the fourth to fifth decade with a small female predilection. Little is known about the cause of PA. The notable risk factor is a prior history of radiation exposure.[7] PAs show translocations involving 12q13-15[8] or 8q12[9] in 40% to 70% of PAs involving *HMGA2* (12q13-15) and *PLAG1*

Table 1
Basic immunohistochemical staining profile for biphasic tumors

Immunomarkers	Staining Pattern
Low-molecular-weight cytokeratins	Luminal ductal cells: strongly positive Abluminal myoepithelial/basal cells: variable to negative
High-molecular-weight cytokeratins	Luminal ductal cells: variable to negative Abluminal myoepithelial/basal cells: strongly positive
p63	Luminal ductal cells: variable to negative Abluminal myoepithelial/basal cells: strongly positive
ΔNp63	Luminal ductal cells: negative Abluminal myoepithelial/basal cells: strongly positive
Muscle markers (calponin, smooth muscle actin, smooth muscle myosin heavy chain)	Luminal ductal cells: negative Abluminal myoepithelial/basal cells: positive only in myoepithelial cells
S100	Luminal ductal cells: variable in intercalated duct type cells, otherwise negative Abluminal myoepithelial/basal cells: variably positive
SOX10	Luminal ductal cells: positive Abluminal myoepithelial/basal cells: positive Acini: positive
DOG1	Luminal ductal cells: weakly to moderately positive, intercalated duct type cells only, apical luminal pattern Abluminal myoepithelial/basal cells: variable Acini: strongly positive apical, complete membranous staining in acinic cell carcinoma