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Review Article

# A review: Immunological markers for malignant salivary gland tumors

*P.C. Anila Namboodiripad**

*Professor and Head, Department of Oral and Maxillofacial Pathology, PSM Dental College, Akkikav Post, Byepass Road, Thrissur, Kerala, India*

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ABSTRACT

Salivary gland cancers are rare. Around 8 out of 10 salivary gland tumors (80%) are in the parotid. Just fewer than 2 out of 10 salivary gland cancers develop in the other two salivary glands – the submandibular or sublingual glands. Fewer than 1 in 10 cancers start in the minor salivary glands. There are many different types of salivary gland cancers. The most common is mucoepidermoid carcinoma (MEC). Just over 3 out of 10 (25–35%) salivary gland cancers (SGT, SGC) are of this type. The others include adenoid cystic carcinoma (ACC), acinic cell carcinoma, carcinoma ex-pleomorphic adenoma (Ca-PA), polymorphous low grade adenocarcinoma (PLGA) and some newly discovered salivary gland tumors. Because of the infrequency of salivary gland tumors and their complex histopathological diagnosis, it is difficult to exactly predict their clinical course by means of its recurrence, malignant progression or metastasis. Salivary gland tumors always pose problems in diagnosis.

This review provides an insight into the recent concepts and immunohistochemical markers to diagnose the malignant salivary gland tumors (SGT), thus guiding the Ear, Nose and Throat specialists, Oral and Maxillofacial Surgeons, General Pathologists and other medical and dental specialists thereby enabling them to make correct diagnosis and provide the appropriate treatment.



## 1. Review

### 1.1. *Introduction to salivary gland malignancies*

Salivary gland neoplasms are a rare group of tumors; the annual incidence rate is 1 in 100,000, comprising about 3% of all head and neck neoplasms. These tumors are rare, with an overall incidence of approximately 2.5 cases–3 cases per 100,000 per year in the Western world. Salivary gland tumors account for about 5% of all neoplasms of the head and neck.[1]

Cancer of the salivary gland usually develops in the largest of the salivary glands – the parotid glands around 75% of which only about 20% are malignant, 15% are located in minor salivary glands of the upper digestive tract. 10% arise in the submandibular glands, and less than 1% presents in the sublingual glands.

* Tel.: +91 9567603129.
E-mail addresses: anillasuresh@gmail.com, anilla93@yahoo.co.in.
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## 2. Etiology

The etiology of SGTs is so far unknown. Putative risk factors include cigarette smoking, viral infections, rubber manufacturing workers, genes etc. The only well-established risk factor is ionizing radiation. Atomic bomb survivors and patients undergoing radiation therapy have a substantially higher risk of developing SGTs.[2]

Most patients with malignant tumors of the major or minor salivary glands present with painless swelling, paresthesia or anesthesia.

## 3. Normal histology of acini of salivary gland

Salivary gland tumors represent the most heterogeneous group of tumors of any tissue in the body. Although almost 40 histological types of SGTs exist, some are exceedingly rare. The entire glandular structure of the salivary gland is said to exhibit a two-tiered organization comprising luminal cells (acinar and ductal cells) and abluminal cells (myoepithelial and basal cells).[1]

The luminal cell from normal salivary glands has the following antigen profile:

- the acinar cells are intensely positive to cytokeratins with low molecular weight, weak positive for cytokeratins with high molecular weight, intense positive to Amylase, weakly positive for Lactoferrin, Lysosyme, Carcinoembryonic Antigen (CEA), negative to Epithelial Membrane Antigen (EMA), Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of intercalated ducts is intensely positive to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, intense positive to EMA, Lactoferrin, Lysosyme, weakly positive for CEA and SC, and negative for Amylase, Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of striated ducts shows intense positivity to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, moderately positive for S-100, weak positive to SC and negative for Lactoferrin, Lysosyme, CEA, EMA, Amylase, Vimentin, Actin, Myosin, Alkaline Phosphatase (AP) and ATP-ase;
- the luminal cell of excretory ducts is intensely positive to cytokeratins with high molecular weight, negative to cytokeratins with low molecular weight, moderate positivity for EMA, weakly positive to SC and negative to Lactoferrin, Lysosyme, CEA, Amylase, Vimentin, Actin, Myosin, S-100, Alkaline Phosphatase (AP) and ATP-ase.[3,4]

Although hematoxylin-eosin staining is still the gold standard method used for diagnosis, immunohistochemistry (IHC) can enhance the accuracy of the diagnosis.[5] They can help in differentiating between luminal and abluminal cells (Table 1) and can help in understanding the complex architecture of SGTs and aid in diagnosis.[1,3]

All four cells are usually pan-cytokeratin (CK) [AE1/AE3]-positive; and S-100 protein staining is variable. Both ductal and acinar cells are epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA)-positive, while only acinar cells are α-amylase-positive. Myoepithelial and basal cells are CK14 and p63-positive and are EMA and CEA-negative; the expression of α-smooth muscle actin (SMA), muscle specific actin (MSA), calponin, podoplanin and vimentin are only observed in myoepithelial cells.[4,5]

Abluminal cells are detected for high molecular weight CK (such as E12 or CK14) and myoepithelial cells. In addition, they are stained with antibodies against myoid proteins (such as muscle specific actin, smooth muscle actin or calponin). Another myoepithelial marker is maspin, a serine protease inhibitor that functions as a tumor suppressor and is seen in tumors where both myoepithelial and basal cells are affected such as PA, basal cell adenoma, ACC and epithelial-myoepithelial carcinoma where maspin expression was high. Low proportions were seen in salivary duct carcinomas. Ductal cells are usually negative or show only weak focal immunoreactivity for maspin.[5]

CEA (whose functions include signal transduction, cooperation with proto-oncogenes in cellular transformation and inhibition of proliferation of epithelial tumors) immunoreactivity was usually detected in the cytoplasm of epithelial cells and luminal contents of neoplastic glands.[4]

Adenoid cystic carcinoma (Tables 2a and 3).

ACC occurs due to neoplastic transformation of salivary acinar-type cells and myoepithelial cells and commonly arises in parotid glands and frequently produces a mucinous or basement membrane-like extracellular matrix.

It is a slow-growing tumor with a poor prognosis in long standing cases.[6,18] The underlying cause of ACC is unknown. It is neither inherited nor associated with smoking or alcohol consumption. It may be the result of genetic alteration, a new fused gene (MYB-NFIB) created by the fusion of two broken chromosomes (numbers 6 and 9).[2,7] The most common site of metastatic spread of ACC is to lungs, liver and bone.[18]

Adenoid cystic carcinoma is characterized by a [t (6; 9) (q22-23; p23-24)] translocation of head and neck[19] and the breast.[5,6]

**Table 1 – Immunohistochemical markers for malignant salivary glands.**

| Antigen | Luminal cells | | Abluminal cells | |
|---|---|---|---|---|
| | Acinar | Ductal | Myoepithelial cells | Basal cells |
| CK[AE1/AE3] [Pan-cytokeratin][5] | +ve | +ve | +ve | +ve |
| EMA,CEA[5] | +ve | +ve | −ve | −ve |
| α-amylase-positive[5] | +ve | −ve | | |
| CK14[6] | | | +ve | +ve |
| p 63[5] | | | +ve | +ve |
| α-smooth muscle actin (SMA),[5] Muscle specific actin (MSA)[5] | | | | |
| Calponin[6] | | | +ve | −ve |
| Podoplanin[5] | | | +ve | −ve |
| Vimentin[5] | | | +ve | −ve |
| S-100[4] | Variable | Variable | Variable | Variable |