

MORPHOLOGICAL SUBTYPES OF BENIGN TUMORS OF THE SALIVARY GLANDS: MODERN CONCEPTS

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Abstract: Benign salivary gland tumors represent a heterogeneous group of neoplasms that differ in morphological characteristics, cellular composition, and clinical behavior. This review article discusses current concepts regarding the morphological subtypes of benign salivary gland tumors, including pleomorphic adenoma, monomorphic adenomas, Warthin's tumor, and oncocytoma. Special attention is given to histological features, immunohistochemical markers, and differential diagnosis, which play a crucial role in verifying the diagnosis and determining treatment strategies. Modern morphological diagnostic methods, including histological analysis, immunohistochemistry, and molecular genetic studies, are reviewed as essential tools for accurately distinguishing between benign and malignant processes.

Key words: benign salivary gland tumors, morphology, histological classification, immunohistochemistry, pleomorphic adenoma, Warthin's tumor, oncocytoma.

Introduction. Benign salivary gland tumors are a heterogeneous group of neoplasms characterized by various morphological features and clinical course. Despite their relatively favorable prognosis, these tumors require careful diagnostics, since some of them have a tendency to recurrence and, in rare cases, to malignancy. Studies show that in approximately 70% of cases they are benign, primarily affecting the parotid gland and minor salivary glands [31,34]. The most common benign tumor of the salivary glands is pleomorphic adenoma, which can exhibit significant morphological diversity, which complicates its differential diagnosis. In addition, there are less common forms, such as basal cell adenoma, canalicul adenoma, myoepithelioma, oncocytoma and papillary cystadenolymphoma (Warthin's tumor). Each of these varieties has specific histological and immunohistochemical characteristics, which necessitates their detailed study [1,6,12].

In recent years, there has been significant progress in the field of morphological diagnostics of salivary gland tumors, due to the development of immunohistochemical and molecular genetic methods. This, in turn, increases the importance of complex morphological analysis of these neoplasms for the correct choice of treatment tactics and prognostic assessment.

Purpose. This review article aims to systematize modern data on morphological subtypes of benign salivary gland tumors, taking into account their histological, immunohistochemical and molecular characteristics.

Results. Modern diagnostics of benign tumors of the salivary glands is based on a comprehensive approach, including clinical, morphological, histochemical and molecular genetic analysis.

At the primary stage of diagnostics, a key role is played by histological examination of biopsy or surgical material, which allows determining the tumor architecture, cellular composition and nature of stromal components. However, given the morphological heterogeneity of some subtypes, exclusively traditional histology does not always allow for accurate differential diagnostics [3,7].

Immunohistochemical methods are becoming more important, which allow detecting the expression of specific proteins characteristic of certain cell types. For example, markers of myoepithelial differentiation (S-100, GFAP, p63) are typical for pleomorphic adenoma, while Warthin's tumor is characterized by pronounced expression of cytokeratins and lymphoid markers [17].

Additionally, in complex diagnostic cases, molecular genetic analysis is used to identify characteristic mutations and chromosomal rearrangements. For example, detection of *PLAG1* or *HMGA2* translocation is a significant diagnostic criterion for pleomorphic adenoma [9]. Benign salivary gland tumors (BSG) make up a significant portion of neoplasms in this location, demonstrating a relatively favorable course. According to epidemiological data, they make up from 50% to 80% of all salivary gland tumors, with the largest number of cases being pleomorphic adenoma, which is the most common type of benign neoplasm [11].

Most often, tumors affect the parotid salivary glands, which is explained by their anatomical and physiological features. The parotid gland is involved in the pathological process in approximately 60-70% of cases, while neoplasms of the submandibular and minor salivary glands are much less common. In addition, an age predisposition is noted: the peak incidence is at 40-60 years, although there are cases in young patients [13].

Gender differences in morbidity vary depending on the specific tumor subtype. For example, pleomorphic adenoma is more often diagnosed in women, while Warthin's tumor, on the contrary, predominates in men, which is probably due to the impact of external factors, including smoking.

The histological diversity of DOSG significantly complicates diagnostics: to date, more than 33 different types of these neoplasms have been identified. Advances in imaging and biopsy techniques, in particular the use of fine-needle aspiration biopsy, have contributed to increased diagnostic accuracy and more precise determination of the morphological subtype of the tumor [2,14,36]. In accordance with the morphological features of benign salivary gland tumors, their classification is also carried out, which makes histological and immunohistochemical studies the most important diagnostic methods. Based on the tumor architectonics, the type of cellular composition and stromal component, the main types are distinguished: pleomorphic adenoma, basal cell adenoma, canaliculoma, myoepithelioma, oncocytoma, papillary cystadenolymphoma. Nevertheless, given the large morphological diversity of these tumors, in some cases additional diagnostic methods are required, with immunohistochemical research playing a special role. Thus, pleomorphic adenoma is characterized by expression of myoepithelial differentiation markers: S-100, GFAP, p63 [4]. Warthin's tumor is characterized by high expression of cytokeratins CK7 and CK19, as well as a lymphoid component, which suggests its clear differentiation [35]. Expression of oncocytic markers and mitochondrial proteins, CD117 in oncocytoma, as well as analysis of expression of basement membrane proteins β -catenin, collagen IV in basal cell adenoma also play an important diagnostic role [28,29,30]. For most BSGA, the main method of treatment is surgical resection, which, as a rule, ends favorably. Depending on the location and size of the tumor, as well as the risk of recurrence, the optimal surgical tactics are chosen. However, despite the prevalence of DOSZH, there remains the possibility of an erroneous diagnosis or detection of a malignant process, therefore, for a more detailed and careful study of the problem, it is advisable to conduct further research [3].

Pleomorphic adenoma is the most common benign tumor of the salivary glands, accounting for 60-70% of cases of neoplasms in this localization. The frequency of detection is highest at the age of 30-60 years. In the vast majority of cases, the tumor affects the parotid salivary gland, less often it is diagnosed in the submandibular and minor salivary glands [24]. Clinically, pleomorphic adenoma manifests itself as a slowly growing painless node of dense consistency with clearly defined boundaries. Due to its benign nature, the tumor remains asymptomatic for a long time, however, increasing in size, it can cause a cosmetic defect and compression of surrounding tissues. Despite the benign course, PA is characterized by a tendency to relapse, especially after non-radical removal. In rare cases, carcinoma may develop, which emphasizes the need for timely diagnosis and adequate treatment. Morphologically, pleomorphic adenoma is a mixed tumor containing both epithelial and myoepithelial cells, as well as a stromal component of varying composition. Its name is due to its high histological variability. The tumor node may contain areas of glandular, solid, trabecular, myxoid, chondroid, and even hyaline tissue. The epithelial component is formed by cells with varying degrees of differentiation, capable of forming tubular, glandular, or solid structures. Myoepithelial cells are very polymorphic and can have a stellate, spindle-shaped, or plasma-like shape. The stroma also plays

an important role in the formation of the tumor morphotype. It is the high degree of heterogeneity of the cellular and stromal composition that creates difficulties in diagnosing PA and requires a differentiated approach. Immunohistochemical studies play a key role in confirming the diagnosis of pleomorphic adenoma. Tumor cells express markers S-100, GFAP, p63, CK7, which indicate epithelial and myoepithelial differentiation. Of particular importance is also the assessment of the proliferative activity of the tumor using the Ki-67 marker, the expression level of which in PA usually does not exceed 5-10% [8,22,23].

Immunohistochemical analysis allows not only to clarify the morphological subtype of the tumor, but also differentiates it from other neoplasms, including adenomas, meioepitheliomas and even poorly differentiated carcinomas. The prognosis of PA is generally favorable. However, the long-term existence of uncertainty increases the risk of its malignant degeneration. Malignant degeneration of the tumor is noted in 3-5% of cases, and it is characterized by an aggressive course, as well as invasive growth and metastasis [25]. Monomorphic adenomas are the second large group of benign tumors of the salivary glands, homogeneous cellular structures that do not have an obvious stromal component inherent in pleomorphic adenoma. This group includes basal cell adenoma, canaliculic adenoma and myoepithelioma with their own morphological features, clinical localization and course [10,16]. Basal cell adenoma is a rare tumor, forming less than 2% of all neoplasms of the salivary glands, and occurring mainly on the parotid salivary gland at the age of 50 years. Histologically, BCA is small basaloid cells with hyperchromic nuclei. They are organized into dense islets, trabeculae or tubular structures. The underlying tumor, pleomorphic adenoma, has a similar structure. However, unlike it, BCA does not show manifestations of the myxoid or chondroid stromatous component, which quite clearly differentiates them by histological type [15].

Canaliculic adenoma is a rare benign neoplasm often found in minor salivary glands, mainly in the upper lip and buccal mucosa. This disease is most often found in elderly patients, mainly in women.

Histologically, in most cases, CA is characterized by elongated columnar cells, narrow channels that are lined with a single-layer epithelium. The absence of cellular atypia and a low proliferation index indicate the benign nature of the tumor. Canaliculic adenoma clinically presents itself as a small, dense node. In rare cases, multiple tumor nodes are possible. The treatment method is surgical excision, after which relapses are extremely rare [19,26].

Myoepithelioma is a salivary gland tumor that arises from myoepithelial cells; it accounts for less than 1% of all salivary gland neoplasms. It can affect both major and minor salivary glands. Microscopically, myoepithelioma is characterized by a predominance of myoepithelial cells of various shapes, including plasmacytoid, spindle, epithelioid, and stellate, which form solid, trabecular, or reticular growth patterns. Myoepithelioma lacks a glandular component, which distinguishes it from pleomorphic adenoma. Clinically, myoepithelioma appears as a slow-growing painless mass similar to other salivary gland neoplasms. An "invasive" growth pattern may rarely develop, making complete surgical removal difficult. Despite the benign natural history, some types of myoepithelioma may recur, especially with incomplete removal [20,33]. Warthin's tumor, or papillary cystadenolymphoma, is a benign tumor of the salivary glands, which usually affects the parotid gland. It is the second most common benign neoplasm after pleomorphic adenoma, accounting for 10 to 15% of all cases. Warthin's tumor is the second pre-pathological process of the salivary glands. In the past, the prevalence of the process was most noted in men, but in the last 20 years, a decrease in sexual imbalance has been observed. Smoking is a known risk factor for Warthin's tumor, and the increase in the number of female smokers explains the decrease in male imbalance [27].

Histologically, Warthin's tumor is characterized by a bilayered epithelial formation and the formation of papillomas in cystic cavities. The inner layer of the papillomas is lined with tall cylindrical cells with eosinophilic cytoplasm, rich in mitochondria complex, giving them oncocytomorphology. The cyst cavity is filled with serous secretion or a mass with cholesterol crystals. Warthin's tumor is also characterized by thin-walled blood vessels, areas of fibrosis, and lymphoid follicles [21,32].

Oncocytoma most often affects the parotid salivary gland. The morphological components of oncocytoma are specialized epithelial cells of large size, abundant eosinophilic cytoplasm and a large number of mitochondria, which give the cells a granular appearance. Histologically, the tumor is represented by solid islands or trabeculae of oncocytes separated by thin layers of vascularized connective tissue. The cell nuclei are large, round with finely dispersed chromatin [18].

Although benign neoplasms of the salivary glands account for less than 3%, they must be differentiated from time to time, since some of them may look like complex tumors poorly separated from the surrounding tissues [11].

The determining criteria are the histological, cytological structure and immunohistochemical study data (Table 1) [5,4,16].

Table 1. Modern methods of morphological verification of salivary gland tumors.

Method	Main characteristics
Histological analysis	Hematoxylin and eosin staining to assess tumor structure; special stains (PAS, mucin dyes) to detect mucin-producing tumors.
Immunohistochemical examination (IHC)	Ki-67 marker for assessing proliferative activity; S-100, GFAP – diagnostics of pleomorphic adenoma; P63, CK5/6 – detection of adenoid cystic carcinoma; TTF-1, PAX8 – exclusion of metastases.
Cytological diagnostics (FNAB)	Obtaining cellular material for analysis; highly informative in pleomorphic adenoma and Warthin's tumor; limited possibilities in differentiating oncocytoma and oncocytic carcinoma.
Molecular genetic research	Identification of PLAG1, HMGA2 mutations in pleomorphic adenoma and CRTC1-MAML2 in mucoepidermoid carcinoma.

Conclusion. Benign salivary gland tumors have diverse morphology, which complicates their diagnosis. Modern methods, including histology, immunohistochemistry and molecular diagnostics, have significantly increased the accuracy of verification. The main method of treatment remains surgical resection, which provides a favorable prognosis. However, the need to differentiate benign tumors from malignant ones emphasizes the importance of further research and improvement of diagnostic approaches.

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