

SALIVARY GLAND TUMORS: CURRENT CONCEPTS IN DIAGNOSIS, CLASSIFICATION AND TREATMENT

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Primljen/Received: 13. 07. 2026.

Prihvaćen/Accepted: 05. 09. 2026.

Online First: September 2026

Abstract: Salivary gland tumors are a rare and highly heterogeneous group of neoplasms with diverse histopathological features, biological behavior, and clinical outcomes. Most arise in the parotid gland, where benign lesions predominate, whereas tumors of the sublingual and minor salivary glands have a substantially higher probability of malignancy. Clinical presentation ranges from slowly enlarging painless masses to aggressive lesions associated with pain, facial nerve dysfunction, local invasion, and distant metastases. Diagnosis integrates clinical examination, imaging, fine-needle aspiration cytology, selected core needle biopsy, and histopathological evaluation supported by immunohistochemistry and molecular testing. Surgery remains the cornerstone of treatment, with postoperative radiotherapy used for adverse pathological features. Advances in molecular pathology have identified recurrent alterations that refine diagnosis and enable biomarker-directed treatment in selected advanced cancers. This review summarizes current concepts in epidemiology, classification, diagnosis, treatment, molecular pathology, and multidisciplinary management of salivary gland tumors.

Keywords: salivary gland tumors, salivary gland neoplasms, parotid gland, diagnosis, fine-needle aspiration, surgery, molecular pathology, targeted therapy.

INTRODUCTION

Salivary gland tumors represent one of the most histologically diverse groups of neoplasms encountered in head and neck pathology. Their rarity, together with remarkable morphological heterogeneity and variable clinical behavior, continues to pose substantial challenges for clinicians, radiologists, pathologists, and oncologists. According to current epidemiological data, these tumors account for approximately 3–5% of all head and neck neoplasms and less than 1% of all

malignant tumors worldwide. Although uncommon, they are clinically important because appropriate diagnosis and management directly influence facial nerve preservation, functional outcomes, local disease control, and long-term survival (1, 2).

Approximately 70–80% of salivary gland tumors arise in the parotid gland, where nearly four out of five lesions are benign. In contrast, tumors originating in the submandibular, sublingual, and minor salivary glands demonstrate progressively increasing rates of malignancy. This inverse relationship between gland size and malignant potential remains one of the fundamental clinical principles guiding the diagnostic evaluation of salivary gland masses (1, 2).

Over the past decade, significant advances have transformed the understanding of salivary gland neoplasia. The fifth edition of the WHO Classification of Head and Neck Tumours introduced important refinements in tumor classification, while wider use of immunohistochemistry, fluorescence in situ hybridization (FISH), and next-generation sequencing has improved identification of diagnostically and therapeutically relevant genetic alterations (1, 2).

Diagnosis relies on a multidisciplinary strategy integrating clinical assessment, imaging, cytological evaluation, and histopathological confirmation, while treatment—surgical excision for most tumors, increasingly supplemented by radiotherapy, reconstructive techniques, and molecularly targeted therapies—has become progressively individualized as actionable genomic alterations create new options for recurrent or metastatic disease (2-6).

The aim of this review is to summarize current evidence regarding the epidemiology, classification, clinical presentation, diagnosis, and contemporary treatment of salivary gland tumors, emphasizing recent developments in molecular pathology and precision oncology that are reshaping clinical practice.

EPIDEMIOLOGY AND RISK FACTORS

Salivary gland tumors (SGTs) are uncommon and biologically heterogeneous neoplasms. Epidemiological estimates should distinguish malignant major salivary gland cancers from the broader group of benign and malignant salivary gland tumors. According to the ESMO–EURACAN Clinical Practice Guideline, major salivary gland cancers account for approximately 5% of head and neck cancers in Europe. The worldwide crude and age-adjusted incidences are approximately 0.69 and 0.57 cases per 100,000 population per year, respectively; in Europe, the corresponding rates are approximately 1.3 and 0.67 per 100,000 per year. Incidence estimates for all SGTs vary more substantially according to case definition, anatomical site, population, and registry methodology. Large population-based registries, including the Surveillance, Epidemiology, and End Results (SEER) Program, have demonstrated a slight increase in reported incidence over the past two decades, most likely reflecting improved diagnostic imaging, cytopathology, and registration rather than a true rise in disease occurrence (3).

Approximately 65–80% of all salivary gland tumors are benign, whereas malignant tumors account for 20–35% of cases. The anatomical site strongly influences the probability of malignancy. Nearly 70–80% of tumors develop in the parotid gland, where approximately three-quarters are benign. Conversely, 40–50% of tumors arising in the submandibular gland are malignant, while more than 80% of tumors originating in the sublingual gland are malignant. Minor salivary gland tumors account for approximately 10–20% of all salivary gland neoplasms, with malignancy reported in up to 70–90% of cases (3, 7).

Pleomorphic adenoma remains the most common benign salivary gland tumor, accounting for nearly half of all salivary gland neoplasms. Warthin tumor represents the second most frequent benign lesion and occurs almost exclusively within the parotid gland. Among malignant tumors, mucoepidermoid carcinoma is the most prevalent histological subtype, followed by adenoid cystic carcinoma, acinic cell carcinoma, polymorphous adenocarcinoma, salivary duct carcinoma, and secretory carcinoma (1, 2, 7).

The incidence of salivary gland tumors increases with age, with peak occurrence during the fifth and sixth decades of life. Benign tumors generally present at a younger age than malignant lesions. Most epidemiological studies report a slight female predominance overall, although Warthin tumor remains more common in males because of its strong association with cigarette smoking. Pediatric salivary gland tumors are

rare, representing less than 5% of all cases; however, the relative proportion of malignant tumors is considerably higher in children than in adults (7).

Geographical differences also exist: higher reported incidences in North America and Western Europe likely reflect greater access to specialized diagnostics rather than true variation, while data from Southeastern Europe remain limited by registries that rarely report salivary gland tumors separately.

RISK FACTORS

The etiology of salivary gland tumors is multifactorial and remains incompletely understood. Nevertheless, several environmental, occupational, genetic, and viral factors have consistently been associated with an increased risk of tumor development.

IONIZING RADIATION

Ionizing radiation represents the most firmly established environmental risk factor. Numerous epidemiological studies have demonstrated an increased incidence of salivary gland tumors among individuals exposed to therapeutic radiation involving the head and neck, particularly during childhood, with latency periods frequently exceeding two decades. Although the dose from routine dental imaging is substantially lower, some observational studies suggest a modest risk increase among heavily exposed individuals, underscoring the importance of appropriate radiological protection (7).

GENETIC ALTERATIONS

Recent advances in molecular pathology have fundamentally improved the understanding of salivary gland tumorigenesis. Specific chromosomal rearrangements and gene fusions characterize several tumor subtypes. *PLAG1* and *HMGA2* rearrangements are strongly associated with pleomorphic adenoma, whereas the *CRTC1:MAML2* fusion is highly characteristic of mucoepidermoid carcinoma and has favorable prognostic implications. Secretory carcinoma is defined by the *ETV6:NTRK3* fusion, while *HER2* amplification and androgen receptor expression are frequently observed in salivary duct carcinoma. These molecular alterations have become increasingly important not only for diagnosis but also for therapeutic decision-making (1, 2, 8, 9).

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE

Occupational exposure to nickel compounds, silica dust, asbestos, rubber manufacturing products, wood dust, and industrial solvents has been associated

with increased incidence in several studies. Although absolute risk remains low, chronic exposure may contribute to epithelial DNA damage and malignant transformation (7).

VIRAL INFECTION

Epstein–Barr virus (EBV) has been implicated in lymphoepithelial carcinoma of the salivary glands, particularly in endemic regions such as Southeast Asia and among Inuit populations. Human papillomavirus (HPV) and cytomegalovirus (CMV) have also been investigated; however, current evidence regarding their role in salivary gland carcinogenesis remains inconclusive (1, 2).

LIFESTYLE FACTORS

Unlike head and neck squamous cell carcinoma, smoking has not been consistently linked to most salivary gland malignancies. An important exception is Warthin tumor, which has a well-established association with cigarette smoking. Alcohol has not been identified as an independent risk factor (3, 6). Overall, tumor development likely results from complex interactions between environmental exposures and tumor-specific molecular alterations.

WHO CLASSIFICATION OF SALIVARY GLAND TUMORS (2022)

The fifth edition of the WHO Classification of Head and Neck Tumours (2022) introduced substantive refinements rather than a simple expansion of the diagnostic list. Newly recognized or reclassified benign entities include sclerosing polycystic adenoma, keratocystoma, intercalated duct adenoma and striated duct adenoma, whereas microsecretory adenocarcinoma and sclerosing microcystic adenocarcinoma were added among malignant entities. Cribriform adenocarcinoma of salivary gland origin is incorporated as a subtype of polymorphous adenocarcinoma, and mucinous adenocarcinoma is organized into papillary, colloid, signet-ring and mixed patterns. The classification also removes several lesions not occurring predominantly in salivary glands from the salivary chapter (1, 2).

For practical clinical purposes, salivary gland tumors are classified into four principal categories: 1) benign epithelial tumors; 2) malignant epithelial tumors; 3) mesenchymal tumors; 4) hematolymphoid and secondary (metastatic) tumors

Among benign epithelial neoplasms, pleomorphic adenoma remains the most common entity, followed by Warthin tumor, basal cell adenoma, canalicular adenoma, oncocytoma, myoepithelioma, and several rare adenomas. Although benign, pleomorphic adenoma

possesses a well-recognized potential for malignant transformation into carcinoma ex pleomorphic adenoma, particularly after prolonged duration or recurrent disease.

Malignant epithelial tumors constitute an exceptionally heterogeneous group. Mucoepidermoid carcinoma remains the most frequent malignant subtype worldwide, whereas adenoid cystic carcinoma is distinguished by its characteristic propensity for perineural invasion and delayed distant metastasis. Acinic cell carcinoma generally demonstrates a favorable prognosis, while salivary duct carcinoma represents one of the most aggressive entities, frequently exhibiting *HER2* overexpression and androgen receptor positivity. Secretory carcinoma, recognized as a distinct entity because of the *ETV6::NTRK3* gene fusion, has emerged as an important example of molecularly defined salivary gland cancer (1, 2, 8).

A major conceptual advance in WHO 2022 is the explicit integration of recurrent molecular alterations into tumor definitions where sufficiently characteristic: *MAML2* rearrangements in mucoepidermoid carcinoma, *MYB::NFIB/MYBL1* rearrangements in adenoid cystic carcinoma, *ETV6::NTRK3* in secretory carcinoma, *PRKD*-family alterations in polymorphous adenocarcinoma, *EWSR1::ATF1* in hyalinizing clear cell carcinoma, and *PLAG1/HMGA2* alterations in pleomorphic adenoma (though these still require morphological correlation). Molecular findings thus function differently across entities—some defining, some supportive in difficult differentials, others primarily predictive biomarkers (1, 2, 8).

CLINICAL PRESENTATION

The clinical presentation of salivary gland tumors is highly variable and depends on the anatomical site, histological subtype, tumor size, and biological behavior. While most benign lesions present as slowly enlarging, painless masses, malignant tumors often demonstrate more aggressive clinical features, including rapid growth, pain, facial nerve dysfunction, fixation to surrounding tissues, and regional lymph node involvement (3, 7).

Parotid gland tumors usually present as unilateral, painless swellings located anterior or inferior to the ear. Because approximately 75–80% of parotid tumors are benign, a slowly growing, mobile mass with preserved facial nerve function is generally suggestive of a benign lesion, most commonly pleomorphic adenoma or Warthin tumor. Nevertheless, every persistent parotid mass should undergo comprehensive diagnostic evaluation to exclude malignancy.

Submandibular gland tumors typically present as firm masses beneath the mandible and warrant in-

creased suspicion given their higher malignancy rate. Sublingual gland tumors are rare but carry the highest malignant potential among major salivary glands, so floor-of-mouth lesions require prompt investigation and early surgical management.

Minor salivary gland tumors most often occur in the hard/soft palate, buccal mucosa, lips, tongue, and retromolar region; unlike major-gland tumors, most are malignant. Patients usually present with painless submucosal nodules, though ulceration, bleeding, dysphagia, or speech disturbances may develop in advanced disease.

Several clinical findings strongly suggest malignancy and warrant urgent evaluation. These include rapid tumor enlargement, persistent pain, facial nerve weakness or paralysis, fixation to adjacent tissues, skin invasion, mucosal ulceration, cervical lymphadenopathy, and recurrent tumors after previous surgery. Facial nerve dysfunction is particularly important because it is highly suggestive of malignant parotid disease and is associated with advanced local invasion and poorer prognosis.

Certain subtypes show characteristic behavior: adenoid cystic carcinoma causes extensive perineural invasion with pain or paresthesia even in small tumors; mucoepidermoid carcinoma behaves according to histological grade; and salivary duct carcinoma typically presents as an aggressive, rapidly enlarging mass with early metastases. Because clinical findings alone cannot reliably distinguish benign from malignant disease, any salivary gland mass persisting beyond two to three weeks without infection should undergo further diagnostic assessment.

DIAGNOSTIC WORK-UP

Accurate diagnosis of salivary gland tumors requires a multidisciplinary approach involving clinical examination, radiological imaging, cytological or histological sampling, and comprehensive pathological evaluation. The primary objectives of preoperative assessment are to determine tumor location, estimate the probability of malignancy, define local extent, evaluate regional lymph nodes, and facilitate optimal treatment planning (3, 6).

Clinical assessment begins with careful inspection and palpation, evaluating size, consistency, mobility, fixation, and skin involvement; facial nerve function deserves particular attention in parotid tumors, as preoperative palsy strongly indicates malignancy. Regional cervical lymph nodes should be systematically examined, as lymphatic metastases significantly influence staging, prognosis, and surgical planning.

Ultrasonography (US), owing to its accessibility, lack of ionizing radiation, and low cost, is generally

the preferred first-line imaging modality for superficial lesions, providing excellent visualization of margins, vascularity, and cystic components while allowing real-time image-guided FNAC. Magnetic resonance imaging (MRI) is the modality of choice for most tumors given its superior soft-tissue resolution, accurately demonstrating deep lobe involvement, skull base extension, and perineural spread, although overlap between benign and malignant appearances remains considerable. Computed tomography (CT) is particularly valuable for evaluating osseous invasion and advanced tumors extending into the mandible, temporal bone, or skull base, and is commonly used for staging and assessing pulmonary metastases. Positron emission tomography/CT (PET/CT) has an increasingly important, though not routine, role in selected patients with high-grade malignancies, recurrent disease, or suspected distant metastases (3, 6).

Fine-needle aspiration cytology (FNAC) remains the preferred initial sampling technique for many salivary gland masses, being minimally invasive, safe, and useful for preoperative risk stratification. Diagnostic accuracy varies with tumor subtype, sampling adequacy, and operator/cytopathologist experience, so FNAC is best interpreted through the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC), which links standardized diagnostic categories to an estimated malignancy risk and recommended management. This is particularly valuable when cytology is nondiagnostic or indeterminate, in which case repeat FNAC, core needle biopsy (CNB), or definitive surgery may be considered according to imaging findings (4, 5, 10).

Ultrasound-guided CNB is a complementary rather than universal alternative to FNAC, particularly useful when FNAC is nondiagnostic, lymphoma is suspected, or preserved tissue architecture is needed for additional molecular testing; its use should be individualized according to lesion accessibility and local expertise (3, 6).

Definitive diagnosis relies on histopathological examination of the surgical specimen. Besides conventional morphology, immunohistochemistry plays an essential role in differentiating morphologically similar entities. Commonly used markers include cytokeratins, SOX10, S100 protein, p63, DOG1, androgen receptor, HER2, mammaglobin, and GATA3, depending on the suspected diagnosis (1, 2, 8).

Molecular diagnostics have become increasingly integrated into routine pathological practice. Detection of characteristic gene fusions, including *PLAG1*, *HMGA2*, *CRTC1:MAML2*, and *ETV6::NTRK3*, not only facilitates diagnosis but also identifies patients who may benefit from targeted therapies. Consequently,

modern salivary gland pathology has evolved from purely morphological classification toward integrated histomolecular diagnosis (1, 2, 8, 11).

TREATMENT

The management of salivary gland tumors has evolved considerably over the past decade owing to advances in surgical techniques, radiotherapy, molecular pathology, and targeted systemic therapies. Because of the remarkable histological diversity and variable biological behavior of these tumors, treatment should always be individualized and planned within a multidisciplinary tumor board consisting of head and neck surgeons, radiologists, pathologists, radiation oncologists, and medical oncologists (3, 6).

Surgery remains the cornerstone of treatment for both benign and malignant salivary gland tumors. The primary objective is complete tumor excision with histologically negative surgical margins while preserving facial nerve function whenever oncologically feasible (3, 6).

For benign parotid tumors, the extent of surgery should be individualized according to size, location, relationship to the facial nerve, and surgeon expertise. Extracapsular dissection is not a universal alternative to parotidectomy but a tailored option for carefully selected, mobile, favorably located lesions; deep-lobe extension, multifocality, or diagnostic uncertainty generally warrants a formal parotidectomy-based approach. In pleomorphic adenoma, complete excision with an adequate margin is essential, as pseudopodia extensions may cause recurrence after inadequate surgery.

Malignant tumors generally require more extensive resection; total parotidectomy is indicated when the deep lobe is involved or complete removal otherwise cannot be achieved. Facial nerve preservation should be attempted unless there is clear tumor invasion, in which case segmental resection with immediate nerve reconstruction should be considered.

Submandibular gland tumors are managed with complete gland excision and adequate margins, with careful preoperative planning given their higher malignancy rate. Sublingual and minor salivary gland tumors are treated by complete excision with sufficient oncological margins; reconstruction may be required to restore speech, swallowing, and oral function.

Management of the clinically node-negative (cN0) neck should be risk-adapted rather than based on a single list of tumor types. The probability of occult nodal metastasis depends on the primary site, T category, histological grade and subtype, patient factors, and radiological or pathological risk features. For parotid carcinoma, low-risk patients with T1–T2 low-grade disease may be observed or managed with selec-

tive staging approaches, whereas T3–T4 and/or high-grade disease represents a substantially higher-risk setting in which elective neck dissection (END) or elective neck irradiation (ENI) should be considered. For cN+ disease, comprehensive therapeutic neck dissection is generally indicated (3, 6).

Postoperative radiotherapy should likewise be individualized according to the primary site and pathological risk profile. Contemporary ESMO recommendations support postoperative irradiation for T3–T4 disease, intermediate- or high-grade histology, close or incomplete resection margins, and perineural invasion; regional postoperative irradiation is indicated for pathological nodal involvement and is intensified in the presence of extranodal extension. Elective nodal treatment follows the same risk principles used for elective neck management and must account for the site of origin and expected lymphatic drainage. IMRT or VMAT is preferred when available because of conformal target coverage and improved sparing of critical normal tissues (3, 6, 12, 13).

Unlike head and neck squamous cell carcinoma, systemic chemotherapy has historically shown only modest efficacy and is usually reserved for recurrent, metastatic, or unresectable disease. Commonly used regimens include platinum-based combinations with taxanes, fluoropyrimidines, cyclophosphamide, or anthracyclines, with low objective response rates and uncommon durable responses—shifting therapeutic interest toward biomarker-driven strategies (3, 6).

MOLECULAR PATHOLOGY AND TARGETED THERAPY

The integration of molecular diagnostics into routine clinical practice represents one of the most important advances in contemporary salivary gland oncology. Several tumor entities are now characterized by specific genetic alterations that serve not only as diagnostic biomarkers but also as potential therapeutic targets (8, 11, 14).

Pleomorphic adenoma frequently demonstrates *PLAG1* or *HMGA2* alterations, whereas mucoepidermoid carcinoma commonly harbors *MAML2* rearrangements. These alterations are primarily important in integrated diagnosis and should not be conflated automatically with predictive therapeutic biomarkers. Molecular testing is most clinically consequential when it identifies an actionable alteration in recurrent, metastatic or unresectable disease.

Secretory carcinoma is characterized by recurrent *ETV6* rearrangements, most commonly *ETV6:NTRK3*. In patients with an *NTRK* fusion, TRK inhibition with larotrectinib or entrectinib represents a biomarker-de-

financed therapeutic option. The fusion should be demonstrated by an appropriate validated molecular method; immunohistochemistry alone may serve as a screening tool but is not sufficient to establish a treatment-defining NTRK fusion in all settings (14, 15).

Salivary duct carcinoma should undergo AR and HER2 assessment, particularly in recurrent or metastatic disease. ESMO–EURACAN recommends confirming AR/HER2 status in metastatic disease: AR-positive tumors (strong positivity in > 70% of cells) may be considered for androgen deprivation therapy, and HER2-positive tumors (IHC 3+ or amplified) for HER2-directed therapy—both reserved for biomarker-selected patients (3, 6, 16, 17).

Immunotherapy's role in salivary gland malignancies remains under investigation, with generally modest response rates to checkpoint inhibitors, though selected patients with high tumor mutational burden or PD-L1 expression may benefit (3, 14).

In recurrent, metastatic or unresectable disease, broader molecular profiling with next-generation sequencing should be considered when feasible, to identify diagnostically or therapeutically actionable fusions, amplifications or mutations; systemic treatment selection should be discussed in a multidisciplinary setting, ideally within a clinical-trial framework (3, 14).

PROGNOSIS

The prognosis of salivary gland tumors varies considerably according to histological subtype, tumor grade, clinical stage, surgical margin status, and the presence of regional or distant metastases. Unlike many other head and neck malignancies, salivary gland cancers encompass a broad spectrum of biological behavior, ranging from indolent low-grade neoplasms with excellent long-term outcomes to highly aggressive carcinomas associated with poor survival (3, 7, 18).

Tumor stage at diagnosis is the most important prognostic factor: localized disease generally achieves excellent outcomes after complete excision, while advanced-stage tumors show significantly lower survival. Five-year overall survival exceeds 90% for low-grade carcinomas but is substantially poorer for high-grade malignancies such as salivary duct carcinoma and carcinoma ex pleomorphic adenoma (3, 6, 18).

Histological subtype is also decisive: mucoepidermoid carcinoma's prognosis tracks closely with grade, while adenoid cystic carcinoma shows relatively slow local progression but a marked tendency toward late distant (particularly pulmonary) metastases—warranting follow-up beyond ten years.

Perineural invasion is among the most important adverse pathological features and is particularly common in adenoid cystic carcinoma. Numerous studies have demonstrated its association with increased local recurrence, decreased disease-free survival, and poorer overall prognosis. Similarly, lymphovascular invasion, positive surgical margins, extranodal extension, and cervical lymph node metastases are consistently associated with inferior oncological outcomes (3, 13, 18).

Completeness of surgical resection is one of the few modifiable prognostic factors: microscopically negative margins reduce recurrence risk, whereas incomplete excision—particularly in pleomorphic adenoma—markedly increases recurrence and malignant transformation (3, 6, 19). Molecular biomarkers have emerged as additional prognostic indicators: *CRTC1:MAML2*-positive mucoepidermoid carcinomas generally do better than fusion-negative tumors, whereas *HER2* amplification, *TP53* alterations, and high proliferative indices predict more aggressive behavior (8, 14). Because tumors such as adenoid cystic carcinoma may recur many years later, lifelong surveillance with regular clinical examination and imaging is often recommended (18).

Table 1. Current treatment recommendations for salivary gland tumors

Clinical scenario	Preferred treatment
Benign tumors	Tailored surgical excision; extracapsular dissection only in carefully selected parotid lesions
Low-risk malignant tumors	Surgery; neck management according to site-specific occult nodal risk
Intermediate/high-risk malignant tumors	Surgery with risk-adapted END/ENI and postoperative RT according to T stage, grade, margins, perineural and nodal factors
Positive or close margins	Re-excision when feasible; otherwise risk-adapted postoperative radiotherapy
Locally advanced unresectable disease	Definitive radiotherapy when surgery is not feasible; systemic therapy individualized
Recurrent/metastatic disease	Molecular profiling and biomarker-directed therapy when an actionable alteration is identified; clinical trial when available

*Source: Adapted from current ESMO–EURACAN, ASCO, and NCCN recommendations (3, 6, 22).

FUTURE PERSPECTIVES

Management is undergoing a transformation driven by molecular pathology and precision oncology, with histological classification increasingly complemented by molecular profiling to identify actionable genomic alterations (8, 11, 14). Next-generation sequencing (NGS) enables comprehensive genomic characterization, improving diagnostic accuracy and personalized treatment selection for advanced disease, and is expected to become integral to standard diagnostic algorithms as additional biomarkers are identified (8, 11, 14).

Targeted therapies against NTRK fusions, *HER2* amplification, and androgen receptor signaling have already shown encouraging activity; future trials will determine their optimal integration into multimodal strategies (14, 20, 21) (Table 1). Artificial intelligence is another evolving field, with machine learning showing promising results in differentiating benign from malignant lesions on imaging, although further validation is needed before clinical implementation (14). Continued international collaboration and molecularly stratified trials will be essential for improving evidence-based management of these rare neoplasms.

CONCLUSION

Salivary gland tumors comprise a rare but exceptionally heterogeneous group of neoplasms that continue to present significant diagnostic and therapeutic challenges, requiring a multidisciplinary approach involving surgeons, radiologists, pathologists, radiation oncologists, and medical oncologists. Recent advances in imaging, cytopathology, and molecular diagnostics have substantially improved diagnostic accuracy, and the incorporation of molecular alterations into the 2022 WHO Classification represents a major step toward precision medicine.

Surgical excision remains the cornerstone of treatment, postoperative radiotherapy continues to play a crucial role in the presence of adverse pathological features, and targeted therapies against specific molecular alterations have introduced new options for recurrent and metastatic disease, marking the beginning of a new era in personalized oncology. Future research should focus on prospective multicenter studies, molecularly guided treatment strategies, and the integration of artificial intelligence into diagnostic workflows—advances expected to improve patient stratification and long-term oncological outcomes for these uncommon but clinically important neoplasms.

Abbreviations:

AI - artificial intelligence;

AR - androgen receptor;

CMV - cytomegalovirus;

CNB - core needle biopsy;

CT - computed tomography;

EBV - Epstein–Barr virus;

END - elective neck dissection;

ENI - elective neck irradiation;

ESMO - European Society for Medical Oncology;

EURACAN - European Reference Network on Rare Adult Solid Cancers;

FISH - fluorescence in situ hybridization;

FNAC - fine-needle aspiration cytology;

HER2 - human epidermal growth factor receptor 2;

HPV - human papillomavirus;

IHC - immunohistochemistry;

IMRT - intensity-modulated radiotherapy;

MRI - magnetic resonance imaging;

MSRSGC - Milan System for Reporting Salivary Gland Cytopathology;

NGS - next-generation sequencing;

PD-L1 - programmed death-ligand 1;

PET/CT - positron emission tomography/computed tomography;

RT - radiotherapy;

SEER - Surveillance, Epidemiology, and End Results;

SGTs - salivary gland tumors;

TP53 - tumor protein 53;

US - ultrasonography;

VMAT - volumetric modulated arc therapy;

WHO - World Health Organization.

Acknowledgments: None.

Financial Support: This research received no external funding or sponsorship.

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this paper.

Author Contributions & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content and the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. Authors contributions: conceptualization-MK; methodology-MK, BK; validation-BK; formal analysis-BK; investigation-BK; data curation-BK; writing - original draft- MK, BK; Writing - review and editing-MK, BK; supervision-MK.

Note: The authors claim that artificial intelligence was not used in this study.

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Sažetak

TUMORI PLJUVAČNIH ŽLEZDA: SAVREMENI KONCEPTI
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Tumori pljuvačnih žlezda predstavljaju retku i izrazito heterogenu grupu neoplazmi različitih histopatoloških karakteristika, biološkog ponašanja i kliničkih ishoda. Najčešće nastaju u parotidnoj žlezdi, gde prevladavaju benigne lezije, dok tumori sublingvalne i malih pljuvačnih žlezda imaju znatno veću verovatnoću malignosti. Klinička slika varira od sporo rastućih bezbolnih masa do agresivnih lezija praćenih bolom, disfunkcijom facijalnog živca, lokalnom invazijom i udaljenim metastazama. Dijagnostika objedinjuje klinički pregled, radiološku dijagnostiku, aspiracionu citologiju tankom iglom, biopsiju debelom iglom u odabranim slučajevima te histopatološku procenu uz imu-

nohistohemijska i molekularna ispitivanja. Hirurgija ostaje osnova lečenja, dok se postoperativna radioterapija primenjuje kod nepovoljnih patoloških karakteristika. Napredak molekularne patologije omogućio je precizniju dijagnostiku i ciljano lečenje odabranih uznapredovalih malignih tumora. Ovaj pregledni rad prikazuje savremene stavove o epidemiologiji, klasifikaciji, dijagnostici, lečenju i multidisciplinarnom zbrinjavanju tumora pljuvačnih žlezda.

Cljučne reči: tumori pljuvačnih žlezda, neoplazme pljuvačnih žlezda, parotidna žlezda, dijagnoza, aspiracija tankom iglom, hirurgija, molekularna patologija, ciljano terapija.

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How to cite this article: Kasumović M, Kalbić B. Salivary gland tumors: current concepts in diagnosis, classification and treatment. *Sanamed.* Online First, September. 2026. doi: 10.5937/sanamed0-69157.

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