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Exploring Advanced Diagnostic Techniques for Salivary Gland Disorders: A Narrative Overview

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ABSTRACT

Accurate diagnosis of lesions and tumors in the salivary glands demands an in-depth knowledge of their complex cellular structure. These glands comprise various cell types, such as epithelial, ductal, mesenchymal, and myoepithelial cells, which together create a multifaceted architecture that complicates the diagnostic process. In addition, external influences such as infections, viruses, and genetic mutations can contribute to changes in salivary gland function and pathology. Consequently, understanding the latest World Health Organization classification of salivary gland neoplasms is crucial for correct diagnosis and effective treatment strategies. This review examines recent advances in diagnostic techniques to develop an efficient method for diagnosing salivary gland disorders. This study demonstrated that the combination of multiple salivary biomarkers leads to the most favorable outcomes. The screening protocol, which included a combination of salivary biomarkers, proved highly effective in accurately diagnosing early-stage oral squamous cell carcinoma. Ultimately, the use of salivary biomarkers holds significant potential for the early detection of oral squamous cell carcinoma.

Keywords: Diagnostic approaches SGTs, Salivary gland (SG) diagnosis, Advanced methods for diagnosing SG tumors, Salivary gland investigations, Radiological investigation of salivary glands

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Introduction

Salivary glands play a pivotal role in oral health by secreting fluids essential for digestion, defense, lubrication, taste sensation, and buffering the mouth. These glands can be categorized into two main groups: the major and minor glands. The major glands include the parotid, submandibular, and sublingual glands, while the minor glands are distributed throughout the tongue, buccal mucosa, labial mucosa, and palatal region. Of the major glands, the submandibular is the second largest, followed by the parotid, with the sublingual being the smallest of the three [1]. Structurally, the glands are composed of acinar cells, ductal cells, and myoepithelial cells. Their branched duct systems transport saliva from the glandular endpieces into the oral cavity. Acinar cells are responsible for producing saliva, and myoepithelial cells surround the acini and intercalated ducts. The extracellular matrix, along with immune cells, stromal cells, myofibroblasts, and nerve fibers, encases these cellular structures. The proportion of acinar cells varies across the glands, impacting the nature of their secretions. For instance, the parotid gland mainly consists of serous acini, leading to the production of watery saliva. In contrast, the submandibular and sublingual glands, classified as mixed glands, contain both mucous and serous acini. The submandibular gland is primarily serous, with mucinous acini making up only about 10% [2, 3].

In their 2023 study, Kumari *et al*. investigated the disputed classification of nasopharyngeal tubal glands, offering insights into their taxonomy [4]. Their findings highlighted the presence of seromucous glands in the submucosal layer near the nasopharyngeal end, which were lined by respiratory epithelium. These tubal glands showed alpha-SMA positivity, suggesting myoepithelial cells, although this expression was weaker compared to seromucous glands in the trachea. Interestingly, no salivary alpha-amylase was detected in the cadaveric tissue samples, and amylase levels were notably lower in nasal secretion when compared to oral samples. This suggests that nasopharyngeal tubal glands differ significantly from classic salivary glands, sharing similarities with seromucous glands found in the respiratory tract, with a functional role in both the auditory tubes and respiratory system [5].
Salivary gland tumors are typically categorized as benign or malignant [6]. These tumors can be particularly challenging to diagnose due to their complex cellular and structural features, making them a unique subset of head and neck cancers. Adenoid cystic carcinoma and mucoepidermoid carcinoma are the most common malignant tumors of the salivary glands. The histological diversity and intricate classification of these tumors present significant diagnostic challenges for clinicians, pathologists, and surgeons [7-9].
Non-invasive diagnostic methods, such as salivary biomarkers and sialochemistry, are increasingly being utilized for health monitoring and disease diagnosis. By analyzing the biochemical and molecular characteristics of saliva, abnormalities can be detected, aiding in the identification of both normal and pathological processes. Salivary biomarkers have shown promise in detecting autoimmune disorders, such as Sjogren’s syndrome, periodontal disease, and various types of cancer [10, 11].
This study aims to examine the typical characteristics of salivary gland diseases and introduce modern diagnostic approaches and techniques for distinguishing these conditions. The objective is to provide a comprehensive overview of the current diagnostic methods used for identifying salivary gland disorders.

Materials and Methods

A systematic search of various databases was performed between June 28, 2022, and August 15, 2023, focusing on English-language publications. The databases searched included PubMed, Scopus, Science Direct, Web of Science, and the Saudi Digital Library (SDL). The following search terms were employed: salivary gland (SGs) diagnosis, salivary gland assessments, advanced diagnostic techniques for SG tumors, radiological evaluations of salivary glands, histological examinations of salivary glands, salivary gland biomarkers, and diagnostic methodologies for salivary gland tumors (SGTs). Inclusion and exclusion criteria were carefully defined. Studies such as case reports, case series, systematic reviews, meta-analyses, and any articles published before 1980 were excluded from the review. On the other hand, inclusion criteria encompassed review articles, case-control studies, cross-sectional studies, and clinical trials written in English, with a publication date range from 2010 to August 15, 2023. The review focused on various diagnostic areas, including clinical examinations, radiological methods, surgical assessments, molecular/genetic testing, saliva analysis, and blood tests. Each investigator was assigned specific topics for the article search.
The relevant articles were systematically recorded in an Excel spreadsheet by the corresponding investigator. Each article was then evaluated against the exclusion and inclusion criteria. In total, 142 articles were retrieved from the databases: PubMed (92), SDL (44), Web of Science (1), ScienceDirect (4), and Scopus (1). After applying the selection criteria, 45 articles were excluded. This included 11 case reports, 2 case series, 9 articles published before 2018, 16 systematic reviews or meta-analyses, 4 articles unrelated to the study focus, and 3 non-English publications. Ultimately, 97 articles met the criteria for inclusion, with 59 articles selected for use in this narrative review. The details are presented in **Tables 1 and 2**.

Table 1. Distribution of the number of studies included in the review

Total Articles	Excluded Articles	Selected Articles	Included Articles
142	45	97	60

Table 2. Distribution of the number of studies extracted from databases in the review

Databases	Number
PUBMED	92

SDL	44
SCIENCEDIRECT	4
WEB OF SINCE DIRECT	1
SCOOP	1
Total	**97**

Results and Discussion

Diagnostic approaches for salivary gland disease

Clinical evaluations

The clinical presentation of salivary gland disorders often manifests as localized pain or swelling, particularly in small salivary glands. These symptoms may be linked to the paranasal regions, leading to epistaxis or nasal obstruction, and sometimes, painless swelling or issues with tooth alignment. In addition, individuals may experience a persistent cough or a sore throat. A thorough assessment of the patient's medical history, including any systemic conditions and medications, is essential. Salivary gland issues are frequently associated with systemic disorders such as diabetes, arteriosclerosis, hormonal imbalances, and neurological conditions. For instance, older women, particularly those around 60 years of age with a history of rheumatoid arthritis or spinal cord diseases, have a notably higher likelihood of developing Sjögren's syndrome [12]. The primary salivary glands can be most effectively evaluated through palpation, along with an examination of the saliva excretion, which is typically performed for the parotid and submandibular glands [13].

Extraoral examination

Extraoral inspections involve the following steps

- Position the patient about 1–2 meters away from the examiner, ensuring they are facing directly forward.
- The examiner should check for any asymmetry, changes in color, pulsation, or any discharge from the sinuses on both sides.
- Note any enlargement of the major or minor salivary glands, which could occur on either side.
- Inspect for swelling in the preauricular region, which may be difficult to detect if it is deep in the parotid tail or within the gland tissue.
- Ask the patient to clench their jaw to engage the masseter muscle. This helps differentiate swelling in the submandibular gland, typically found just beneath and to the inside of the mandible's angle.

Extraoral palpation

- To enhance the visibility of the parotid and submandibular glands, the patient's head should be tilted forward.
- The examiner has the option of standing either in front of or behind the patient during the palpation.
- Palpation of the parotid glands is performed by positioning the fingers in front of the ears to feel for any swelling. The Stensen duct can be more easily palpated when the patient clenches their teeth.
- In a healthy individual, the parotid gland is difficult to palpate.
- The submandibular gland is best examined bimanually: one hand places a finger inside the mouth, beneath the lower molars, while the other hand positions a finger externally in the submandibular triangle.
- The Wharton duct travels anteromedially along the floor of the mouth, opening at the lingual frenum.
- When examining the submandibular and sublingual glands and their ducts, a bimanual approach (using the pads of the fingers) is advised. The examiner should assess the size, consistency, surface characteristics, tenderness, and movement of any abnormalities concerning the surrounding skin and tissues.
- The sublingual gland is typically not palpable.
- It is important to note that swellings of salivary or lymphatic glands do not move when the patient swallows, unlike swellings associated with the thyroid or larynx, which elevate during swallowing.
- A thorough examination of the neck for signs of lymphadenopathy should also be conducted.

Intraoral examination (inspection of the oral cavity)

- Inspect for asymmetry, discoloration, and pulsation, and evaluate the duct orifices for possible obstructions.
- Examine the buccal mucosa, palate, and floor of the mouth for any ulcerations, as these areas are common locations for malignant minor salivary gland tumors.

Imaging techniques for salivary gland disorders

Panoramic radiographs

Panoramic radiographs are widely employed across various dental fields, serving as a common tool used by general practitioners and dental specialists. The image quality plays a crucial role in ensuring its accurate interpretation. Conventional radiographs have been extensively utilized in dentistry and oral-maxillofacial medicine, particularly for diagnosing conditions like submandibular sialoliths, tooth decay, fractures, and other essential oral health concerns. Sialolithiasis, one of the leading obstructive diseases affecting major salivary glands, results from calcium salts accumulating around organic debris such as mucus, ductal epithelial cells, bacteria, or foreign particles [14-16].

Cone beam computed tomography (CBCT)

Salivary gland diseases, including infections, obstructions, immune system disorders, and both benign and malignant tumors, can arise at any point in life. Radiologic imaging has become an indispensable part of diagnosis, treatment planning, and assessment, especially with the ongoing advancements in healthcare. CBCT, introduced by Piero Mozzo *et al*. in 1998, has revolutionized dental radiology by providing highly accurate 3D images, offering excellent spatial resolution for bones and teeth. Over time, CBCT has largely replaced conventional panoramic images due to its superior accuracy and lower radiation exposure. Despite its advantages, CBCT has limitations, such as poor resolution for soft tissues, requiring practitioners to have an in-depth understanding of head and neck anatomy to produce high-quality images. CBCT has proven particularly effective in diagnosing sialolithiasis, showing greater sensitivity in detecting salivary stones when compared to other imaging techniques like ultrasonography [17-22].

Computed tomography (CT) scans

CT scans are often the preferred method for evaluating masses in or around salivary glands and for assessing non-inflammatory gland enlargement. These scans provide valuable insights that guide treatment decisions. Unlike traditional sialography, CT scans do not usually require contrast material and are less invasive. They are highly sensitive, offering detailed anatomical data that helps in localizing masses within the salivary glands, particularly the parotid glands, and assessing their potential impact on surrounding structures, including the facial nerve and neurovascular networks. CT imaging also assists in evaluating the vascularity of tumors [23].

Sialography

Sialography involves injecting contrast material into the ducts for radiographic examination, helping to evaluate the ductal anatomy and detect abnormalities. It is particularly useful in pre-surgical planning for the removal of salivary gland masses. However, it is not suitable for patients with iodine allergies or acute inflammation of the salivary glands. This technique is beneficial in assessing the chronic pathology of salivary ducts, such as in Sjögren syndrome, and can aid in curative treatments like mechanical dilation and gland irrigation. Additionally, various minimally invasive surgical interventions, such as sialoendoscopy, transmucosal surgical approaches, and stone fragmentation techniques, are available for treating these conditions [24, 25].

Ultrasound imaging

Ultrasound imaging uses high-frequency sound waves to generate images of the salivary glands, helping to detect abnormalities like cysts, tumors, and inflammation. It became a crucial diagnostic tool in clinical practice in the 1970s and 1980s. Due to the superficial location of the salivary glands and their accessibility to ultrasound, they have become a key focus for diagnosis and treatment. Ultrasound is particularly useful in diagnosing inflammatory and obstructive conditions in the salivary glands. However, it is less effective for detecting fine parenchymal abnormalities or assessing deep-seated glands [26].

Magnetic resonance imaging (MRI)

MRI of the head and neck, including functional imaging, is essential when there is a suspicion of a neoplasm. It helps to accurately identify the tumor's location and its extent, particularly when deep tissues or nerves are involved. MRI can also provide valuable insights into lymph node and bone involvement and can help predict the nature of a lesion through diffusion-weighted and dynamic contrast-enhanced sequences. Salivary gland carcinomas, which are rare and diverse, particularly benefit from MRI, as it is radiation-free and offers detailed diagnostic information [27].

Positron emission tomography (PET)

Positron emission tomography (PET) is a vital diagnostic tool in clinical settings, widely used for detecting diseases due to its capability to capture functional images that reveal metabolic and biological processes at the molecular level. The precision and effectiveness of PET imaging are often limited by the technology used in the PET detectors. However, when combined with computed tomography (PET/CT), this imaging method becomes a non-invasive technique that allows the examination of both physiological and pathological activities in the body, providing the added benefit of anatomical localization. During PET scans, radiotracers are employed, which decay by emitting positrons, positively charged particles. These positrons travel a short distance through tissues before colliding with negatively charged electrons, resulting in the emission of two high-energy photons (511 keV) that travel in nearly opposite directions (180º). The simultaneous detection of these emitted photons by detectors allows for the construction of a three-dimensional PET image. Additionally, CT data is gathered during the scan and, when combined with PET data, enhances the precision of radiotracer localization. Nuclear medicine plays a crucial role in clinical practice by offering valuable diagnostic alternatives, ultimately improving patient care and quality of life. This section will delve into the radiopharmaceuticals used in positron emission tomography (PET) [16].

Surgical intervention and molecular diagnosis

Sialendoscopy

Sialendoscopy has emerged as a reliable and effective method for both diagnosing and treating benign obstructions in the salivary glands, offering valuable benefits in the field of oral and maxillofacial surgery. The procedure involves using endoscopes to navigate the salivary ducts, enabling the visualization of blockages and the ability to treat them directly. These endoscopes function as dual-purpose tools, facilitating both diagnosis and treatment through a working channel that accommodates instruments like drills, stone baskets, and fiber optic lasers to break down and remove salivary stones. Regarding anesthesia, both monitored anesthesia care (MAC) and general anesthesia (GA) be suitable for sialendoscopy, depending on the patient's condition. Overall patient satisfaction and tolerance of post-surgical pain appear to be similar with both methods, although GA tends to be preferred for future procedures. More research is needed to determine the best criteria for selecting an appropriate anesthesia approach. Ultimately, sialendoscopy remains the technique of choice for treating parotid obstructive sialadenitis [28-34].

Fine needle aspiration cytology (FNAC)

FNAC is widely regarded as a standard technique for the preoperative evaluation of masses in the salivary glands, especially in the case of head and neck tumors. It is a minimally invasive, safe procedure that provides essential diagnostic information, ensuring proper management of these conditions. While FNAC is generally associated with minimal risks, rare complications like bleeding, facial nerve injury, or fibrosis have been documented. Despite these infrequent risks, FNAC remains a recommended procedure for evaluating salivary gland masses due to its low invasiveness and high diagnostic accuracy [12, 35, 36].

Surgical biopsy

A surgical biopsy is the process of extracting tissue from a living patient for further examination, which can include visual inspection, microscopic analysis, or chemical tests. In diagnosing salivary gland lesions, surgical biopsy is considered the definitive method, especially when there are concerns about potential tumors. Histopathological analysis remains the gold standard for understanding the nature, prognosis, and characteristics of lesions. Although advances in immunohistochemistry and molecular pathology have enhanced diagnostic precision, histomorphology remains the primary basis for classification according to the World Health Organization (WHO). The diagnostic process can be complicated by morphological similarities between lesions, making additional diagnostic methods essential. This review explores the updates in the WHO's latest classification, addresses challenges in diagnosis, and highlights useful antibodies for better diagnosis. Recent research by Alsanie *et al*. gathered data from multiple centers worldwide to examine the demographics, anatomical locations, and histological types of salivary gland tumors (SGTs). This extensive research revealed that the majority of SGTs are benign (65%) with a slight female predominance (54%). Most cases occur in individuals between the ages of 40 and 70 years, with a marked difference in age for benign versus malignant tumors. Pleomorphic adenoma was found to be the most common benign tumor, while mucoepidermoid carcinoma was the most common malignant tumor. SGTs predominantly occur in the major glands (68%), with the parotid gland being the most frequent site for benign tumors (70%) and minor glands being more commonly involved in malignant tumors (47%) [37-39].

Advanced molecular and biological testing

Antibody testing plays a vital role in identifying antibodies associated with autoimmune diseases of the salivary glands, such as Sjögren's syndrome. Proteomic analysis focuses on the protein profile of saliva to pinpoint specific markers indicative of salivary gland diseases. Biomarker detection identifies molecules present in saliva that could signal conditions like Sjögren's syndrome or oral cancer. Polymerase chain reaction (PCR) is used to detect specific genetic material, which aids in diagnosing infections or identifying mutations that may be linked to salivary gland diseases. Fluorescence in situ hybridization (FISH) uses fluorescent tags to locate particular genes or chromosomes, which is useful for diagnosing specific types of tumors [40, 41].

Biomarkers are biological indicators that reflect the effects of diseases or therapies. They can provide crucial insights into a patient's health status, helping to predict and diagnose various conditions. While some biomarkers are easy to measure, such as blood pressure or heart rate, others are more complex, such as those related to cell cycles. Biomarkers are an essential part of advancing diagnostic and therapeutic fields [42-44].

Salivary biomarkers have proven useful in diagnosing salivary gland diseases, especially in complicated cases where the final diagnosis might be unclear. Over 100 different salivary biomarkers are currently identified, including inorganic, protein, and DNA-, RNA-, and microRNA-related markers, as well as those linked to metabolomics. These biomarkers are particularly important in assessing the risk of malignancies. A good biomarker can be consistently measured with little variation. Combining multiple biomarkers enhances diagnostic accuracy and helps in prognosis [45-50].

Saliva analysis

Saliva is primarily water, making up 99% of its content, along with essential electrolytes like sodium, potassium, calcium, and magnesium. It also contains enzymes that catalyze chemical reactions in the oral cavity and immunoglobulins that protect against pathogens. Glycoproteins in saliva help maintain oral health by providing a protective layer on the epithelial surface. Additionally, saliva contains trace amounts of albumin, peptides, and polypeptides, which are important for oral health [51-53].

Saliva analysis offers great potential for diagnosing various diseases and monitoring the outcomes of treatments. The effectiveness of saliva as a diagnostic tool can be influenced by individual variations in its flow and composition, which may be affected by factors such as age, diet, medication, and underlying conditions. One major advancement is the use of salivary biomarkers to detect oral squamous cell carcinoma (OSCC) in its early stages. Biomarkers such as mRNA, miRNA, DUSP100, s100P, IL-8, IL-1B, TNF-a, and MMP-9 have been identified in saliva, and a screening protocol has been developed to assess their potential for early OSCC diagnosis.

Blood screenings

Blood tests are commonly used in the initial evaluation of salivary gland disorders, but their value requires careful consideration. These tests are often conducted to check for markers of inflammation, infection, or autoimmune disorders that may affect the salivary glands. A study analyzing 182 patients with Salivary Gland Tumors (SGT) between January 2010 and May 2015 revealed that patients with malignant SGTs had lower lymphocyte counts, higher neutrophil percentages, and greater neutrophil-to-lymphocyte ratios (NLRs) compared to those with benign tumors. These findings suggest that a combination of NLR and lymphocyte percentage could serve as an effective inflammatory marker for distinguishing between low- and high-grade malignant parotid tumors. These measures are cost-effective and commonly used in clinical practice. A 2023 study developed a nomogram for distinguishing between benign and malignant parotid gland tumors using clinical features and preoperative blood markers. The nomogram, which included smoking status, pain, facial paralysis, and the lymphocyte-to-monocyte ratio (LMR), proved reliable for differentiating between benign and malignant tumors, offering a more effective preoperative diagnostic approach [54, 55].

Conclusion

Various advanced diagnostic techniques are now available for identifying diseases affecting the salivary glands. It is essential to implement clinical guidelines for managing patients with salivary gland conditions, including both lesions and neoplastic diseases. Radiological methods should be the primary diagnostic tool when there is no history of neoplastic lesions. According to the literature, ultrasound is the preferred method for initial imaging of major salivary gland disorders, particularly when used alongside fine needle aspiration (FNA), which helps improve diagnostic accuracy. For a more comprehensive understanding of the disease's extent and nature, computed tomography (CT) and magnetic resonance imaging (MRI) are superior, especially in evaluating salivary gland tumors (SGTs). Positron emission tomography (PET), when combined with CT or MRI, is particularly useful for detecting metastasis or secondary tumors in the salivary glands. Sialography remains valuable in cases with recurrent glandular lesions or neoplasms. The next critical step involves surgical procedures to obtain histological samples, which is considered the definitive method for diagnosing salivary gland issues, with immunohistochemistry (IHC) playing a significant role in confirming diagnoses. Moreover, a promising diagnostic innovation, the SalvGlandDx panel, developed by Freiberger *et al*. [56], utilizes next-generation sequencing (NGS) to detect salivary gland neoplasms. This tool is the first of its kind, designed to provide a single test for detecting gene alterations, mutations, fusions, and gene expression changes. Additionally, by integrating genetic mapping from the Saudi Human Genome Project, early diagnostic methods based on genetic analysis are poised to complement histological findings, offering a gold standard for salivary gland disease diagnosis.

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