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SALIVARY GLAND DISORDERS (HT HOFFMAN, SECTION EDITOR)

Salivary Gland Neoplasms

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Abstract

Purpose of Review To give an overview of diagnosis and treatment of salivary gland neoplasms and highlight the contribution of recent literature.

Recent Findings The newly adapted Milan classification system for cytologic diagnosis provides risk of malignancy and clinical management strategies for parotid neoplasms with high PPV and NPV. Reconstruction for partial parotidectomy and total parotidectomy defects continues to advance toward greater cosmesis and facial symmetry.

Summary New diagnostic advances will aid in clinical decision making and patient management. Surgically based therapy continues to be favored in both benign and malignancy lesions. Management of the neck is important in high grade salivary malignancy and reconstruction of defects should be considered in order to improve cosmetic outcomes.

Keywords Salivary gland tumor · Parotid malignancy · Parotid reconstruction · Salivary gland cytology

Introduction

Salivary gland tumors are relatively rare neoplasms which make up approximately 3–5% of all head and neck tumors and 0.5% of all malignancies [1]. Salivary gland tumor classification includes differentiation between major and minor salivary glands as well as benign versus malignant pathology. Most clinicians use the 80/20 rule for salivary gland neoplasms: 80% are benign, 80% occur in the parotid gland, and 80% are pleomorphic adenomas. However, there is some variation of these incidences in the literature [2].

Historically, surgery was considered for every salivary gland tumor. Advances in fine needle aspiration biopsy and radiographic imaging have led to recommendations for pre-operative evaluation with imaging and biopsy to guide treatment planning. Analyses within the literature have suggested that ultrasonography, CT, and MRI are all feasible methods in diagnosing salivary tumors without significant differences in diagnostic accuracy [1]. Fine needle aspiration is recommended for diagnosis and to help drive treatment recommendation. It can help to determine recommendations for observation versus excision. For malignant lesions, fine needle aspiration cytology (FNAC) also allows appropriate pre-operative counseling and planning regarding extent of resection, facial nerve management, the need for elective neck dissection, the potential role of postoperative radiation treatment, and the urgency of surgical scheduling. Ultrasound guidance, particularly for submandibular and parotid gland lesions, may increase accuracy of needle aspiration [3].

The Milan System for reporting salivary gland cytopathology has recently been introduced to help guide diagnosis and management according to risk of malignancy in different categories. This is analogous to the Bethesda system classification for thyroid cytopathologic diagnosis. This system was introduced in response to diagnostic challenges in FNAC diagnosis due to morphologic overlap between different malignant tumors and even between benign and malignant tumors [4]. The Milan System is a six-category schema that provides risk of malignancy in each classification in order to further guide ancillary testing and management plan as well as to remove some of the ambiguity often seen in FNAC interpretation [4]. The six-tiered system seen in Table 1 provides risk

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of malignancy and clinical management strategies for these well-defined categories. It has been shown to have high PPV and NPV which further supports its utility in clinical practice [5•].

Benign Salivary Tumors

Benign tumors make up approximately 80% of salivary neoplasms. They generally present as a painless, slow-growing mass. Patients may be asymptomatic for months to even decades. Table 2 shows the WHO classification of salivary tumors. Amongst benign tumors, pleomorphic adenoma is the most common, 84% of these occur in the parotid gland while 8% occur in the submandibular gland, 6.5% occur in the minor salivary glands, and the remainder occur in the sublingual gland [7]. They present more often in women and middle-aged individuals [2]. Histopathologically, they are made up of a mix of epithelial and mesenchymal components. Within the parotid gland, most tumors originate in the superficial lobe. They are generally unilateral, and rarely multifocal or bilateral. Non-urgent surgical resection is recommended due to the expectation of growth. Additionally, these lesions have a risk of malignant potential ranging from 3 to 15% [8]. It is important to note that pleomorphic adenomas have a high rate of recurrence with tumor spillage and incomplete excision. As such, enucleation should be avoided with complete excision the goal of every operation. Gland-sparing techniques such as extracapsular excision and partial parotidectomy have been demonstrated to have low recurrence rates in experienced hands. Often, the limitation of the width of extent of margin is the proximity of the facial nerve. Witt found that rate of recurrence for previously mentioned gland-sparing techniques was less than 3%, while enucleation had a recurrent rate of 25% [9]. Tumors that recur typically do so 7–10 years after initial surgery. Revision surgery can be challenging due to scar tissue from previous reoperation and the fact that these recurrent tumors are often multifocal. There is evidence showing that use of post-operative adjuvant radiation can help to prevent further recurrence in patient with recurrent pleomorphic adenoma [10], but risks and benefits of radiation must be weighed on a case by case basis.

Warthin's tumors are the second most common benign salivary tumor. They occur almost exclusively in the parotid gland, making up 25–32% of parotid lesions. They are most commonly found in Caucasian males with a history of smoking tobacco. Approximately 10–15% are bilateral. Histologically, they are comprised of epithelial cells resting on dense lymphoid stoma with variable geminal centers. They contain cystic spaces which are narrowed by polypoid projections of lymphoepithelial elements. Surgical resection of larger tumors is favored. Warthin tumors often occur in the tail of the parotid and are therefore amenable to a simple transcervical approach. Alternatively, due to their benign nature and low risk of malignancy (1%), these tumors can also be observed if they are asymptomatic and not causing cosmetic deformity.

Amongst benign lesions, patients diagnosed with pleomorphic adenomas should be offered surgical excision unless there is concern for increased risk of complication based on patient or tumor factors. Age and patient life expectancy play a role since size and risk of malignancy increases over time. The type of surgery is dependent on the location of the tumor. The majority of tumors are located in the parotid gland with the superficial lobe being the most common tumor location. Superficial parotidectomy with facial nerve dissection is the traditional treatment in these cases. Patients with smaller superficial lobe tumors can be considered for partial superficial parotidectomy or extracapsular dissection, particularly if the location of the tumor lends itself to this procedure. Tumors located in the posterior-inferior aspect of the gland are often behind the course facial nerve, and tumors located in the anterior aspect of the gland are often between branches of the facial nerve. These locations are well-suited for gland-sparing approaches. These methods have been shown to be safe for benign tumors and even oncologically sound in the

Table 1 Milan System for Classification for Salivary Gland Cytology: implied risk of malignancy and recommended clinical management

Diagnostic category	Risk of malignancy (%)	Management
I. Non-diagnostic	25	Clinical and radiologic correlation/repeat FNAC
II. Non-neoplastic	10	Clinical follow up and radiological correlation
III. Atypia of undetermined significance (AUS)	20	Repeat FNAC or surgery
IV. Neoplasm		
Benign	< 5	Surgery or clinical follow up
Salivary gland neoplasm of uncertain malignant potential (SUMP)	35	Surgery
V.Suspicious for malignancy (SM)	60	Surgery
VI. Malignant	90	Surgery

Adapted with permission from: Kala C. et al. J Cytol. 2019 Jul-Sep; 36(3): 160–164) [4]

Table 2 WHO 2017 Classification of Salivary Gland Tumors

Malignant tumors	**Benign tumors**
Mucoepidermoid carcinoma	Pleomorphic adenoma
Secretory carcinoma	Myoepithelioma
Adenoid cystic carcinoma	Basal cell adenoma
Sebaceous carcinoma	Warthin tumor
Acinic cell carcinoma	Oncocytoma
Lymphoepithelial carcinoma	Lymphadenoma
Polymorphous adenocarcinoma	Cystadenoma
Carcinosarcoma	Dialadenoma
Clear cell carcinoma	Ductal papillomas
Basal cell carcinoma	Sebaceous adenoma
Intraductal carcinoma	Canalicular adenoma and other ductal adenoma
Adenocarcinoma, NOS	
Salivary duct carcinoma	
Myoepithelial carcinoma	
Epithelial-myoepithelial carcinoma	
Carcinoma ex pleomorphic adenoma	
Poorly differentiated carcinoma	
Undifferentiated carcinoma	
Large cell neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	
Non-neoplastic epithelial lesions	**Benign soft tissue lesions**
Sclerosing polycystic adenosis	Hemangioma
Nodular oncocytic hyperplasia	Lipoma/sialolipoma
Lymphoepithelial sialadenitis	Nodular fasciitis
Intercalated duct hyperplasia	
Hematolymphoid tumors	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	

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appropriate low-grade tumors [11, 12]. Patients with deep lobe tumors should be considered for transcervical excision with dissection of the facial nerve. When these tumors involve the parapharyngeal space transoral excision can be considered alone or combined with transcervical excision [13]. The modified Blair incision has been widely used for surgical access. In recent years, rhytidectomy incisions have gained popularity for improved cosmesis and can be utilized for both benign and malignant cases in adults and children [14–16]. Additionally, contour defect correction should be considered for patients undergoing superficial parotidectomy. For benign tumors leaving behind a smaller defect, this is most commonly accomplished with fat grafting or sternocleidomastoid rotational flap. Raising a superficial musculoaponeurotic system flap can also be considered in the surgical approach. In addition to fat grafting, SMAS flap has been shown to give patients improved facial symmetry as well as to decrease the incidence of Frey syndrome [16]. Caution should be used when considering these approaches in patients with autoimmune diseases relating to perivasculitis and in those who are smokers [14].

Malignant Tumors

Salivary gland malignancies are rare, comprising 3–5% of head and neck malignancies and making up 2–3 cases/100,000 people per year. Table 2 shows the WHO classification of malignant salivary gland tumors showing the diversity in histologic subtypes. Amongst this diverse histology, there is additionally varied behavior from indolent to aggressive. These tumors are generally divided into high-grade and low-grade categories based on these behaviors and histologic features. Seventy percent of these malignancies occur in the parotid gland posing challenges to the facial nerve and leaving a contour defect which must be dealt with after resection. Respectively, 8% of malignant lesions occur in the submandibular gland and 22% occur in minor salivary glands. Treatment for these tumors is primarily surgical with possible adjuvant radiation depending on pathologic features and tumor grade. It has been well established that better oncologic control has been achieved with surgically driven treatment with the addition of appropriate adjuvant therapy [17, 18].

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy and makes up 30% of all parotid cancers. It is categorized as low-, intermediate-, or high- grade histology with high-grade tumors histology generally having association with male sex, older age, and large tumors which are more locally aggressive and have higher rates of nodal and distant metastases [19, 20]. It is important to note that FNA sensitivity for low-grade MEC is relatively low, making these a more challenging lesion to diagnose. Correlation with MRI imaging characteristics can aid in the decision-making process [21]. Treatment of these tumors should be tailored to the grade and predicted behavior of the tumor. Low-grade tumors can typically be treated with surgery alone, while intermediate and high-grade tumors should be treated with elective neck dissection and adjuvant radiation due to high rates of occult nodal metastases and propensity for recurrence [19].

Adenoid cystic carcinoma is the second most common salivary gland malignancy of the parotid gland. It typically occurs between the fourth and sixth decade of life with a slight predisposition toward women [22]. There are three histologic subtypes: tubular, cribriform, and solid. Patients with solid-type tumors have more aggressive behavior and high rate of distant metastasis [19]. Perineural invasion is a hallmark feature of adenoid cystic carcinoma dictating adjuvant radiation therapy after surgical excision of these tumors. Nodal metastases are relatively rare with incidence of occult nodal disease in 7% of patients [23]. Distant metastases however are common (31%) especially years after initial diagnosis and treatment, most commonly to lung (80%) and bone (15%), demonstrating a role for pulmonary imaging in these patients. Overall prognosis is dictated by distant failures; however, these patients with distant metastases can have an indolent course usually drawn out over 10 to 15 years.

Acinic cell carcinoma is a low-grade malignancy that accounts for 10–15% of parotid tumors. It generally follows an indolent course; however, it tends to be more aggressive when found in the parotid gland compared to minor salivary glands [19]. Treatment is typically limited to surgical excision based on low-grade tumor histology. Radiation is added for higher-stage tumors or nerve involvement.

Salivary ductal carcinoma is a rare but locally aggressive malignancy most commonly found in older male patients and associated with poor prognosis. It is histologically similar to high-grade ductal carcinoma of the breast. It typically presents with a rapidly growing mass with or without facial palsy. Nodal metastases are common and despite resection and adjuvant radiation, there is a high incidence of locoregional recurrence and/or distant metastases [19]. Prognosis is poor with 5-year overall survival of 43% [24]. Twenty percent of tumors overexpress HER2 which is associated with a poor prognosis. This can provide an opportunity however for molecular targeted therapy or androgen deprivation therapy as an adjuvant treatment.

Carcinoma ex pleomorphic adenoma is a rare tumor which arises from long standing or recurrent pleomorphic adenoma. The incidence increases from 1.5% at 5 years to 10% after 15 years [25]. The malignant component is often high grade; however, low-grade carcinoma may also occur. Malignant component presentation is often manifested by rapid growth, fixation, facial palsy, and regional lymphadenopathy. Up to 70% will develop locoregional recurrence and/or distant metastases. A recent population study found a 5-year overall survival of 49.1% [19, 26].

Adenocarcinoma not otherwise specified has variable incidence. It is reported with high incidence is some series and is less commonly in others. This is likely because these tumors exhibit ductal differentiation but lack resemblance to other well-defined salivary gland malignancies. Since many salivary malignancies are by definition adenocarcinoma, this is likely why there is variable incidence in pathologic diagnosis. These tumors can be high or low grade; thus, dictating extent of surgical treatment and addition of adjuvant therapy.

Most patients presenting with salivary gland malignancy are asymptomatic. However, patients presenting with rapidly growing mass, facial weakness, trismus, and enlarging cervical lymph nodes are at higher risk of malignancy. Workup of salivary gland malignancy includes imaging and biopsy as previously discussed for benign tumors. FNAB should be performed and cytopathologic diagnosis can be critical in identifying the need for urgency of surgical treatment as well as the need for elective neck dissection in patients with significant risk of occult disease. PET-CT may be useful in assessing regional and distant metastases in patients with biopsy-proven malignancy and can be useful in identifying the need for additional surgery as well [19].

Surgery is the mainstay of treatment for malignant salivary gland tumors. Pre-operative facial nerve assessment should be performed, and facial nerve monitoring is advocated by the authors for parotidectomy for both benign and malignant tumors. For low-grade malignancy, surgical treatment is often sufficient. For low-grade parotid malignancies, this is often limited to superficial parotidectomy. For high-grade tumors and those involving the facial nerve, total parotidectomy is favored. In patients with pre-operative facial nerve palsy, the surgeon should be prepared to perform nerve resection and facial reanimation. Intraoperative frozen section can help define clear nerve margin resection proximally and distally. The operation may extend to the temporal bone if necessary, to obtain negative proximal nerve margin. Mastoidectomy can also be performed as a way of exposing and identifying the facial nerve trunk in tumors that abut the stylomastoid foramen.

Adequate exposure for parotidectomy is most commonly performed with modified Blair incision with extension into the neck if neck dissection is required. Facelift incision can be used for select malignancies with favorable size and anatomic position for this approach.

Nodal metastasis in salivary malignancy has been shown to reduce survival and often requires additional treatment including neck dissection with or without adjuvant radiation therapy. Neck dissection should be performed in patients with known nodal metastases. For patients without regional disease on imaging, there is some variation in recommendations for elective neck dissection. A recent NCDB study of 22,652 patients with parotid malignancies, advocated elective neck dissection in patients with any high-grade malignancy, and observation in patients with low-grade malignancy, epithelial myoepithelial carcinomas, and basal cell adenocarcinomas [23]. This was based on a threshold of > 10% risk of occult nodal disease. They found that all low-grade variants of all histopathologies had occult nodal incidences of < 10% [23]. There is evidence in the radiation oncology literature that for patients with high-grade salivary malignancy who are N0 and planned to undergo surgical resection and post-operative radiation that elective neck dissection did not necessarily improve locoregional recurrence in these patients compared to elective neck irradiation [27, 28]. Therefore, in patients who will receive adjuvant radiation therapy for high grade malignancy, elective neck dissection versus elective neck irradiation are both options. Neck dissection allows for histological assessment, and thus more accurate information for radiation planning. The appropriate extent of elective neck dissection is not well-defined for primary salivary malignancies; however, the consensus for patients with high-grade disease or advanced-stage tumors generally includes level IB-3 with some practitioners also advocating for inclusion of level IV [29].

For patients undergoing superficial or total parotidectomy for both benign and malignant tumors, contour defect

management should be considered. Options include abdominal fat grafts, dermal flap graft, local rotational flaps including sternocleidomastoid flap, regional flaps including submental artery island flap, and free flaps, most commonly the anterolateral thigh flap that can be deepithelialized and buried under the facial and neck skin. The anterolateral thigh flap has been found to be favorable in reconstruction of large volume defects. The tissue is able to offer symmetric tissue bulk compared to the contralateral side and additionally can withstand radiation-induced contracture, thereby allowing for more desirable long-term soft tissue volume and facial symmetry [30]. Facial reanimation is not impeded by flap presence in cases in which it is indicated. In patients who are not ideal free flap candidates, the submental artery island flap has also been found to give suitable tissue bulk for the parotid contour defect management. Advantages include ease of raising the flap, no requirement for separate incision, and no need for higher-level post-operative monitoring [31•].

Metastatic Tumors

Metastatic lesions most commonly present in the parotid gland and are most commonly from cutaneous malignancy. The most common metastatic lesion is cutaneous squamous cell carcinoma followed by cutaneous malignant melanoma and Merkel cell carcinoma. Surgically based therapy is favored in the form of total parotidectomy. In cases of metastatic skin cancers involving the parotid gland, the incidence of occult neck disease is high and elective neck dissection or elective neck irradiation is recommended [32]. Neck level IB-III should be included at a minimum. However, nodal spread can be found in all neck levels from cutaneous squamous cell carcinoma and melanoma, therefore particularly in cases with known nodal disease, complete neck dissection including level V can be performed [32]. Site of the primary and extent of nodal disease should be considered in determine levels of dissection.

Conclusion

Salivary gland neoplasms are a diverse group of tumors. Utilization of imaging and FNAC can help to guide management and treatment decisions for both benign and malignant tumors. The new Milan classification system has established six well-defined categories of cytology with associated risk of malignancy. It has been shown to have high PPV and NPV and should be utilized to aid clinical decision making when diagnosing and treating these lesions. Surgically based therapy continues to be favored in both benign and malignancy lesions. Management of the neck is important in high-grade salivary malignancy and reconstruction of defects should be advocated for and can be accomplished with favorable cosmetic results.

Compliance with Ethical Standards

Conflict of Interest Anne C. Kane and David Cognetti declare that they have no conflict of interest.

William R. Ryan reports personal fees from Medtronic and Olympus.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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