The Evaluation and Management of Carcinoma of the Minor Salivary Glands

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KEYWORDS

• Minor salivary gland • Salivary gland carcinoma • Mucoepidermoid carcinoma
• Adenoid cystic carcinoma

KEY POINTS

- The minor salivary glands are located throughout the upper aerodigestive tract.
- Salivary gland carcinomas are a rare malignancy affecting the head and neck accounting for less than 3% of all head and neck malignancies. Of malignant tumors of the salivary glands, less than 15% are in the minor glands.
- Compared with the major salivary glands masses, which tend to be benign, about 80% of all tumors of the minor glands are malignant.
- Minor salivary gland malignancies are often detected late because of the location, and the fact that they are not capsulated may influence their invasive potential into adjacent tissues.
- Adequate surgical resection of minor salivary gland tumors, even when higher grade malignancy, has the potential to yield 5-year survival rates of greater 70%.

INTRODUCTION

The salivary glands are secretory glands located in the head and neck that produce saliva and release it into the oral cavity via ductal systems (**Table 1**). Saliva functions as a lubricant for the protection of oral cavity structures and in the clearance and digestion of food. There are three major paired glands: (1) parotids, (2) submandibular glands, and (3) sublingual glands. There are approximately 400 to 700 minor salivary glands located throughout the upper aerodigestive tract. The minor salivary glands function similarly to the major glands. The minor salivary glands are affected by similar pathologies from infection and dysfunction to tumor growth. In contrast to the major salivary glands, in which benign tumors are more common, the likelihood of a tumor of the minor salivary glands being benign or malignant is nearly equivalent. This review

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Table 1
Staging of minor salivary gland carcinoma per American Joint Committee on Cancer 8th edition guidelines

T Stage	Size	Extent
T1	<2 cm	No extraparenchymal extension
T2	2–4 cm	
T3	>4 cm	Any extraparenchymal extension
T4a	Any size	Invasion of skin, mandible, external auditory canal, or facial nerve
T4b		Invasion of skull base or pterygoid plates; or encasement of the carotid artery

focuses on the identification and management malignant neoplasms that affect these minor salivary glands.

ANATOMY AND PHYSIOLOGY

The minor salivary glands develop during the twelfth week of gestation from the ectoderm of the oral cavity and nasopharynx. They are mainly concentrated into four regions: (1) buccal, (2) labial, (3) palatal, and (4) lingual. They are unencapsulated glands that are typically submucosal in location but are found within the oropharyngeal musculature.[1] Blood supply to the minor salivary glands comes from regional vasculature. The minor salivary glands receive postganglionic parasympathetic fibers from the submandibular ganglion. The only exception are the palatine minor salivary glands, which are innervated by postganglionic parasympathetic fibers from the sphenopalatine ganglion.

Each salivary gland is composed of secretory units made of acinar cells and myoepithelial cells. The ductal systems are made of epithelial cells. The functional cells of the salivary glands are the acinar cells. There are three types of acinar cells: (1) serous cells that secrete a waterier saliva; (2) mucus cells that secrete a thicker, mucoid saliva; and (3) mixed cells that secrete saliva with mixed characteristics. The myoepithelial cells function to help move the acinar cell secretions into the ductal system and then into the oral cavity. The major function, then, of the minor salivary glands is the production of saliva, a lubricant that also has antimicrobial protective properties.[1]

EPIDEMIOLOGY

Salivary gland neoplasms are fairly uncommon with a reported incidence of 0.4 to 2.6 per 100,000 people. They occur typically in the sixth to seventh decade of life and have a slightly higher incidence in men than women. Most salivary neoplasms occur in the parotid glands. Eighty percent are found to be benign. By contrast, 80% of minor salivary gland neoplasms tend to be malignant. Overall, salivary gland carcinoma represents less than 3% of all head and neck malignancies,[2–4] of which only 10% to 15% are from the minor glands.[5]

The pathologies affecting minor salivary glands are the same as those affecting the major glands. The most common benign neoplasm is the pleomorphic adenoma. Of malignant tumors found in the minor salivary glands, the most common are mucoepidermoid carcinoma (39%–40%), adenoid cystic carcinoma (24%–31%), and polymorphous low-grade adenocarcinoma (PLGA) (12%–24%).[6,7] The most common site of minor salivary gland tumor is the soft palate, followed by the nasal cavity, and then the tongue.[8,9]

Common benign and malignant pathologies identified in a large study of minor salivary glands tumors are listed next in order of most frequent to least[10]:

Benign
- Pleomorphic adenoma
- Basal cell adenoma
- Cystadenoma
- Myoepithelioma
- Oncocytoma
- Sialadenoma papilliferum

Malignant
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- PLGA
- Adenocarcinoma not specified
- Basal cell adenocarcinoma
- Clear cell carcinoma
- Salivary ductal carcinoma
- Carcinoma ex pleomorphic adenoma
- Mucinous adenocarcinoma
- Sebaceous carcinoma

RISK FACTORS FOR SALIVARY GLAND CARCINOMA INCLUDE

- Tobacco use
- Alcohol use
- History of radiation to the head and neck
- History of any cancer
- Human immunodeficiency virus (HIV) infection

Protective factors may be related to diet.[2,3,8] Vitamin C and fiber from fruit and vegetable sources have been found to lower the risk of salivary gland cancer. Diets high in cholesterol are associated with increased risk.[3]

PRESENTATION

Patients typically present with asymptomatic, painless swelling or mass. Patients presenting later in their disease course may have pain. It must be borne in mind that pain at presentation is a red flag for a perineural invasion associated with malignant tumors or malignant conversion in a benign tumor. In patients who do present with symptomatic masses, their symptoms tend to be related to mass effect or infiltration of adjacent structures. Minor salivary gland carcinoma of the sinonasal cavity can present with epistaxis or nasal obstruction. In the oropharynx and larynx, masses may result in dysphagia, dysphonia, or dyspnea. Physical examination may reveal a submucosal mass with adherent mucosa with or without overlying ulceration (**Fig. 1**).[2,11,12]

The differential diagnosis for this presentation includes acute necrotizing sialometaplasia, mucocele, and mucus retention cysts.[1,13]

Acute Necrotizing Sialometaplasia

This is a benign lesion most commonly seen on the palate. The lesion presents as a painful mass that eventually ulcerates. In this early stage, these lesions can look similar to basal cell carcinomas or other neoplasms with rolled edges over a central ulceration. As this disease process progresses, the lesion mucosalizes and heals over a

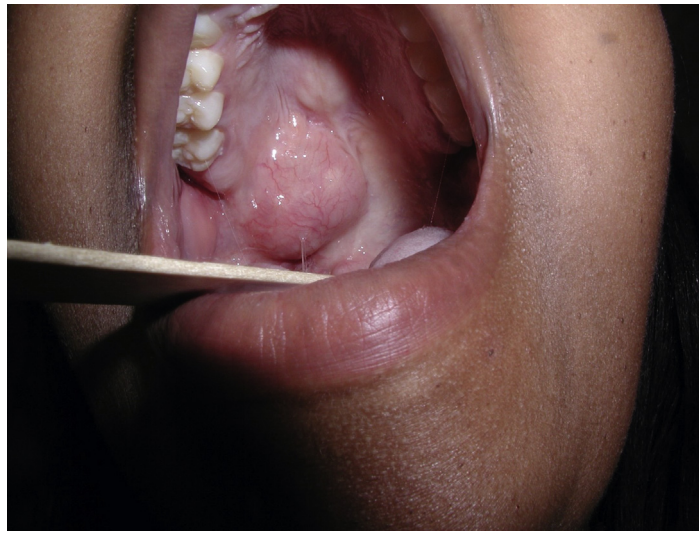

Fig. 1. Patient with enlarging hard palatal mass found to be adenoid cystic carcinoma. (*Courtesy of* Dr. Boyd Gillespie.)

period of several weeks. However, most tumors are often biopsied and/or surgically excised before this stage because of their concerning clinical presentation and appearance. On pathologic evaluation, the squamous metaplasia can appear similar to mucoepidermoid carcinoma.

Mucocele

Mucoceles present as a painless or painful oral submucosal mass. They typically occur after trauma that results in injury to the salivary duct and are characterized by submucosal accumulation of saliva with surrounding inflammation and granulation tissue without a true epithelial capsule.

Mucus Retention Cyst

These also present as a painless oral mass and result from an obstruction of a salivary duct resulting in mucoid salivary accumulation. Unlike mucoceles, mucus retention cysts they have a capsule lined by ductal epithelium. They more commonly affect the major salivary glands.

OTHER LESS COMMON PATHOLOGIES INCLUDE

- Lymphoepithelial cysts (see most commonly in HIV patients)
- Metastatic cutaneous malignancy, especially melanoma
- Benign masses, including epidermoid cysts, fibromas, and bony tori of the mandible or hard palate

IMAGING

Imaging is used to further characterize size and extent of the tumor. Initial imaging may involve ultrasound to characterize the nature of the mass (solid, cystic, or mixed) and location (intraglandular or extraglandular). For more definitive imaging, MRI is preferred over computed tomography (CT) in the case of minor salivary glands given

their size and the need to define tumor from surrounding soft and neural tissues. Precontrast and postcontrast MRIs are used to identify perineural spread, especially along the palatine nerves for palatal masses. MRI can also be used to differentiate between benign and malignant masses. On T2-weighted imaging, benign masses tend to be hyperintense, whereas malignant masses are hypointense. CT is complementary to MRI and helps with determination of bony erosion or invasion. Finally, PET scanning should be performed in cases of confirmed malignancy to rule out regional disease and systemic metastasis (**Figs. 2–4**).[2,14,15]

DIAGNOSIS

Tissue diagnosis is usually obtained through fine-needle aspiration, which has a sensitivity and a specificity of 87% to 96%.[16] Incisional biopsy is not routinely recommended because it can result in tumor violation and possibly impact recurrence potential.[17] However, the value of obtaining a diagnosis before surgical intervention is important for planning of surgical margins, extent of surgery, and reconstruction. Consequently, depending on the clinical presentation, site of tumor, and access, a biopsy can be obtained either through methods described previously, such as ultrasound-guided fine-needle aspiration, or core biopsy, incisional biopsy, or an excisional biopsy. Preoperative planning with imaging allows identification of nearby nerves and vasculature that may be at risk for injury during resection or that may need to be resected based on tumor proximity or obvious involvement (**Fig. 5**).

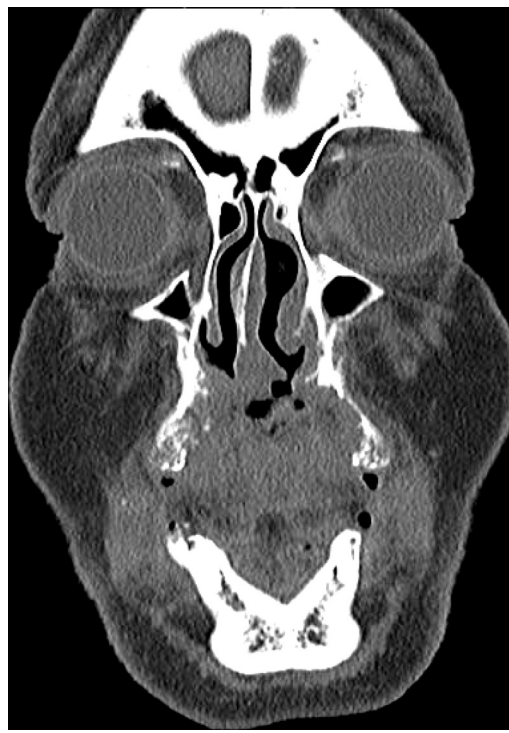

Fig. 2. A 74-year-old man with mucoepidermoid carcinoma of a hard palate minor salivary gland. CT without contrast showing destructive lesion of the anterior maxilla.

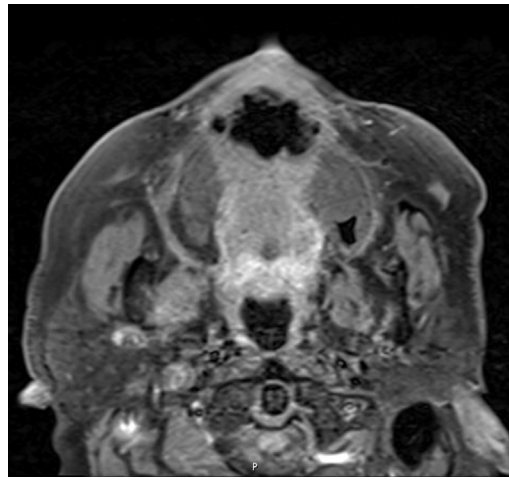

Fig. 3. Same patient as in Fig. 2. T2 fat-suppressed MRI showing oronasal fistula secondary to destructive lesion of the hard palate.

INVOLVEMENT OF THE HEALTH CARE TEAM

As with all malignancy, management of patients with salivary gland carcinoma involves a multidisciplinary approach; therefore, it is important to begin involving other providers early on. It is preferable that the patient sees the radiation and medical oncologist preoperatively so that they these specialists have the opportunity to make an independent evaluation of the tumor. This is vital for multidisciplinary discussions, tumor mapping, and treatment planning. Referrals should also include rehabilitative services, such as speech and language pathology for pretreatment swallow evaluation and post-treatment therapy; to nutrition to ensure adequate intake and supplementation recommendations for during and after treatment; to dentistry for

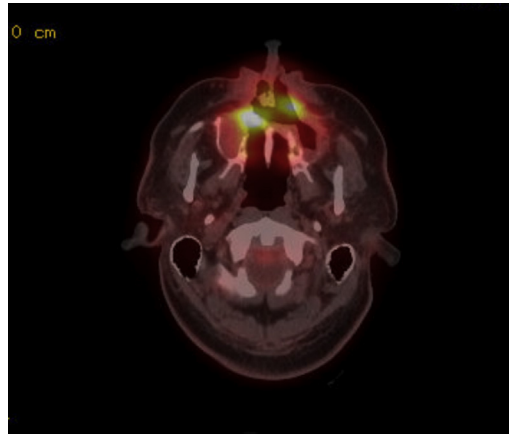

Fig. 4. Same patient as in Fig. 2. PET imaging showing hypermetabolic uptake at the hard palate and maxilla alveolar ridge at the site of the fistula with maximum standardized uptake value of 14.2.

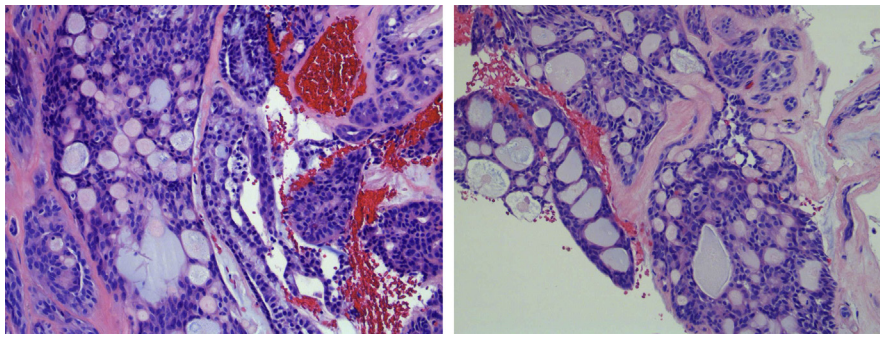

Fig. 5. Histopathologic slides depicting adenoid cystic carcinoma of the soft palate from the case in Fig. 2. (*Courtesy of* Tracy Rauch, MD, Baton Rouge, LA.)

dental extractions, especially in patients undergoing radiation therapy; and, where available and appropriate, to psychology or counseling services. Assessment of patient's social situation and planning transportation, disposition, and financial considerations are an important part of the overall treatment experience and impact efficiency of care.

MANAGEMENT

The mainstay of therapy for minor salivary gland carcinoma is surgical resection with or without adjuvant radiation based on grade and staging of the tumor. If the surgical margins involve bony resection (ie, the maxilla or mandible) adequate consideration must be given to appropriate reconstruction; in most scenarios a free tissue transfer is necessary and is usually performed at the time of surgical excision.[9] Lymph node dissection is based on clinical and/or radiographic findings of suspicious nodes or grade of the tumor.[2,8] For node-negative necks, elective neck dissection is dependent on the histologic type of the tumor, as is described while discussing individual pathologic types. Neck irradiation is an option for the management of occult metastasis in clinically node-negative necks, especially when malignant pathology is discovered incidentally after surgical management of a minor salivary gland neoplasm.[18,19] When indicated for management, a selective dissection of relevant nodal basin for the location of the primary (eg, I-IV or I-III) is performed.[20]

Radiation alone is not routinely recommended for primary management of minor salivary gland malignancies because it tends to have inferior long-term survival rates. A study of all types and locations of minor salivary gland cancer by Salgado and colleagues[21] looked at radiation outcomes in terms of local and distant control. Local control was only 87.9% at 5 years and 80.5% at 10 years. The rates of distant metastasis were 17% at 5 years and 37% at 10 years.[21]

Local recurrence is not uncommon with salivary gland malignancies. Distant metastases are most commonly to the lungs. As such, all patients with any minor salivary gland carcinoma require long-term follow-up.[2,20] Recurrence is managed similarly with surgery and/or reirradiation. The goal of management for recurrence may be local tumor control or palliation.[2,8]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma arising from the mucus and epidermal cells of salivary glands is categorized into low-grade or high-grade types based on cell types.

Low-grade tumors feature more mucous cells, whereas high-grade tumors are dominated by squamous cells with significant atypia similar in appearance to squamous cell carcinoma. More recently, there has been the delineation of intermediate-grade tumors that are formed of sheets of squamous cells but retain a more cystic-like structure similar to low-grade tumors.[22]

Low-grade tumors are managed with wide local resection only. Neck dissection and adjuvant radiation are not indicated.[20] High-grade tumors tend to be locally invasive and also have a significant potential for regional metastasis with an occult rate of metastasis being 21%. Consequently, high-grade minor salivary gland carcinomas are managed with surgical resection and neck dissection or adjuvant therapy (for occult local metastasis). Long-term survival is generally good with overall 5- and 10-year disease-free survival rates of 75% to 78% and 68% to 75%, respectively.[6,23]

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma arises from the epithelial and myoepithelial cells of the salivary glands. The tumor tends to be infiltrative at presentation. Although it is slow growing, it has a strong propensity for distant metastasis, even more so than local metastasis. Late distant metastasis is a distinguishing feature of adenoid cystic carcinoma that contributes to its lower long-term survival rates.[24] There are three histologic types (cribriform, tubular, and solid), with solid having the worst prognosis.

Management requires complete surgical excision and adjuvant radiation. Occult regional lymph node metastasis is uncommon, so elective neck dissection is not recommended routinely.[20] Furthermore, studies have shown that prognostic outcome for adenoid cystic carcinoma is not significantly changed by the involvement of local nodes at time of diagnosis.[12] However, similar to mucoepidermoid carcinoma, many authors argue for postoperative neck irradiation for protection against occult metastasis.[18,19] Mortality from adenoid cystic carcinoma is typically related to distant metastasis with 5- and 10-year survival rates of 68% to 79% and 37% to 63%, respectively.[6,23]

Polymorphous Low-Grade Adenocarcinoma

PLGA is a rare tumor that uniquely tends to affect minor salivary glands, although it can occur in the major glands. It is most commonly seen in palatal minor glands. Like other adenocarcinomas, this tumor arises from the mucus-secreting acinar cells of the salivary glands. The cells grow in uniform single-layer strands that form a variety of patterns. The most common are tubular, solid, and papillary; however, there have been other well-characterized patterns found, such as microcystic or cribriform. A clear association between pattern type and prognosis has not yet been well defined.[25–27]

PLGAs are considered low grade because they tend to be slow growing with lower rates of metastasis compared with other minor salivary gland malignancies. As such, management is based on primary local control with wide surgical excision. Adjuvant radiation is not usually necessary. Local metastasis occurs at a rate of 5% to 15%; therefore, elective neck dissection is not routinely recommended. A review of patients diagnosed and treated for PLGA of the head and neck in the SEER database by Patel and colleagues[26] supports this recommendation. Of 460 cases, 322 underwent surgical resection alone. Of those only 15 patients without clinical evidence of nodal disease underwent elective neck dissection; 94.7% did not undergo any neck dissection. The 5-year disease-free survival rate for the entire population (including the 5.3% who underwent elective neck dissection) was 99.3%.[26,27]

LONG-TERM OUTCOMES

In general, tumor of the oral cavity, especially palatal minor salivary gland carcinomas, have the best outcomes.[28] Sinonasal tumors and minor salivary gland carcinomas have the worst prognosis, regardless of histologic type. The 5-year survival rates for minor salivary gland carcinomas found in the oral cavity, oropharynx, and sinonasal cavities are around 84% to 89%. However, at 10 years, the survival rate is 74% for oral cavity tumors and drops to 59% for oropharyngeal tumors and 57% for sinonasal tumors.[7]

Based on final pathologic staging, the 5- and 10-year overall survival rates are as follows: for T1 tumors, 92% and 82%; for T2 tumors, 82% and 60%; for T3 tumors, 95% with a significant drop in survival to 24%; and for T4 tumors, 73% and 53%. Of note is the more severe drop in survival at 10 years in the T3 group compared with the T4 group. Hay and colleagues[7] comment this is likely the result of a smaller sample size for the T3 population given the inability of a tumor in the oropharyngeal space to get very large without invasion of major structures, necessitating upstaging. With nodal involvement the 5-year survival rate drops from 90% for N0 to 62% to 67% for N1 and N2. At 10 years for pathologically node-positive disease the survival rate is 33% to 40%.[7]

The overall survival rates based on all histologic subtypes of minor salivary gland carcinomas are 66% and 57% at 5- and 10-years, respectively. Disease-free survival ranges from 48% to 68% at 5 years and 37% to 68% at 10 years. However, the survival between 5 and 10 years for mucoepidermoid carcinoma and PLGA is stable. Adenoid cystic carcinoma tends to present with late distant metastasis and there is a considerable drop in survival between the 5- and 10-year marks.[6,11,20,29]

SUMMARY

Minor salivary glands are widely present throughout the upper aerodigestive tract, but tumors of these glands are an uncommon pathology of the head and neck. Minor salivary gland neoplasms have a high malignant potential; consequently, it is imperative to maintain a high level of suspicion when a concerning lesion is identified. Management is essentially surgical with adjuvant therapy when indicated resulting in good long-term survival rates for early stage tumors. A multimodality approach is required for advanced-stage tumors wherein primary nonsurgical therapy is a viable option for patients who have technically unresectable disease or do not want to opt for surgical management.

CLINICS CARE POINTS

- A high level of suspicion should be maintained for lesions of the aerodigestive tract to rule out minor salivary gland neoplasm given the high rate of malignancy in tumors of these glands.
- Any concerning lesions should undergo biopsy for definitive tissue diagnosis.
- The gold standard for imaging of the minor salivary glands is MRI to determine size and perineural involvement. CT and PET scanning can also be performed to evaluate for bony erosion and metastasis.
- Management of any stage or histologic type is primarily based on surgical excision with or without adjuvant radiation.

- The most common histologic types are mucoepidermoid carcinoma and adenoid cystic carcinoma. These can be locally aggressive but have good 5-year disease-free survival rates with appropriate surgical and radiation treatments.
- Neck dissection at time of surgical resection is indicated for node-positive disease and could be an alternative to neck irradiation for a clinically negative neck.
- The role of postoperative adjuvant radiation is to manage occult local metastasis in patients who are clinically free of nodal disease and for whom elective neck dissection is not planned.
- The decision on elective neck dissection or elective neck irradiation is multifactorial and depends on clinical presentation, tumor site, histology, and patient factors; consequently, indication for neck dissection is best discussed in a multidisciplinary setting and personalized to each patient's unique presentation and circumstances.
- These tumors are associated with high local recurrence rates; thus, long-term follow-up is imperative to allow early diagnosis and treatment of recurrence.

DISCLOSURE

Nothing to disclose.

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