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A review of Salivary gland Neoplasms and its management

Thiagarajan Shivakumar Nair.V.Sudhir Joshi Poonam Chaturvedi Pankaj

Tata Memorial Centre, Mumbai India

Abstract: Salivary gland neoplasm are a diverse group of tumors which are often benign and commonly arise from the parotid gland. PubMed search engine was used to search for relevant articles. The main challenge in the management of these tumours is to distinguish them between benign and malignant types and treat them accordingly. FNAC is a very useful investigation in this regard with high accuracy. MRI or CT scan are also useful, in knowing the extent of lesion especially when the tumour involves the deep lobe or extends to parapharyngeal space. Most of the low grade tumours and benign lesions can be managed by surgery alone whereas high grade and advanced lesions will require adjuvant treatment in the form of radiotherapy. Chemotherapy is mostly used in the palliative set up, whereas molecular targeted therapy is still in experimental stage only. In this article, we review the literature to highlight the current understanding in the evaluation and management of salivary gland neoplasms.

Key Words: Salivary gland, Neoplasms, management

Introduction:

Salivary gland tumors are a diverse group of neoplasms. The incidence of these tumors worldwide is between 0.05-2/100,000 population (1). Salivary gland tumors constitute about 0.5% of all cancers and 5% of head and neck malignancy (2). About 64-80% are located in the parotids (commonly in the superficial lobe), 7-11% in the submandibular glands and the remainder being distributed between the sublingual (1%) and the minor salivary glands (9-23%) (3). Malignant tumors comprise 15–32% of parotid tumors, 41–45% of submandibular tumors and 70–90% of sublingual tumors, and 50% of all minor salivary gland tumors (3,4,5). Most of the malignancies are adenocarcinoma of the parotid. The median age at presentation is usually above 40 years with its incidence increasing with age and more among men (2). Approximately 5% of all salivary gland tumors occur in patients younger than 16 years. Relative survival for adults diagnosed with salivary gland cancer is 66.6% at five years, with a significant difference between men and women (58 and 72%, respectively) (6,7,8). Five-year relative survival decreases markedly with age.

Methods and materials:

PubMed and Google scholar was used to identify the most relevant articles, rather than to look at all the available literature in this topic of salivary gland neoplasm. No particular inclusion or exclusion criteria were used to include articles for this review. This review does not aim to be wholly comprehensive of all the literature on salivary gland neoplasm management. It highlights the most relevant articles in the literature, and discusses the most important finding in each study, which the authors considered were of importance in the management of the condition. Articles between 1984 to 2012 were looked to pool in the latest information regarding these neoplasms.

Etiology:

Causes are largely unknown. Whilst most other head and neck cancers are strongly related to smoking and drinking, these do not play a role in the salivary glands (9). Irradiation may cause tumors as was observed among the Japanese survivors of the Hiroshima & Nagasaki bombing and also among patients who received radiation for benign conditions (eg: acne, adenoids) at a younger age (10). Strong co-relation exists between EBV infection and lymphoepithelial carcinoma, however they are restricted to Asian patients predominantly. There is also an association with UV-radition exposure and BCC of skin. Hodgkins lymphoma, Medulloblastoma, immunosupression, HIV , are all associated with salivary gland malignancy as seen in several studies (11,12,13,14,15). Occupational exposures in rubber manufacturing, nickel, wood industry, and hairdressing salons or beauty shops are all associated with these tumors (16,17).

Histopathology:

Salivary gland tumors are the most diverse with at least 24 different types recognized by the World Health Organization (WHO) (Table 1) (18).Grades reflects the biological nature of the tumor (low and high-intermediate are placed in high risk category) and correlates significantly with prognosis (19,20). Some tumors are known to be high grade or biologically aggressive (Sebaceous carcinoma, Mucinous adenocarcinoma, carcino-sarcoma,carcinoma ex- pleomorphic adenoma, squamous cell carcinoma (SCC), high-grade mucoepidermoid adenoid-cystic carcinoma), some are low grade (acinic cell, low-grade adenocarcinoma, polymorphous low grade,clear cell & basal cell

carcinoma, Low grade mucoepidermoid carcinoma, Epithelial-myoepithelial carcinoma) . High grade salivary carcinomas have a 5 year survival of roughly 40% while low and intermediate grade tumors have a 5 year survival of 85–90% (20).

Clinical features:

Malignant salivary tumors demonstrate a range of biological behaviors. Majority of tumors arise from the parotid (80%) and most of these are benign. Hence the lesions must be first differentiated between inflammatory conditions, autoimmune disorders and other benign lesions before making the diagnosis of malignancy. They may present as slow growing lumps (younger patients) or as aggressive tumors (especially in the elderly) and at times facial palsy may be a presenting feature. But, slow growing tumors does not always exclude malignancy. Malignant tumors of the salivary glands show widely different patterns of growth. The most common ones (adenoid cystic, mucoepidermoid low-grade, acinic cell carcinomas) frequently grow slowly. Invasiveness depends on the grade of the malignancy. Clinical indicators suggesting a malignant salivary gland tumor are: rapid growth rate, pain, facial nerve involvement, and cervical adenopathy. Clinical presentation may also be characterized by medialisation of tonsil in the neck, or palatal fullness, trismus, skin ulceration and fistulas (21,22). Lymphatic spread is usually less common except in a few histological types like ductal carcinomas, high-grade mucoepidermoid carcinomas, carcinomas ex pleomorphic, adenoma and squamous cell carcinomas. The commons sites for distant metastases are the lungs(80%), bone (15%), liver and other sites (5%) and are commonly associated with Adenoid cystic carcinoma, adenocarcinoma NOS, carcinoma ex-mixed tumor, small cell carcinoma and ductal carcinoma.

Symptoms arising due to tumor of minor salivary glands varies according to tumor size, position and location. Majority of them are intraoral and usually cause a painless submucosal swelling. Minor salivary glands are distributed along the entire upper aero-digestive tract.Tumors arising from them produce a variety of symptoms depending on its location. In the oropharyngeal area it can cause a painless lump/ulcers. If the nasopharynx or the nasal cavity is involved this may cause facial pain, nasal obstruction or bleeding. Tumor in the larynx or trachea can cause hoarseness, or dyspnoea.(23). Clinical examination is a very important part of diagnosing these lesions.

Investigations:

Before performing any surgery on the patient a tissue diagnosis is necessary, especially so when malignancy is suspected and an ablative surgery is planned. FNAC may help us in getting this much needed tissue diagnosis, based on which the surgeon can plan the type and extent of the surgical procedure and also counsel the patient regarding the treatment, including the possible need for adjuvant treatment, its associated complications & prognosis. FNAC has a high sensitivity and specificity with an accuracy ranging from 87% to 96% (24), but the technique is operator sensitive. Sensitivity ranges between 73% and 86.6% both in malignant and in benign tumors while specificity was noted to be usually better in benign than in malignant tumors (97% vs. 85%)(25). The risk of seeding along the needle route has been demonstrated to be negligible. It is an inexpensive investigation, simple to perform and, in appropriate hands, it is quite accurate and morbidity is very low.

Ultrasound guided core biopsy (USCB) of the salivary gland, especially the parotid can be useful in establishing the tissue diagnosis, in cases where it is not possible to get a conclusive diagnosis from FNAC alone. USCB is a safe procedure which can be

performed under local anesthesia and in the outpatient basis using a 18-20G needle, with a diagnostic accuracy of 100%, with an added advantage of the core tissue that can be processed for IHC thus avoiding unnecessary open biopsies (26). Open biopsy is usually not recommended due to the risk of seeding. In the presence of small masses in the palate, tongue (minor salivary gland tumor), punch biopsy may be preferable to direct excision, unless the latter provides adequate margins, if the lesion is malignant. The accuracy of frozen section diagnosis is quite controversial, its application is limited. The accuracy rate is better for benign tumors than it is for malignant lesions (98.7% vs. 85.9%) (27) .Ultrasonography can compliment these investigations and has the advantage of being a less expensive alternative with high sensitivity (approximately 100%) and can be used to aid in fine needle aspiration of the glands. Ultrasound proves excellent for differentiating intraglandular from extraglandular lesions, although it is not able to show part of the deeper parotid lobe. CT scan and/or MRI are recommended in the presence of malignant disease or a deep parotid lobe lesion is suspected. MRI is particularly recommended in demonstrating the interface of tumor and surrounding tissues (especially facial nerve) for a correct surgical planning, especially for larger tumors and for those tumors arising in deep structures and/or involving them. The advantages of MRI include also the elimination of dental artifacts and the ability to distinguish between a tumor and obstructed secretions(28).

Prognostic factors:(Table 2)

Survival strongly correlates with clinical stage (table 4) and grade. Histology is also a predictor of the tumor behavior and it contributes to optimize treatment. Tumor stage, histology, grading, facial nerve paralysis, extra-parotid tumor extension and cervical node involvement are the most important tumor-related predictors of survival (29-35)

Treatment:

Treatment in case of salivary gland malignancy is surgical excision with adequate margins followed by adjuvant treatment with radiotherapy. The surgical resection of these glands has to well planned and executed, especially so for parotid tumors due to the presence of the facial nerve within it. Superficial parotidectomy with adequate margins should be sufficient for benign or low grade malignant tumors without any risk factors such as high grade tumor, advanced stage disease, positive or close margins and PNI(36,37), as most of the tumors arise from the superficial lobe. If the Facial nerve function is normal preoperatively, care must be taken to preserve it. The facial nerve should be sacrificed if there is preoperative facial nerve palsy or if the tumor is infiltrating into the nerve or is inseparable from it. Adequate rehabilitative measures like, immediate nerve grafting or eyelid gold implants should be done to avoid postoperative corneal damage.

Malignant tumor arising from the deep lobe is rare and often requires total parotidectomy. For submandibular gland tumors wide excision alone is sufficient in case of benign tumours. Malignant tumours require wider excisions that can be a formal level I clearance or even a supraomohyoid (Level I –III) neck dissection (38).

Incidence of nodal metastasis in salivary gland tumors is 14-20% (39). They occur predominantly in high grade tumor and advanced T-stage disease. Neck can be addressed in these set of patients and in N+ necks.(40). Generally nodes are positive in level II or III. Hence for parotid tumours with nodal metastases, a modified neck dissection will be ideal. However, elective neck dissection is often not required in most circumstances. In certain circumstances were suspicion of nodal metastasis is high, then

level II nodes can be removed and sent for frozen section. If the nodes are found to be positive, then the rest of the neck can be managed accordingly.

Treatment of minor salivary gland tumor is wide surgical excision with adequate margins, similar to squamous cell carcinoma of the oral cavity or elsewhere in the upper aerodigestive tract. Post-operative RT may be indicated as per the presence of high risk features, like positive margins, high grade, advanced stage. The incidence of nodal metastasis is low in minor salivary gland malignancy.

Radiotherapy in the form of photons/electron can be used at the dose of 66-74 Gy(1.8/2 Gy per fraction) for primary and gross cervical lymphadenopathy and 44-64 Gy (1.8/2 Gy per fraction) for uninvolved nodal stations in a definitive set up and in the post-operative set up dose $\geq$ 60 Gy can be given for primary and 44-64 Gy to uninvolved nodal stations (NCCN guidelines-2012 version). Postoperative neutron, heavy ions or proton radiotherapy is recommended, in adenoid cystic carcinoma, since it is associated with a better tumor control than with photons.(41,42).Doses between 15-20 Gy is given depending on the energy and type of fractionation. Neutron beam is also recommended in inoperable or unresectable tumors. Role of postoperative chemoradiation for salivary gland malignancy is not well established. However there are few studies which have explored this option in a small group of patients. Some based on the treating physician discreation(43) and in others based on adverse features such as perineural or nodal involvement and positive margin(44). Chemotherapy regimen used were, platinum-based regimen (43) or 5-FU, Hydroxurea, gemcitabine and paclitaxel (44). Patients having been treated with chemoradiotherapy had a better overall survival (43,44). Hence it seems to be an effective adjuvant treatment in selected patients and warrants further investigation.

For local recurrences surgery, irradiation or re-irradiation can be used alone or in combination as per the individual case if the above are not feasible then palliative chemotherapy can be suggested. For regional relapses a comprehensive neck dissection is advisable followed by adjuvant treatment as the case may be. However their prognosis remains poor.

Distant metastasis are most commonly associated with high grade tumors. Metastases from adenoid cystic carcinoma usually show indolent asymptomatic course. Solitary metastases of lung and liver can be resected. Bone metastases are rare, but if there is a risk of fracture or drug-resistant pain, radiotherapy or surgery is recommended. Palliative chemotherapy either in combination (cyclophosphomide+doxorubicin +cisplatin, or carboplatin+ paclitaxel) or as single agent (Cisplatin, 5-Fluorouracil, Docetaxel) can be tried in these setting (45).There seems to be no obvious advantage of one over the other. The employment of target therapies (eg:imatinib, Traztusumab,Lapatinib) is only currently recommended within clinical trials.

Follow Up:

Patients diagnosed with major salivary gland cancer are at risk of developing second primary cancers, especially in the salivary gland, oral cavity, thyroid, lungs, and kidneys. Though this is less than that for squamous cell carcinoma of upper aerodigestive tract. (46) Local recurrence represents the main cause of treatment failure, followed by cervical neck metastasis and distant metastasis. The relative risk depends on tumor stage and grade, positive nodal disease, facial nerve involvement and extraparenchymal extension. Seventy per cent of local recurrences are observed within the first three years. Hence they should be strictly followed up during this period. Follow up during first year post-treatment: every 2-3 months. Second year: every 2–4

months. Third year: every 3–6 months. Fourth and fifth years: every 6 months. After 5 years once in a year. All salivary gland malignancies require a follow-up period of 20 years for true measures of clinical outcome. Yearly chest X-rays, TSH analysis could be indicated every 6–12 months, in case of neck irradiation.

Conclusion:

Surgery forms the main modality of treatment in salivary gland tumors. FNA and Imaging, especially with MRI is indicated in large or deep parotid lobe tumours, and those suspected to be malignant, in order to decide on the expected extent of resection and to determine the potential risk to the facial nerve. Facial nerve should be identified and preserved whenever it is not involved by the disease. Immediate reconstruction with nerve grafting will help in long term recovery in the facial nerve function. Elective neck dissection in clinically N0 salivary gland cancer is recommended when the primary tumour exhibits high-risk features. Postoperative radiotherapy is useful for tumours at risk of locoregional recurrence.

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Tables:

Table 1: WHO classification

Malignant epithelial tumours	**Benign epithelial tumours**
Acinic cell carcinoma	Pleomorphic adenoma
Mucoepidermoid carcinoma	Myoepithelioma
Adenoid cystic carcinoma	Basal cell adenoma
Polymorphous low-grade adenocarcinoma	Warthin tumour
	Oncocytoma
Epithelial-myoepithelial carcinoma	Canalicular adenoma
Clear cell carcinoma, not otherwise specified	Sebaceous adenoma
	Lymphadenoma
Basal cell adenocarcinoma	Sebaceous
Sebaceous carcinoma	Non-sebaceous
Sebaceous lymphadenocarcinoma	Ductal papillomas
Cystadenocarcinoma	Inverted ductal papilloma
Low-grade cribriform cystadenocarcinoma	Intraductal papilloma
	Sialadenoma papilliferum
Mucinous adenocarcinoma	Cystadenoma
Oncocytic carcinoma	**Soft tissue tumours**
Salivary duct carcinoma	Haemangioma

Adenocarcinoma, not otherwise specified	**Haematolymphoid tumours**
Myoepithelial carcinoma	Hodgkin lymphoma
Carcinoma ex pleomorphic adenoma	Diffuse large B-cell lymphoma
Carcinosarcoma	Extranodal marginal zone B-cell lymphoma
Metastasizing pleomorphic adenoma	
Squamous cell carcinoma	**Secondary tumours**
Small cell carcinoma	
Large cell carcinoma	
Lymphoepithelial carcinoma	
Sialoblastoma	

Table2:Prognostic factors

Author (year)	Tumor size/ Stage	Regional metastasis	Grade	Positive margin	PNI	Age	Sex	Solid histology	Gland location
Villavicencio-Ayala B,et al 2008(30)	+	+	+	+	+				
R. Bryan Bel, et al 2005 (31)	+	+	+			+			
Lima RA,et al 2005(32)	+	+	+			+			
Ellington CL,et al 2011(33)	+					+	+		
Ozdemir C,et al 2011(34)	+		+		+			+	
Carrillo JF,et al 2010(35)	+	+	+	+					

McHugh.CH, et al 2011(36)	+		+	+	+				+

Table 3: TNM stage (AJCC,2010)

PRIMARY TUMOR (T)	**REGIONAL LYMPH NODES (N)**
Tx-Primary tumor cannot be assessed T0-No evidence of primary tumor T1-Tumor 2 cm or less in greatest dimension without extraparenchymal extension* T2-Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension* T3-Tumor more than 4 cm and/or tumor having extraparenchymal extension* T4a-Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve T4b-Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery **Note:* Extraparenchymal extension is clinical or macroscopic evidence of	Nx-Regional lymph nodes cannot be assessed N0-No regional lymph node metastasis N1-Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension N2a-Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, N2b- in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, N2c- in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension N3- Metastasis in a lymph node, more than 6 cm in greatest dimension **DISTANT METASTASIS (M)** M0-No distant metastasis (no pathologic M0; use clinical M to complete stage group) M1-Distant metastasis

invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes

Stage	**TNM**
I	T1N0M0
II	T2N0M0
III	T3N0M0 T1N1M0 T2N1M0 T3N1M0
IVA	T4aN0M0 T4aN1M0 T1N2M0 T2N2M0 T3N2M0 T4aN2M0
IVB	T4bN0-3M0 T1-4N3M0
IVC	T1-4N0-3M1