Cure rates are very poor for most histological types.
Salivary malignancy rises with increasing smoking and alcohol consumption, ionizing radiations, aflatoxins (mainly Aflatoxin B1), race, diet (other than fatty acids), occupation (apart from feed workers) and Epstein-Barr virus (EBV) infection.
Polyunsaturated fatty acids (PUFA) seem to exert a beneficial effect.

**THE CELL AND MOLECULAR BIOLOGY OF SALIVARY CANCER**
- **PCNA** (proliferating cell nuclear antigen) immunoreactivity is high in malignancy. (Also Ki67 antibodies) and thus provides a useful diagnostic tool.
- **Ki67** has prognostic significance in Adenoid Cystic Carcinoma.
- Bcl 2 and apoptotic index are good prognostic markers.
- Bax is proapoptotic (in salivary neoplasms there is decreased Bcl 2 and increased Bax leading to increased apoptosis)
- **Cytokeratin 14** is over expressed
- Fibroblast growth factor (FGF) 1 and 2 over expressed.
- **NO** has tumour promoting activity.
- Thus inducible nitric oxide synthase plays important role in tumourgenesis
- Increased VEGF may be associated.
- **METALLOTHIONEIN** may be a marker of differentiation in malignant salivary tumours.
- Increased Estrogen & progesterone receptors.
- Mucoepidermoid Carcinoma is positive for a variety of Cytokeratin and also Vimentin, α1 Antichymotrypsin, S100, Leu N1.
- Adenoid Cystic Ca ➔ Ki67 antibody, p53
- Mdm2 raised
- Viruses implicated include ➔ HHV8, HPV, CMV

**WHO CLASSIFICATION BY SOBIN AND SHEIFERT**
- **7 Categories (CAM NUTS)**
  1. Adenomas
  2. Carcinomas
  3. Malignant melanomas
  4. Non epithelial tumours
  5. Secondary tumours
  6. Undifferentiated tumours
  7. Tumour like lesions
- Histologically, carcinomas are probably best classified as below:
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Polymorphous low-grade adenocarcinoma
- Papillary cystadenocarcinoma
- Mucinous adenocarcinoma;
- Adenocarcinoma;
- Carcinoma ex pleomorphic adenoma;
- Malignant mixed tumour;
- Squamous cell carcinoma;
- Undifferentiated carcinoma.

**ACINIC CELL CARCINOMA**

- **Low grade malignancy**
  - Although bilateral salivary malignancy is usually very rare, acinic cell carcinoma is the most common and, in terms of salivary tumours, in general, only Warthin's tumour is more likely to follow this behavior.
- Clinically – Painless lump
  - Commonly a solitary encapsulated lesion with well defined margins but multilobulation does occur.
  - Cystic lesions are frequently seen
  - This tumour probably arises from the acinic cells.
- **Histological** Patterns include Follicular, Papillary cystic, Solid microcystic.
  - All these patterns may be seen in one individual tumour.
- Has the best survival rate of any salivary cancer
- Excision of a facial nerve is not justified unless it is grossly involved.
- The tumour has generally been regarded as at the more benign end of the spectrum of malignant salivary disease.

**MUCOEPIDERMOID CARCINOMA**

- This tumour is the most common of the major salivary gland malignancies, accounting for one-third of cases.
- 3 types of cells ➔ Mucoid, Intermediate and Epidermoid
- 3 Grades ➔ Low, Intermediate and High
- Low grade are cystic in consistency
- High grade are solid and have high propensity of LN metastasis.
  - All salivary cancers originate from a common progenitor cell, the intercalated duct reserve cell.
- Low-grade tumours have a five-year survival of 96 percent whereas high-grade tumours are associated with a death rate ten times this.
- The extent and grade of a tumour dictate the treatment.
- For the most favorable tumours a superficial parotidectomy with facial nerve preservation, if possible, is recommended, although a much more radical excision is necessary for patients with large and/or high-grade lesions. An associated elective neck dissection to include level, 2 and 3 for the No neck would also be appropriate. With more severe neck disease a radical neck dissection is necessary
- High grade tumours also require post op radiotherapy
ADENOID CYSTIC CARCINOMA

- Nearly 1/3\(^{rd}\) of all adenoid cystic carcinomas occurred in the major salivary glands, and most of the remainder involved the minor glands.
- 3 Histological subtypes → Cribriform (40%) > Solid (25%) > Tubular (20%) (CST)
- Solid Variant → worst prognosis, rarely cured and 100% recurrence seen at primary site at 30 yrs.
- Patients with tumours of the oral cavity minor salivary glands, particularly the hard palate, fared better than patients with tumours at other sites.
- Distant metastases, particularly to the lung is characteristic of this disease (70% at 5 yrs and 100% at 10 yrs).
- Slow growing tumour (tumour doubling time around an year)
- Also invade peripheral nerves (80% cases)
- Carcinomas involving the larger salivary glands, in particular the parotid gland, may have as much as a four-fold better survival at ten years than those in the minor salivary glands.
- Some patients present with severe pain due to peripheral nerve invasion, and in the parotid gland facial nerve palsy may be evident
- Radical primary surgery is likely to provide the best survival rates at 20 years.
- Palatal lesions for small cancers with clear surgical margins and no nerve spread or bone involvement, local surgery alone was considered adequate.
- Postoperative irradiation should be an integral part of treatment of adenoid cystic carcinoma.
- No prophylactic neck dissection required (like in mucoepidermoid ca)
- Limited role of chemotherapy → Cisplatin + doxorubicin
- (MRI) of the primary site, and of course the neck, but also computed tomography (CT) scans of the lungs and liver and an isotope bone scan.
- Skip lesions in the facial nerve, several centimeters from where tumour invasion apparently terminated, both on frozen section and on later paraffin section histology, certainly take place.
- If gross or frozen section histology involvement of a nerve is found at operation, the nerve should be sacrificed and an immediate nerve graft carried out in the case of the facial nerve.

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA

ADENOCARCINOMA, PAPILLARY CYSTADENOCA & MUCINOUS ADENOCARCINOMA

CARCINOMA EX PLEOMORPHIC ADENOMA

- These tumours account for up to 10 percent of all malignant salivary cancer and tend to arise in the major glands.
- Malignant transformation most commonly took place in men over 40 years of age, in tumours of the deep parotid lobe, in solitary nodules greater than 2 cm diameter and in those patients with a history of a previous operation.
- 3 Histological types
  - Noninvasive Carcinoma
  - Invasive Carcinoma
  - Carcinosarcoma (rare)
- A depth of invasion of less than 1 cm is associated with a five-year survival of approximately 100 percent; if the depth of invasion is greater than the five-year survival is halved. Poor prognosis
**SQUAMOUS CELL CARCINOMA**

- The tumour must arise from the gland itself and not from lymph nodes within the gland. There must be no regional or adjacent tumour especially of the skin and, needless to say, a high-grade mucoepidermoid carcinoma must be excluded.
- Nearly half of all patients have neck node metastases at the time of presentation.
- A locoregional failure rate of approximately 50 percent is to be expected for the parotid but is rather higher in the submandibular gland.
- Distant metastases occur in approximately 10 percent of patients.
- Almost no five-year survivors.

**UNDIFFERENTIATED CARCINOMA**

- These tumours commonly arise from ductal reserve cells and histologically are small-cell cancers
- About 1% of all salivary neoplasms
- Undifferentiated carcinomas of the salivary glands are microscopically identical to the undifferentiated carcinoma seen in the nasopharynx. (thus nasopharyngeal carcinoma must be ruled out)
- Irradiation crucial
- Cure rare < 10%.

**LYMPHOMA**

- Batsakis and Rugezi suggest three criteria for the diagnosis of this disease: extraglandular lymphoma must not be present; there is histological proof that the lymphoma involves the gland parenchyma and not the intraglandular lymph nodes
- Immunohistochemical screening must confirm the presence of lymphoma markers.
- In general, **low-grade non-Hodgkin's lymphoma (NHL)** is either **not treated at all** or, if it is, conservative monomodal management is undertaken with drugs such as **chlorambucil**.
- **High-grade lesions** are usually **treated aggressively** with complex regimens such as **VAPEC-B**.
- Sjogren's syndrome – risk of lymphoma more by 40%
- True extranodal involvement only happens with NHL although Hodgkin's disease may affect intraglandular lymph nodes.

**METASTATIC DISEASE INVOLVING THE SALIVARY GLANDS**

- The superficial parotid lobe contains a median of five nodes and the deep lobe two. Almost all metastases to the salivary glands arise from the skin of the head and neck and involve the parotid lymph nodes
- **Skin tumours posterior to the facial artery** and vein give rise to parotid node metastases in about half of patients, whereas skin cancer anterior to these involve the parotid in only 3 percent of cases
- If parotid metastases are present, a parotidectomy en bloc with a neck dissection in continuity with the primary lesion is indicated.
- Even with such major surgery, five-year survival rates are little more than 10 percent.
HISTOGENESIS

- All salivary cancers arise from two types of pluripotent precursor cells. These are:
  - The intercalated duct reserve cell
  - The excretory duct reserve cell

- Some points:

PAROTID GLAND

- 24 percent of all parotid tumours are malignant
- Facial nerve paralysis as a presenting symptom and sign appears in approximately one-third of patients.
- Although about 10 percent of parotid tumours are of the deep lobe, fortunately, malignancy is fairly unusual at this site.
- It is said to be divided into two unequal parts by the facial nerve and thus the concept of a superficial and a deep lobe is purely one of surgical anatomy.
- Where the facial nerve is grossly involved it must be sacrificed and immediate nerve repair carried out.
- **Mucoepidermoid carcinoma > Adenoid cystic carcinoma.**
- The superficial lobe contains between three and seven nodes whereas the deep lobe contains from nil to three nodes

THE SUBMANDIBULAR GLAND

- 40 percent of submandibular tumours are malignant
- **Adenoid cystic carcinoma > Mucoepidermoid carcinoma**
- Nerve involvement, in particular the Hypoglossal Nerve > Trigeminal Nerve > Facial Nerve.
- Surgery should include a regional dissection of the whole submandibular triangle with the gland and surrounding lymph nodes, including areas 1, 2 and 3.

MINOR SALIVARY GLANDS

- **Adenoid cystic carcinoma > Mucoepidermoid carcinoma**

DIAGNOSIS AND INVESTIGATIONS

- Following symptoms and signs are ominous:
  - Pain
  - Nerve palsy
  - Skin invasion
  - Neck nodes
  - A fibre optic upper airway endoscopy
  - FNAC Salivary gland and LN
  - For large tumours – trucut biopsy
  - Small gland – excision biopsy
A chest radiograph should be performed at the first visit because if metastases are identified there is no point in considering major ablative treatment.

MRI > CT

**TREATMENT**

**Radiotherapy**

Indications for RT (by Guillamondegui et al [1975])
1. High grade carcinoma
2. Recurrent carcinoma
3. Deep lobe cancers
4. Gross/microscopic residual disease following surgery
5. Tumours adjacent to the facial nerve
6. Regional lymph node metastasis
7. Invasion of muscle, bone, skin, nerves or any extra parotid metastasis
8. Any T3 parotid carcinoma (even low grade)

- Surgery with post op radio
- Total dose of 60 Gy in fractions of 2 Gy a day.
- Fast neutron treatment has been compared with standard photon treatment and has shown improved locoregional control BUT devastating damage to the irradiated site, including necrosis, severe fibrosis, loss of function and fistula.

**CHEMOTHERAPY**

- For various reasons salivary cancer has a high rate of distant metastasis with one-fifth of patients succumbing
- For the adeno types, doxorubicin is effective, particularly in combination with cisplatin and perhaps 5-fluorouracil.
- For the squamous malignancies the latter two agents are effective in the initial stages.
SURGERY

- Primary modality
- Sacrifice of the middle ear or even the eye may be justifiable to obtain surgical clearance, although it must be remembered that survival, in general, for patients with such extensive salivary cancer is extremely poor.
- In Parapharyngeal space tumours including the deep lobe of the parotid, the carotid vessels may be encountered and if such involvement is limited the tumour can be dissected off the adventitia of the artery. If involvement of the artery is the only potentially positive margin then excision should be recommended. Unless it is the external carotid artery, repair is necessary and is relatively straightforward using a segment of long saphenous vein
- Essentially, there are three methods of repairing the facial nerve.
- The first is NEURORRHAPHY, which involves middle ear surgery to extend the length of the facial nerve stump, and end to end anaestomosis can then be performed.
- 2nd is interposition graft (greater auricular or sural nerve)
- Of the branches of the facial nerve, the most important is the zygomatic allowing eyelid closure, followed by the buccal to allow the perioral muscles to function
- The distal end of the donor nerve is anastamose to the proximal stump of the facial nerve.
- The third method is nerve transfer and the donor nerve is usually the hypoglossal.
- Tone can be restored to the face but not normal voluntary movement.

TREATMENT OF THE NECK

- Node negative high grade tumours ➔ Selective neck dissection, level 1,2,3.
- For any nodal mets ➔ radical