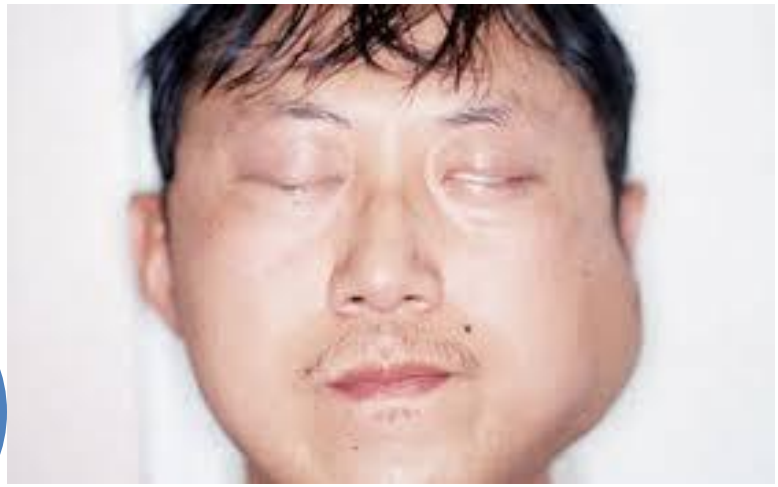
# SALIVARY GLAND TUMORS



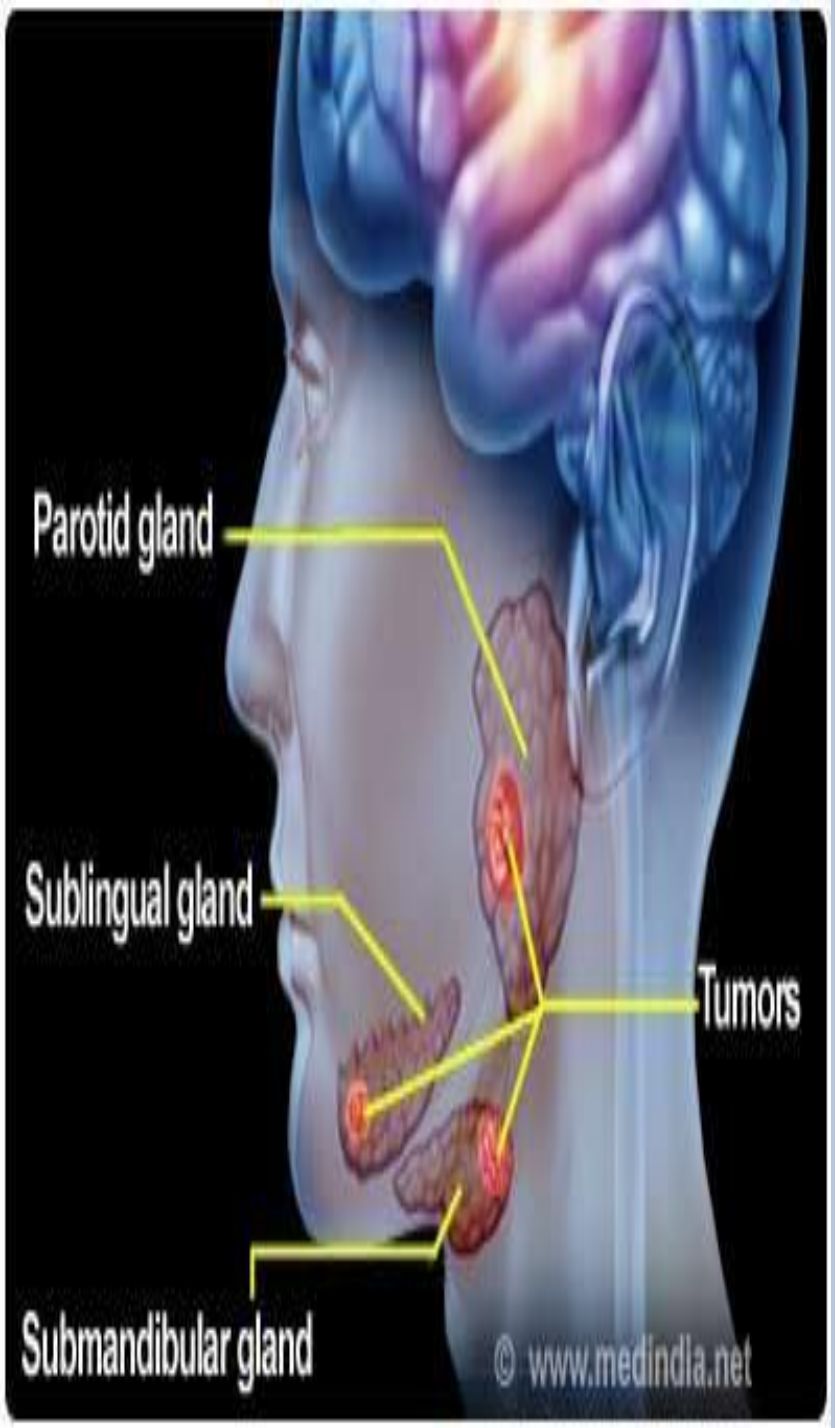
**Prof Dr / Alaa El – Suity**

# INTRODUCTION

- The major salivary glands include the parotid glands, submandibular glands, and sublingual glands. There are also approximately 750 minor salivary glands scattered throughout the submucosa of the oral cavity, oropharynx, hypopharynx, larynx, parapharyngeal space, and nasopharynx.
- Salivary gland neoplasms are rare and constitute 3% to 4% of head and neck neoplasms.
- The incidence of salivary gland neoplasms as a whole is approximately 5.5 cases per 100,000 individuals in the United States, with malignant neoplasms accounting for 0.9 cases per 100,000.

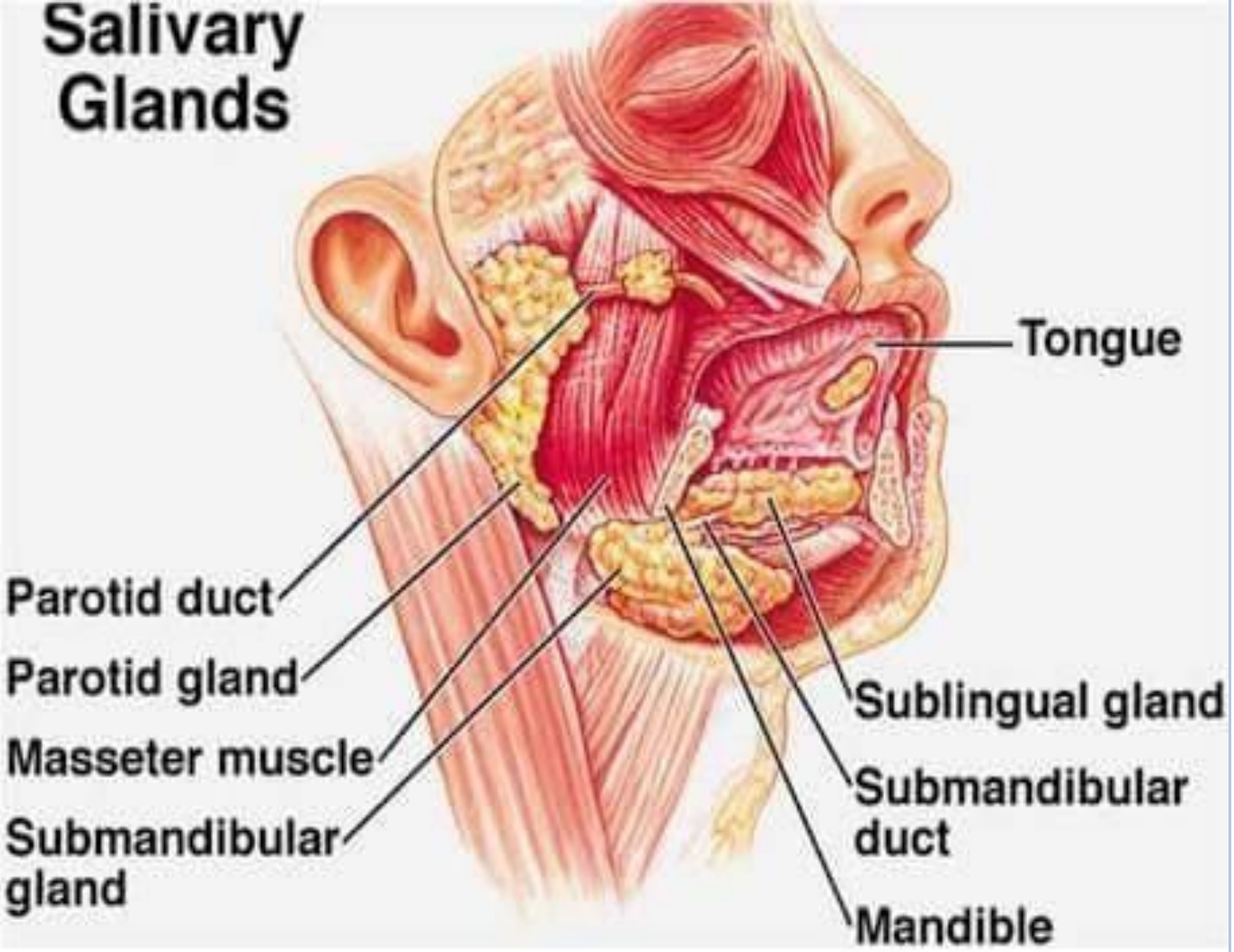
- Mortality from malignant salivary gland neoplasms varies by stage and pathology, but the overall 5-year survival rate is 72%.
- Salivary gland neoplasms most commonly appear in the sixth decade of life.
- Benign neoplasms occur more frequently in women than in men, but malignant tumors are distributed equally between the sexes.

- Most neoplasms arise in the parotid gland (70%), whereas tumors of the submandibular gland (22%) and sublingual and minor salivary glands (8%) are less common. The ratio of malignant to benign tumors varies by site as well parotid gland, 80% benign and 20% malignant; submandibular gland and sublingual gland, 50% benign and 50% malignant; and minor salivary glands, 25% benign and 75% malignant.

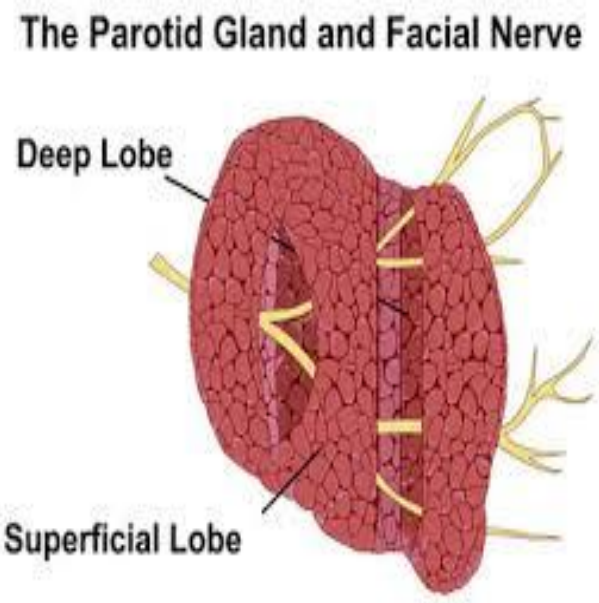


# Embryogenesis

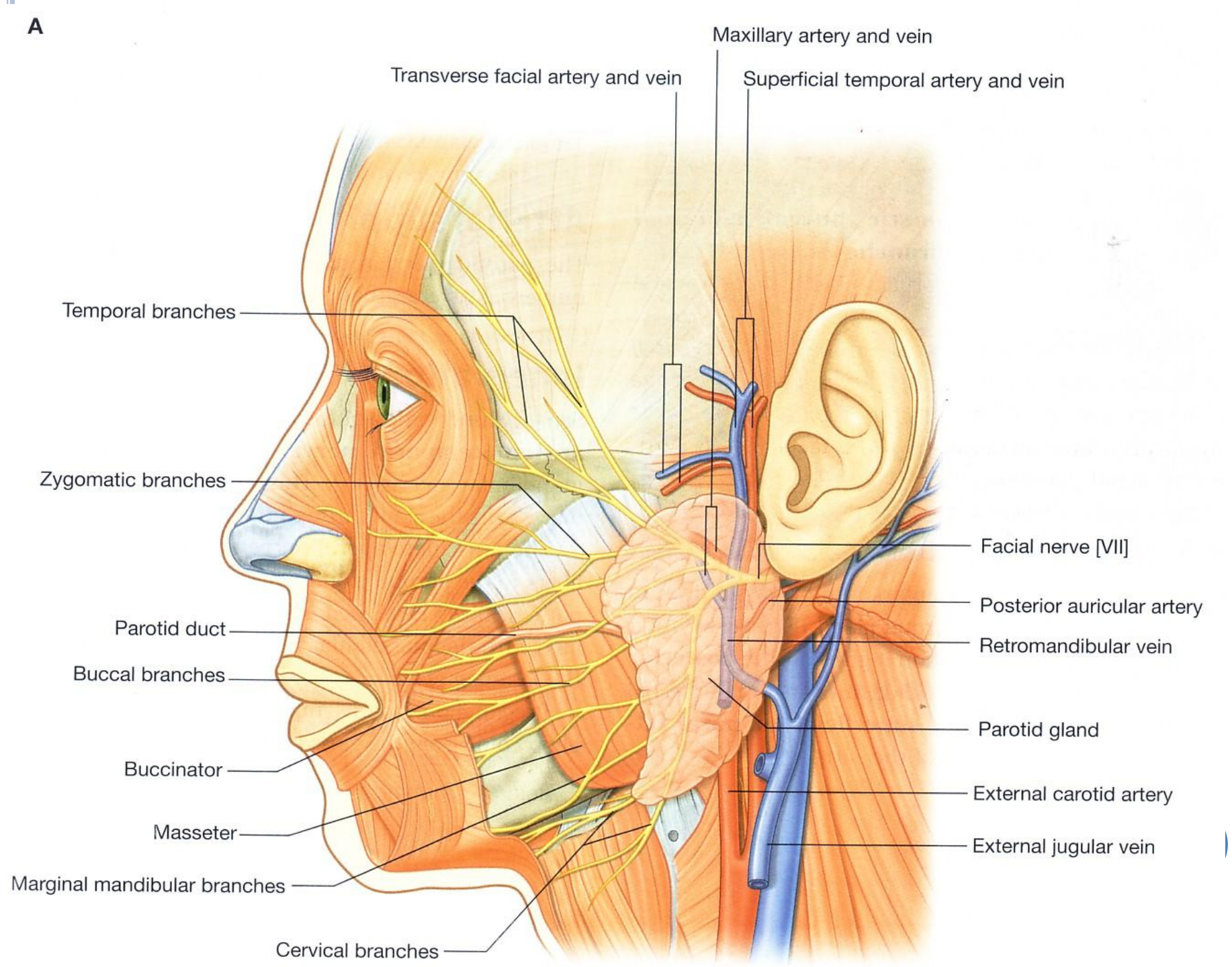
- The salivary glands begin to form at 6-9 weeks' gestation. The major salivary glands arise from ectodermal tissue. The minor salivary glands arise from either ectodermal or endodermal tissue, depending on their location.
- . Embryologically, the submandibular gland forms earlier than does the parotid gland. The resulting associated lymph nodes are outside the gland.
- lymphatic metastases may manifest within the substance of the parotid gland and not the submandibular gland.


Salivary Glands
Tongue
Parotid duct
Parotid gland
Masseter muscle
Submandibular gland
Sublingual gland
Submandibular duct
Mandible

# PAROTID GLAND

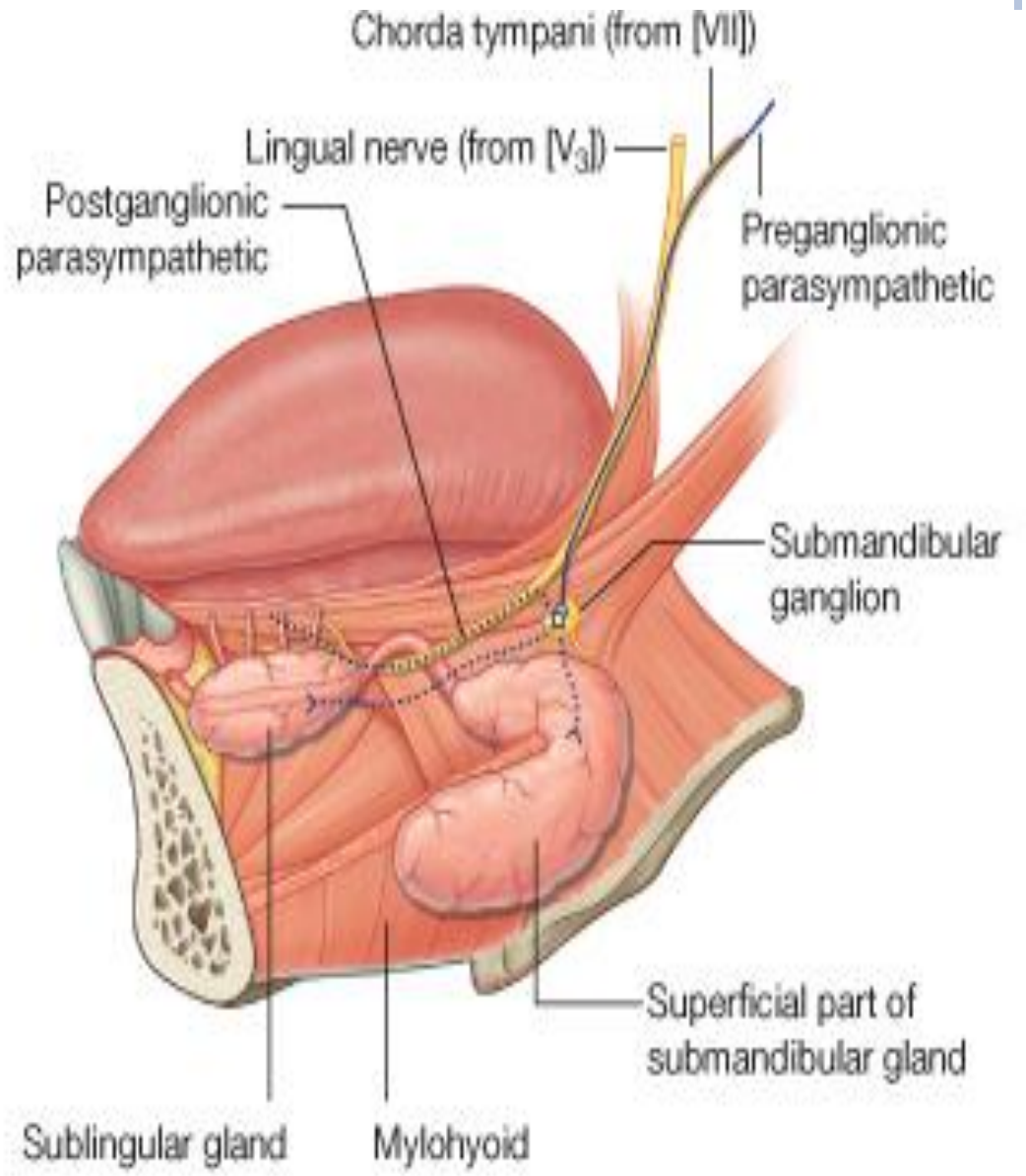



- The largest of the salivary glands
- The parotid compartment contains the parotid gland, nerves, blood vessels, and lymphatic vessels, along with the gland itself.
- The superficial portion contains the facial nerve, great auricular nerve, and auriculotemporal nerve. The middle portion contains the superficial temporal vein.
- . The deep portion contains the external carotid artery, the maxillary artery, and the superficial temporal artery.


A
Maxillary artery and vein
Transverse facial artery and vein
Superficial temporal artery and vein
Temporal branches
Zygomatic branches
Facial nerve [VII]
Posterior auricular artery
Parotid duct
Retromandibular vein
Buccal branches
Parotid gland
Buccinator
External carotid artery
Masseter
External jugular vein
Marginal mandibular branches
Cervical branches

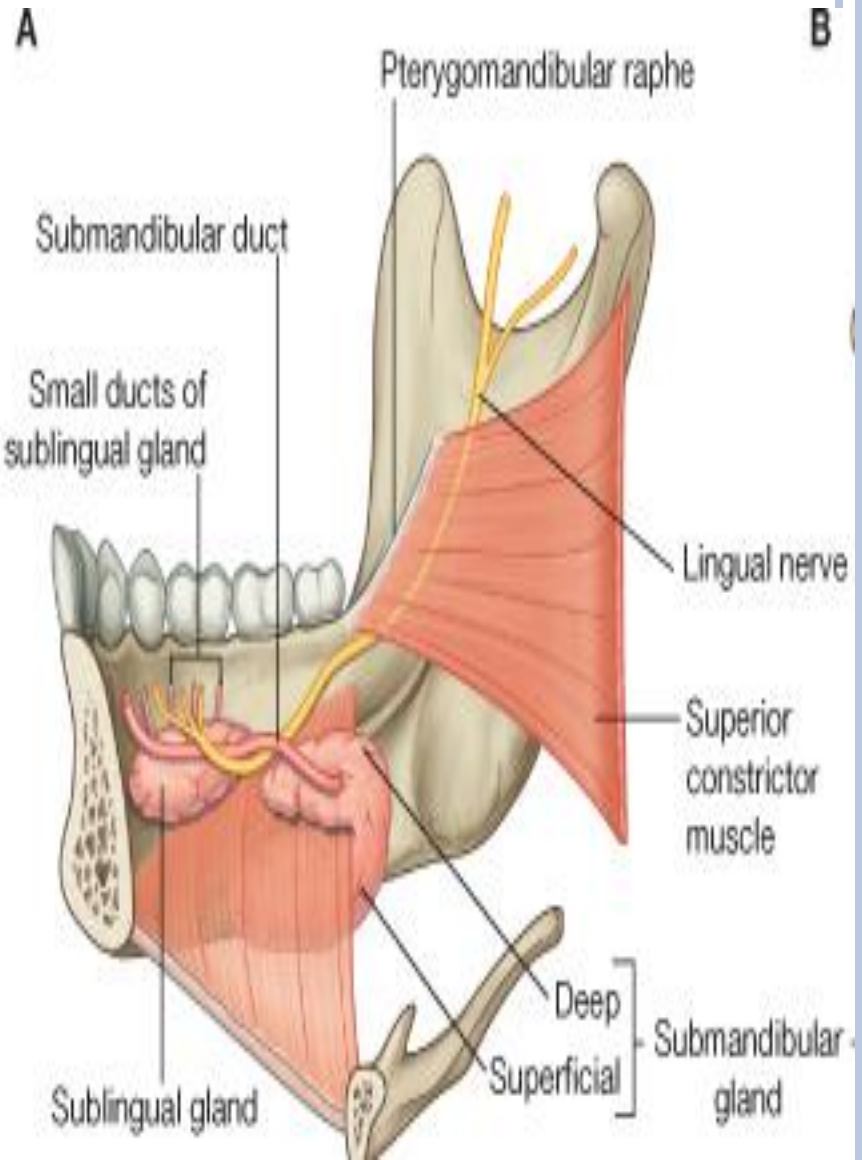
# SUBMANDIBULAR GLAND

- Second largest salivary glands, after the parotid. They are encapsulated glands located anterior and inferior to the angle of the mandible in the submandibular triangle.



# SUBLINGUAL GLANDS

- the smallest of the major salivary glands. Unlike the parotid and submandibular gland, the sublingual gland is unencapsulated. Each gland lies medial to the mandibular body, just above the mylohyoid muscle and deep to the mucosa of the mouth floor.



# Minor salivary glands

- Approximately 600-1000 minor salivary glands are located throughout the paranasal sinuses, nasal cavity, oral mucosa, hard palate, soft palate, pharynx, and larynx. Each gland is a discrete unit with its own duct opening into the oral cavity.

# Tumors of the major and minor salivary glands

## Benign

- Pleomorphic adenoma
- Warthin tumor
- Capillary hemangioma
- Oncocytoma
- Basal cell adenoma
- Canalicular adenoma
- Myoepithelioma
- Sialadenoma papilliferum
- Intraductal papilloma
- Inverted ductal papilloma

## Malignant

- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Basal cell adenocarcinoma
- Sebaceous carcinoma
- Papillary cystadenocarcinoma

# WHO histological classification of tumours of the salivary glands

| | |
|---|---|
| **Malignant epithelial tumours** | |
| Acinic cell carcinoma | 8550/3 |
| Mucoepidermoid carcinoma | 8430/3 |
| Adenoid cystic carcinoma | 8200/3 |
| Polymorphous low-grade adenocarcinoma | 8525/3 |
| Epithelial-myoepithelial carcinoma | 8562/3 |
| Clear cell carcinoma, not otherwise specified | 8310/3 |
| Basal cell adenocarcinoma | 8147/3 |
| Sebaceous carcinoma | 8410/3 |
| Sebaceous lymphadenocarcinoma | 8410/3 |
| Cystadenocarcinoma | 8440/3 |
| Low-grade cribriform cystadenocarcinoma | |
| Mucinous adenocarcinoma | 8480/3 |
| Oncocytic carcinoma | 8290/3 |
| Salivary duct carcinoma | 8500/3 |
| Adenocarcinoma, not otherwise specified | 8140/3 |
| Myoepithelial carcinoma | 8982/3 |
| Carcinoma ex pleomorphic adenoma | 8941/3 |
| Carcinosarcoma | 8980/3 |
| Metastasizing pleomorphic adenoma | 8940/1 |
| Squamous cell carcinoma | 8070/3 |
| Small cell carcinoma | 8041/3 |
| Large cell carcinoma | 8012/3 |
| Lymphoepithelial carcinoma | 8082/3 |
| Sialoblastoma | 8974/1 |
| **Benign epithelial tumours** | |
| Pleomorphic adenoma | 8940/0 |
| Myoepithelioma | 8982/0 |
| Basal cell adenoma | 8147/0 |
| Warthin tumour | 8561/0 |
| Oncocytoma | 8290/0 |
| Canalicular adenoma | 8149/0 |
| Sebaceous adenoma | 8410/0 |
| Lymphadenoma | |
| Sebaceous | 8410/0 |
| Non-sebaceous | 8410/0 |
| Ductal papillomas | |
| Inverted ductal papilloma | 8503/0 |
| Intraductal papilloma | 8503/0 |
| Sialadenoma papilliferum | 8406/0 |
| Cystadenoma | 8440/0 |
| **Soft tissue tumours** | |
| Haemangioma | 9120/0 |
| **Haematolymphoid tumours** | |
| Hodgkin lymphoma | |
| Diffuse large B-cell lymphoma | 9680/3 |
| Extranodal marginal zone B-cell lymphoma | 9699/3 |
| **Secondary tumours** | |

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

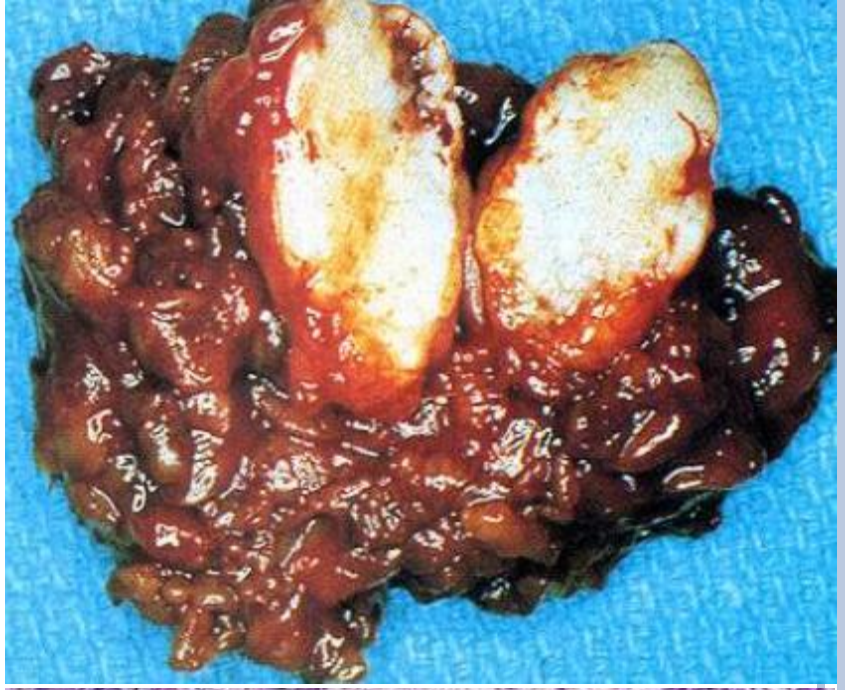
- Most tumors are benign, with pleomorphic adenomas being the most common.
- Pleomorphic adenomas make up 70% of parotid gland tumors and 50% of submandibular gland tumors.
- Warthin tumors (adenolymphomas) account for 5-15% of SGTs. Warthin tumors are the second most common neoplasm of the parotid gland.
- In children, 35% of salivary gland neoplasms are malignant. Mucoepidermoid carcinoma is the most common salivary gland malignancy in children.

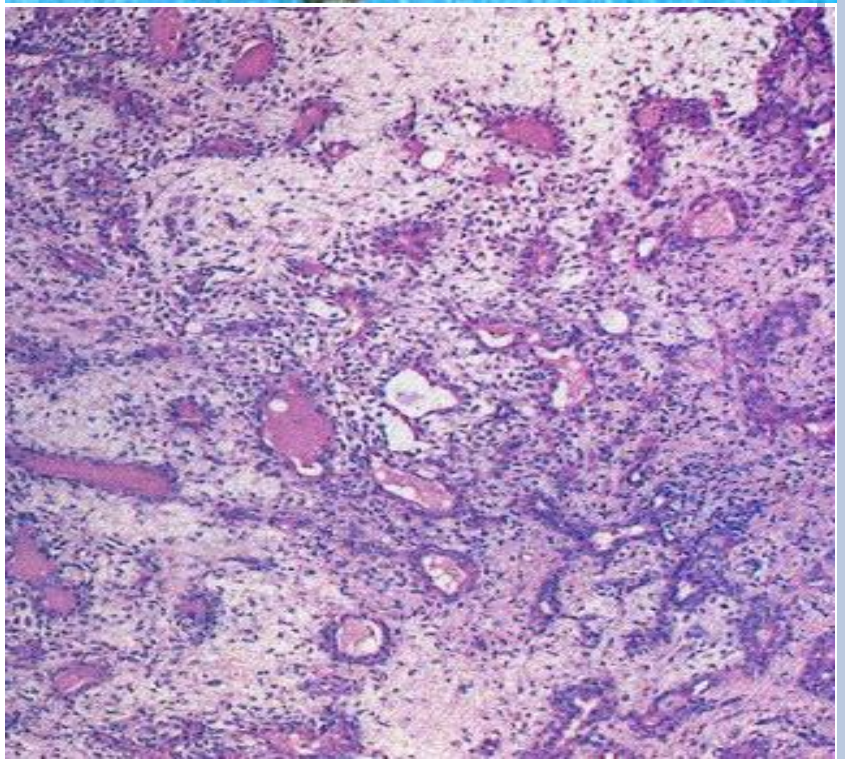
- Mucoepidermoid cancer is the most common parotid malignancy.
- Adenoid cystic carcinoma is the most common malignant tumor of all minor salivary glands and the submandibular gland.
- Secondaries are rare and derived from other malignancies.

# Pleomorphic adenoma

- Grossly: Smooth ,Well-demarcated ,Solid ,Cystic changes ,Myxoid stroma, incomplete capsule that allows expansion

- Histology: Mixture of epithelial, myopeithelial and stromal components.

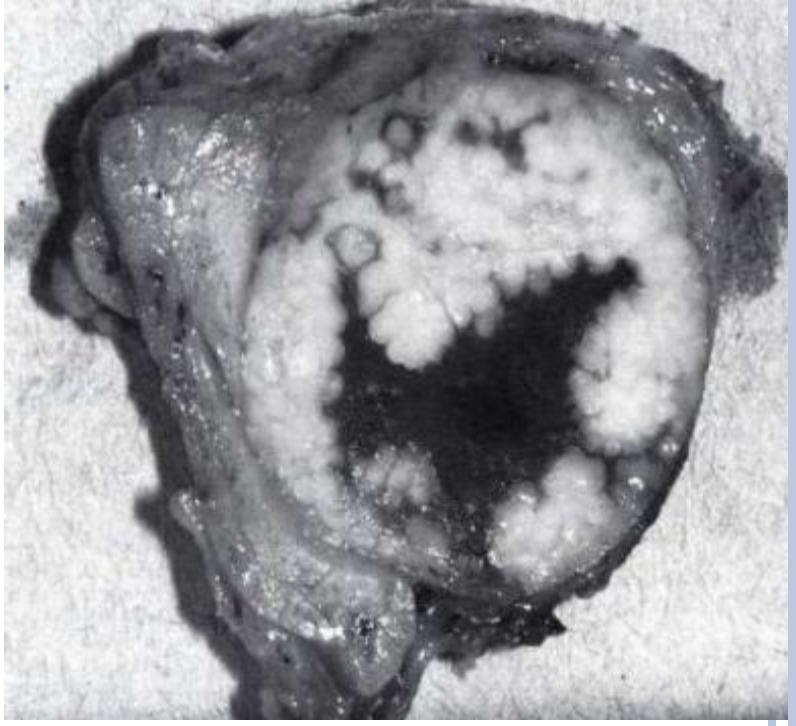




- recurrence rate for salivary gland pleomorphic adenomas is 6.7%, with the first recurrence arising at a median of 7 years.
- recurrence risk factors for these lesions included positive and uncertain resection margins, as well as younger age at diagnosis.
- Those located in the minor salivary glands had a lower recurrence risk than did pleomorphic adenomas in the parotid glands.
- 0.15% of the lesions underwent malignant transformation.

# Warthin's Tumor

- 10% bilateral or multicentric.
- Gross pathology: soft and cystic. Encapsulated, Smooth/lobulated surface, Cystic spaces of variable size, with viscous fluid, shaggy epithelium, Solid areas with white nodules representing lymphoid follicles

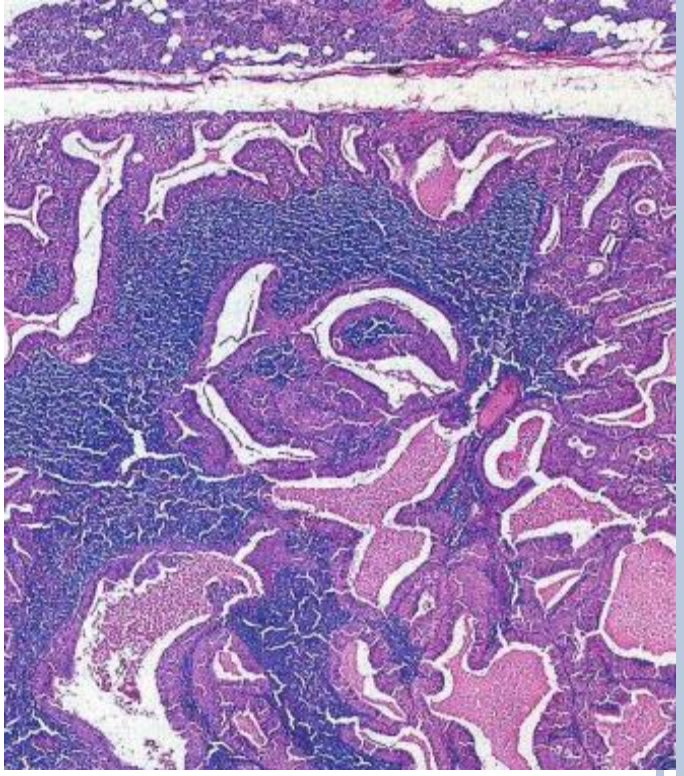


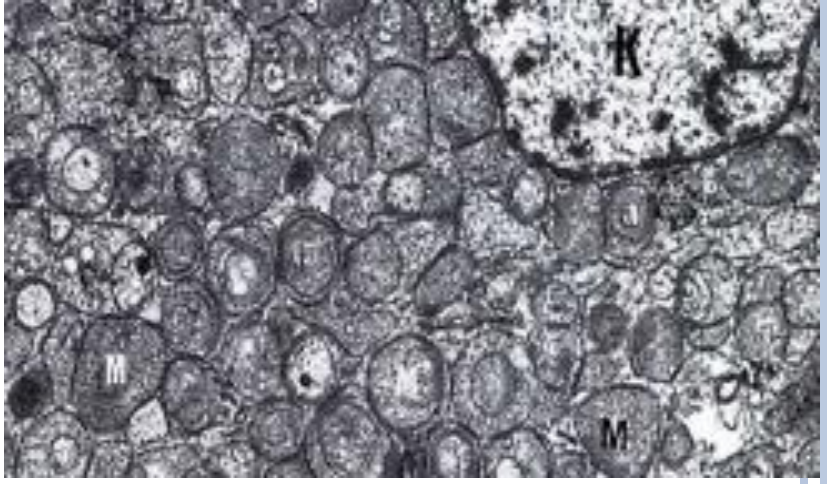
- Histology: Papillary projections into cystic spaces surrounded by lymphoid stroma.

Epithelium: double cell layer Luminal cells, Basal cells

Stroma: mature lymphoid follicles with germinal centers.

Usually affects older people, not dangerous, operated on for cosmotic reasons.





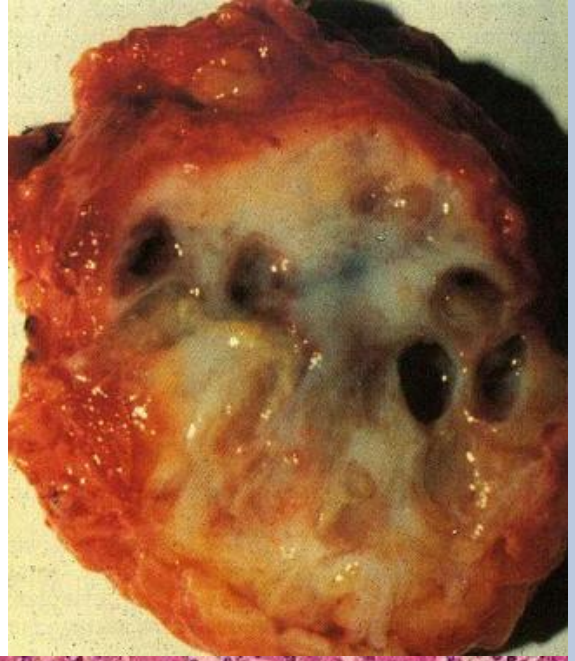

# ONCOCYTOMA

- Electron microscopy: – Mitochondrial hyperplasia
- Benign oncocytomas are smooth and firm, with a rubbery consistency.

# MONOMORPHIC ADENOMA:

Grossly, the tumors are encapsulated and smooth

# Mucoepidermoid Carcinoma



Low-grade :

Mucus cell > epidermoid cells

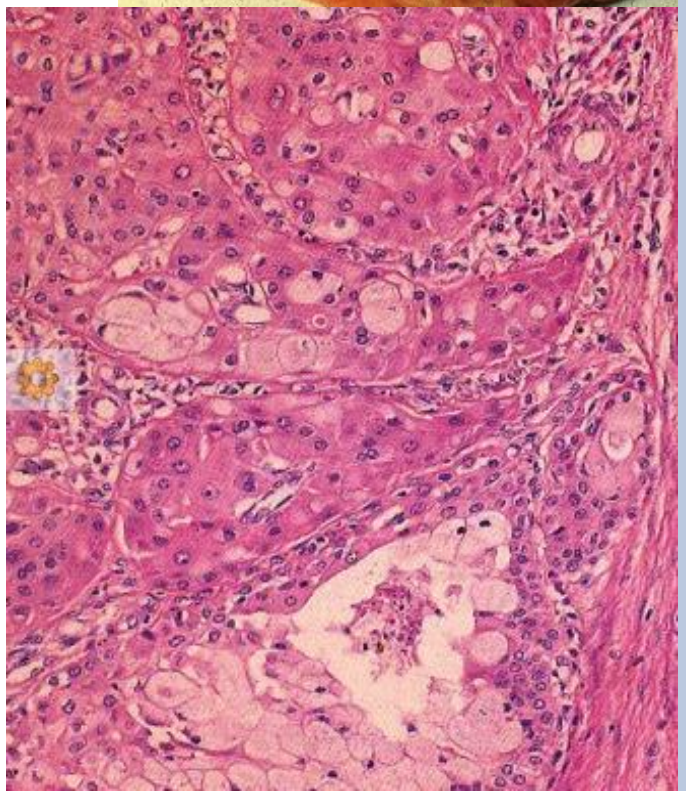
Prominent cysts

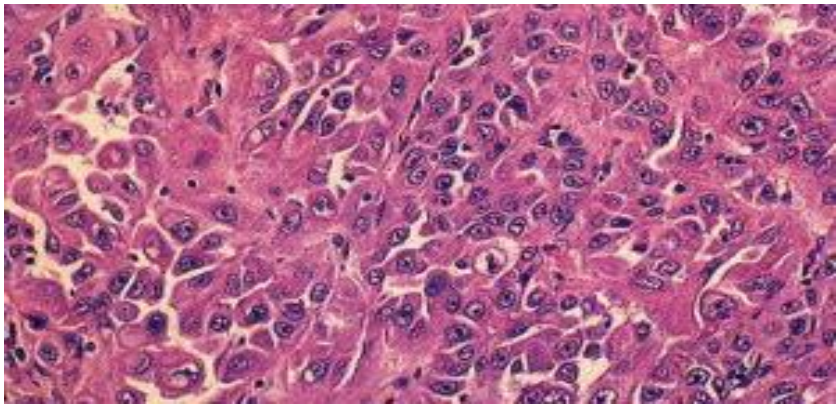
Mature cellular elements.

High-grade :

Epidermoid > mucus

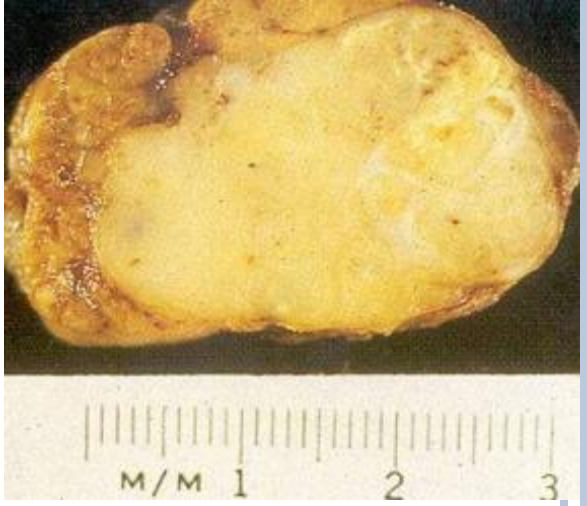
Solid tumor cell proliferation





- Limited local invasiveness and low metastatic potential characterize this tumor, particularly when cytologically low-grade.
- For patients with low-grade tumors without nodal or distant metastasis, 5-year survival is 75-95%, whereas patients with high-grade tumors with lymph node metastasis at the time of diagnosis have a 5-year survival of only 5%. Overall 10-year survival is 50%.

# Adenoid Cystic Carcinoma



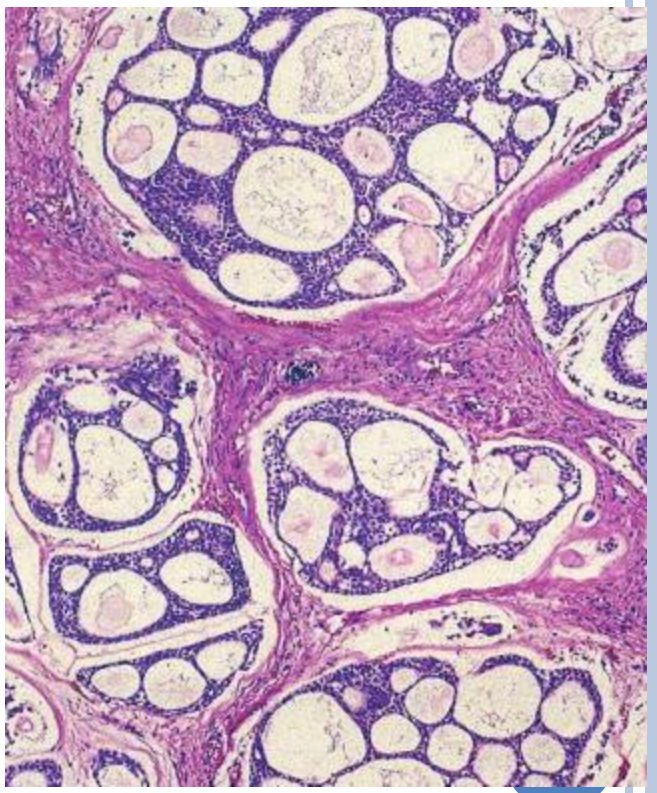

Gross pathology:

Well-circumscribed ,Solid, rarely with cystic spaces. nonencapsulated; they have a gray-pink color and infiltrate the surrounding normal tissues.

Histology:

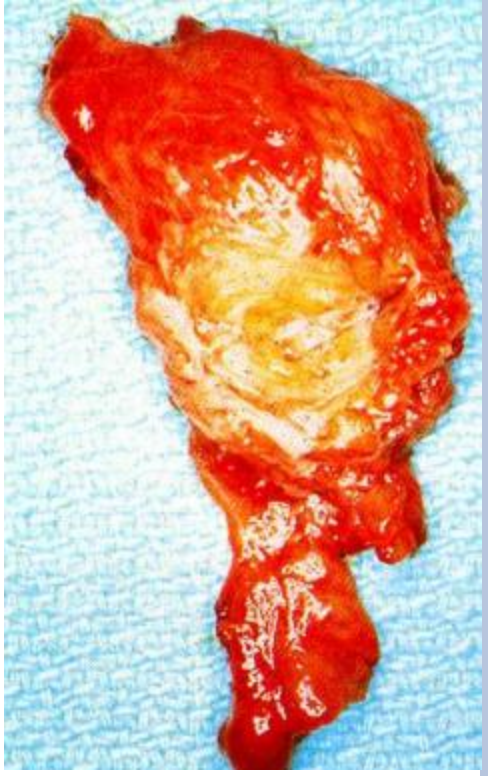
Cribriform pattern ,Most common

“swiss cheese” appearance.



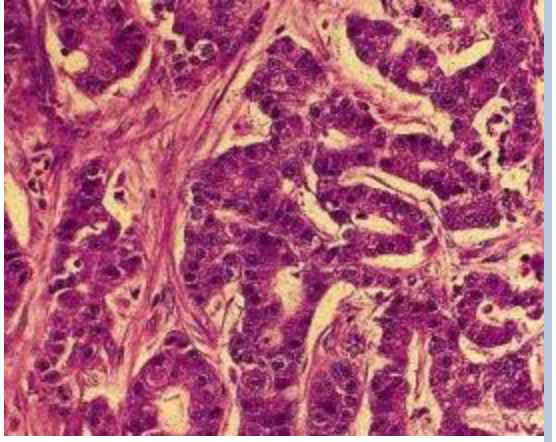
- unpredictable behavior and propensity to spread along nerves. It possesses a highly invasive quality but may remain quiescent for a long time.
- May demonstrate skip lesions along involved nerves. Clear margins do not necessarily mean that the tumor has been eradicated.
- Metastasis is more common to distant sites than to regional nodes; lung metastases are most frequent. This tumor has the highest incidence of distant metastasis, occurring in 30-50% of patients.
- . Overall 5-year survival is 35%, and 10-year survival is approximately 20%.

# Acinic cell carcinoma



- intermediate-grade malignancy with low malignant potential. This tumor may be bilateral or multicentric and is usually solid, rarely cystic.
- Although this tumor rarely metastasizes, occasional late distant metastases have been observed.
- This tumor also may spread along perineural planes.
- Overall 5-year survival is 82%, and 10-year survival is 68%.

# Adenocarcinoma



- This is an aggressive lesion with potential for both local lymphatic and distant metastases.
- Approximately 33% of patients have nodal or distant metastasis present at the time of initial diagnosis.
- Overall 5-year survival is 19-75%, as it is highly variable and related to grade and stage at presentation.

- Primary squamous cell carcinoma:

  rare, and metastasis from other sites must be excluded. Overall 5-year survival is 21-55%, and 10-year survival is 10-15%.

- Sebaceous carcinoma:

  rare parotid malignancy that often presents as a painful mass. It commonly involves the overlying skin.

- Salivary duct carcinoma:

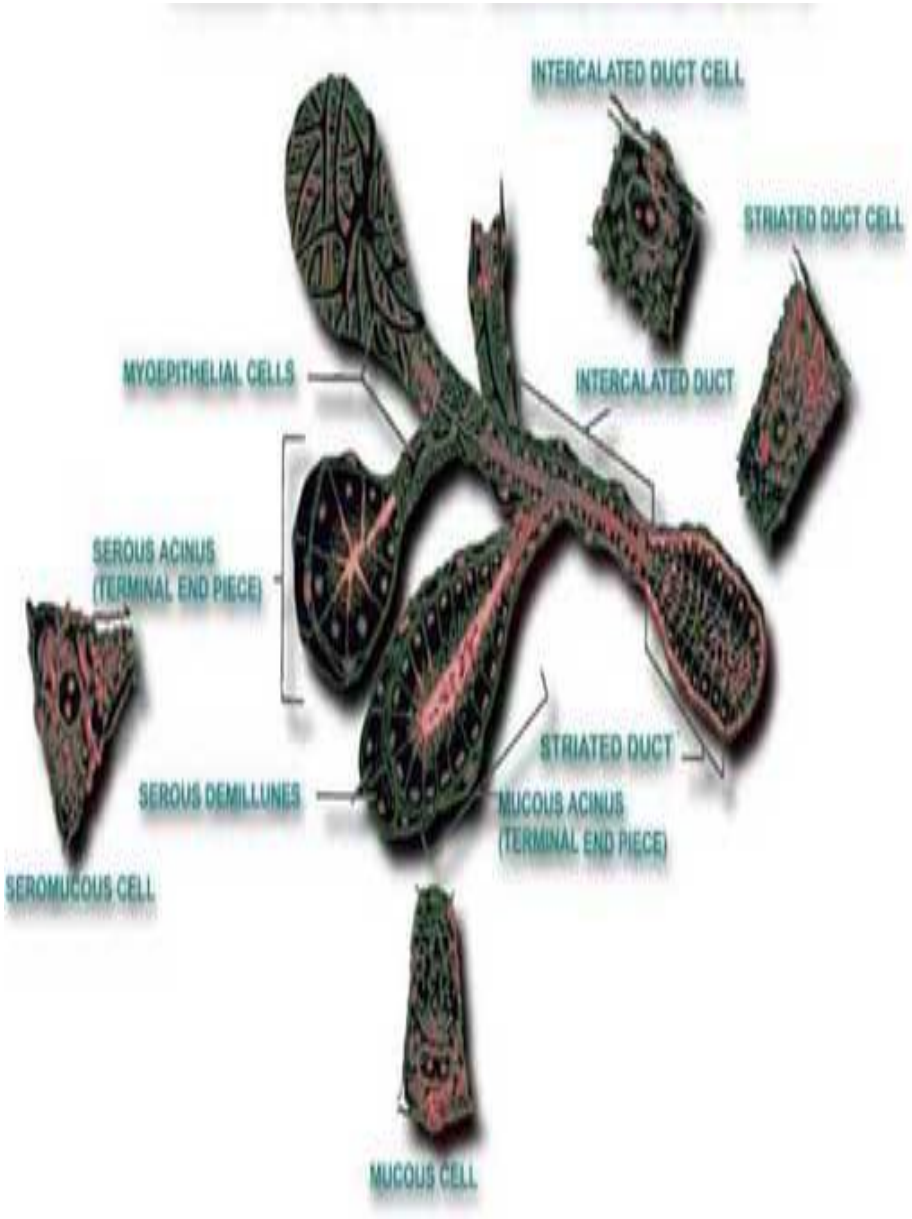
  rare and highly aggressive tumor. Small cell carcinoma exists as 2 types. The ductal cell origin type is mostly benign and rarely metastasizes. The neuroendocrine origin type is often aggressive and has higher metastatic potential.

- Lymphoma:

  most commonly in elderly males. This is also observed in approximately 5-10% of patients with Warthin tumor of the parotid gland, a benign neoplasm.
- The entire parotid is typically enlarged with a rubbery consistency on palpation. Often, regional nodes also are enlarged. Biopsy of enlarged regional nodes avoids unnecessary parotid surgery, as the definitive treatment consists of chemotherapy or radiation therapy.

# Pathophysiology

- According to the multicellular theory of SGTs, pleomorphic adenomas originate from the intercalated duct cells and myoepithelial cells; oncocytic tumors originate from the striated duct cells; acinic cell tumors originate from the acinar cells; and mucoepidermoid and squamous cell tumors originate from the excretory duct cells

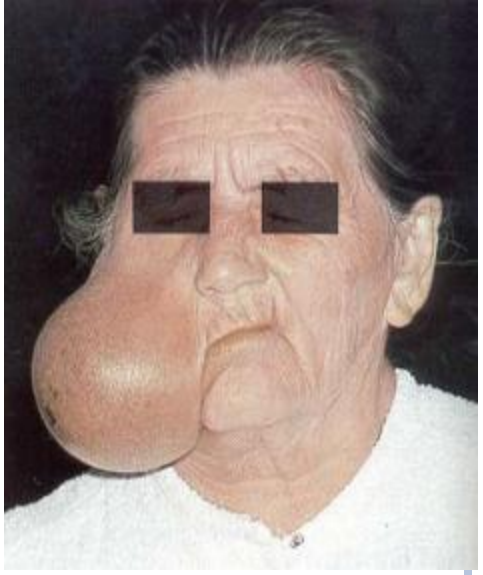


# Etiology

- The etiology of SGTs is unknown
- The involvement of environmental or genetic factors has been suggested.
- Radiation exposure has been linked to the development of the benign Warthin tumor and to the malignant mucoepidermoid carcinoma.
- Epstein-Barr virus may be a factor in the development of lymphoepithelial tumors of the salivary glands.
- Some evidence suggests p53 mutations correlates with a higher rate of tumor recurrence
- H-Ras mutations have been shown in a significant proportion of pleomorphic adenomas, adenocarcinomas, and mucoepidermoid carcinomas.

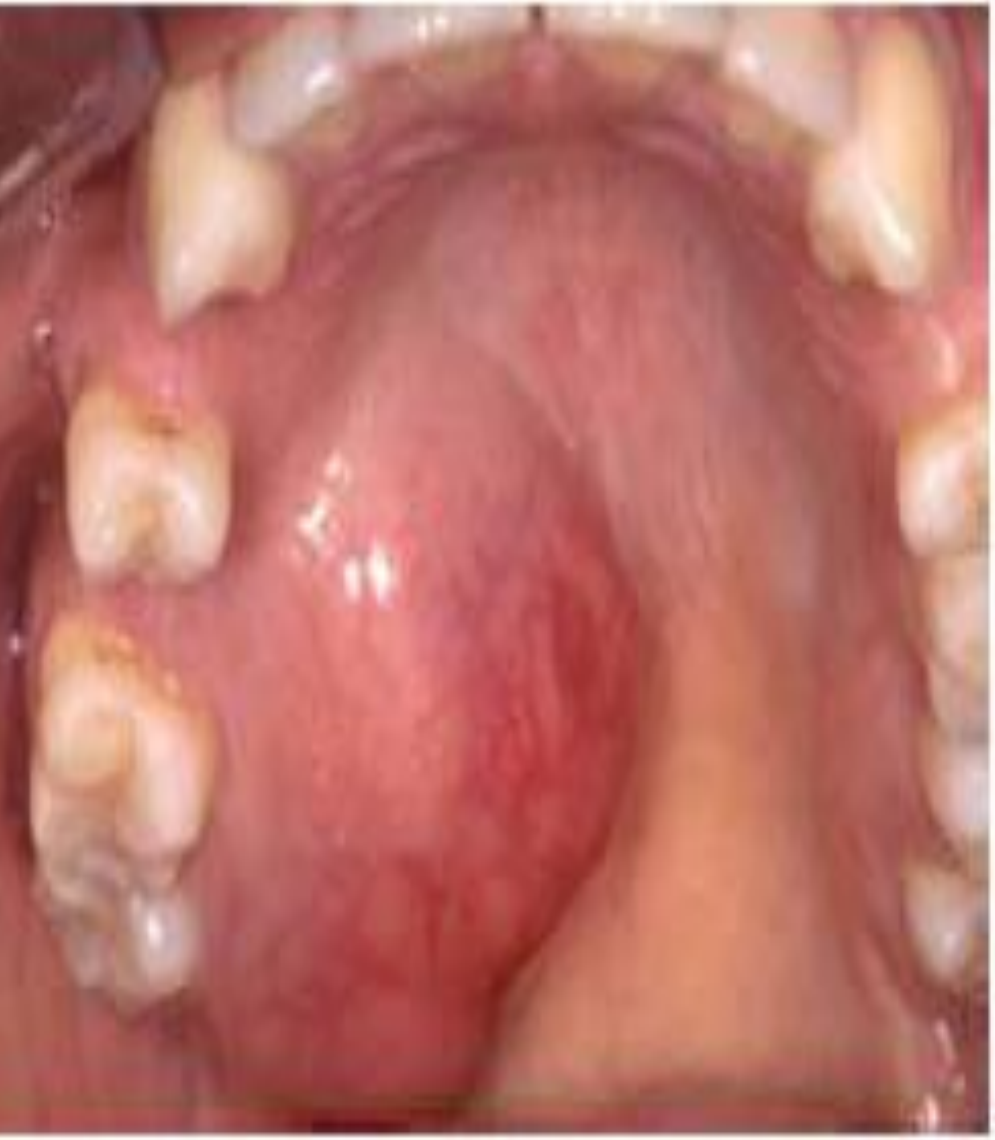
- Tobacco smoking has been associated with the development of Warthin tumors (papillary cystadenoma lymphomatosum).
- Some studies have indicated a relationship between salivary gland malignancies and occupational exposure to silica dust and nitrosamines.

# Presentation



- History :
- Initial history taking should focus on the presentation of the mass, growth rate, changes in size or symptoms with meals, facial weakness or asymmetry, and associated pain. A thorough general history provides insight into possible inflammatory, infectious, or autoimmune etiologies.
- Most patients with salivary gland neoplasms present with a slowly enlarging painless mass. A discrete mass in an otherwise normal-appearing gland is the norm for parotid gland neoplasms.

- . Submandibular neoplasms often appear with diffuse enlargement of the gland in the submandibular triangle, whereas sublingual tumors produce a palpable fullness in the floor of the mouth.
- Minor salivary gland tumors have a varied presentation, depending on the site of origin. Painless masses on the palate or floor of mouth are the most common presentation of minor salivary neoplasm. Laryngeal salivary gland neoplasms may produce airway obstruction, dysphagia, or hoarseness. Minor salivary tumors of the nasal cavity or paranasal sinus can manifest with nasal obstruction or sinusitis. Lateral pharyngeal wall protrusions with resultant dysphagia and muffled voice should raise suspicion of a parapharyngeal space neoplasm.



, 2. Slowly growing, otherwise asymptomatic salivary
nd tumor of the palate. The biopsy showed the pres-
e of a pleomorphic adenoma.

- Facial paralysis or other neurologic deficit associated with a salivary gland mass indicates malignancy. The significance of painful salivary gland masses is not entirely clear. Pain may be a feature associated with both benign and malignant tumors. Pain may arise from suppuration or hemorrhage into a mass or from infiltration of a malignancy into adjacent tissue.

- Physical examination:

- ✓ Thorough general head and neck examination.
- ✓ Note the size, mobility, and extent of the mass, as well as its fixation to surrounding structures and any tenderness.
- ✓ Bimanual palpation of the lateral pharyngeal wall for deep lobe parotid tumors to assess for parapharyngeal space extension.
- ✓ Bimanual palpation for submandibular and sublingual masses also reveals the extent of the mass and its fixation to surrounding structures.
- ✓ Attention to surrounding skin and mucosal sites, which drain to the parotid and submandibular lymphatics. Regional metastases from skin or mucosal malignancies may manifest as salivary gland masses.

- Cervical lymph node basin should be palpated to assess for metastatic disease from a primary lesion of the salivary glands.
- CN VII should be assessed carefully to identify any weakness or paralysis. Facial nerve palsy usually indicates a malignant lesion with infiltration into the nerve.

# Workup

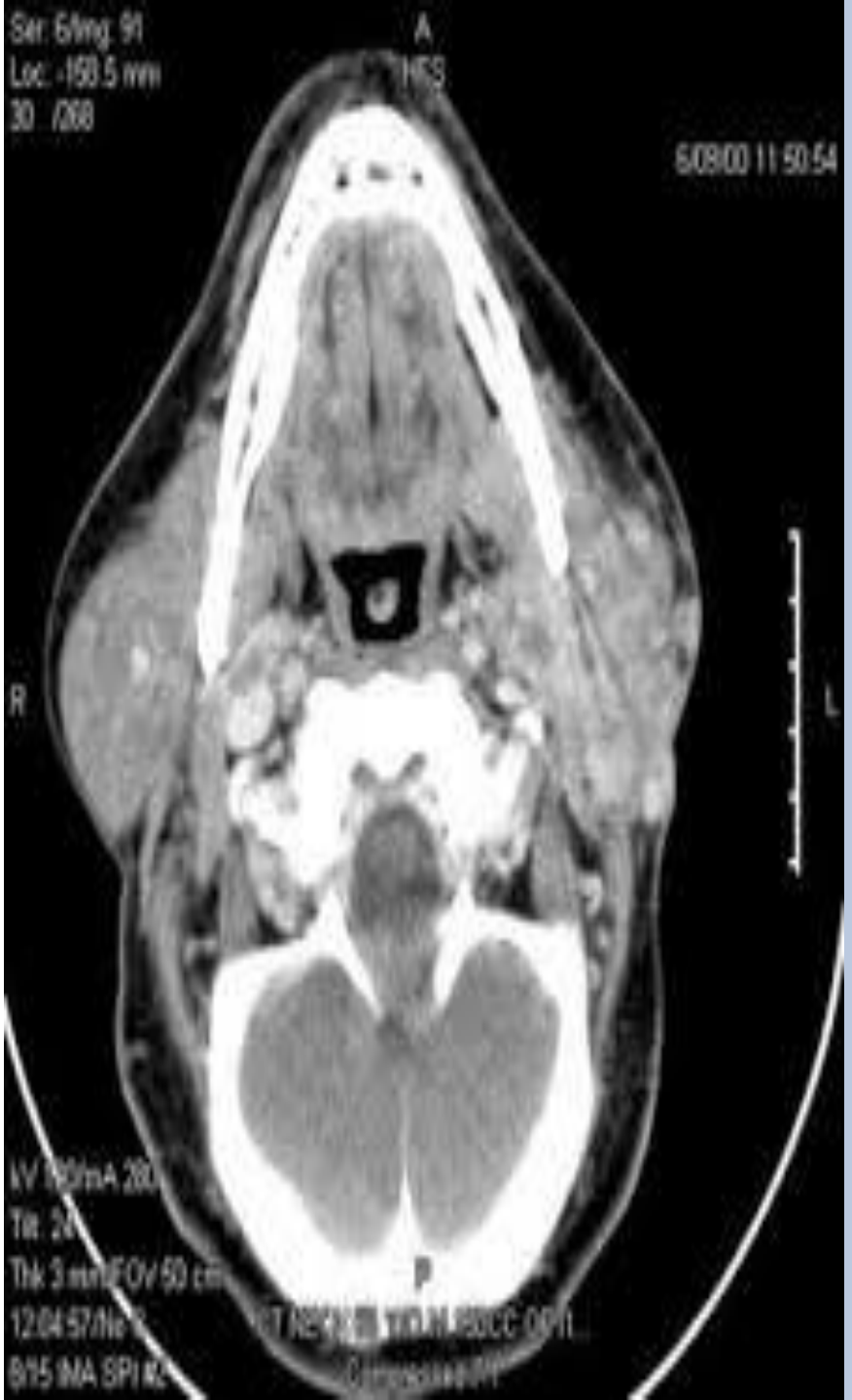
- Ultrasonography:
- reveal type of tumor
- guide fine-needle aspiration to increase the likelihood of getting a good sample, and it can precisely guide core needle biopsies decreasing the need for intraoperative biopsies.
- guide automated core biopsy systems with a sensitivity of 75%, specificity of 96.6%, and accuracy of 91.9%.
- ultrasonographic contrast mediums can demonstrate the vascularity of the tumor before surgery.

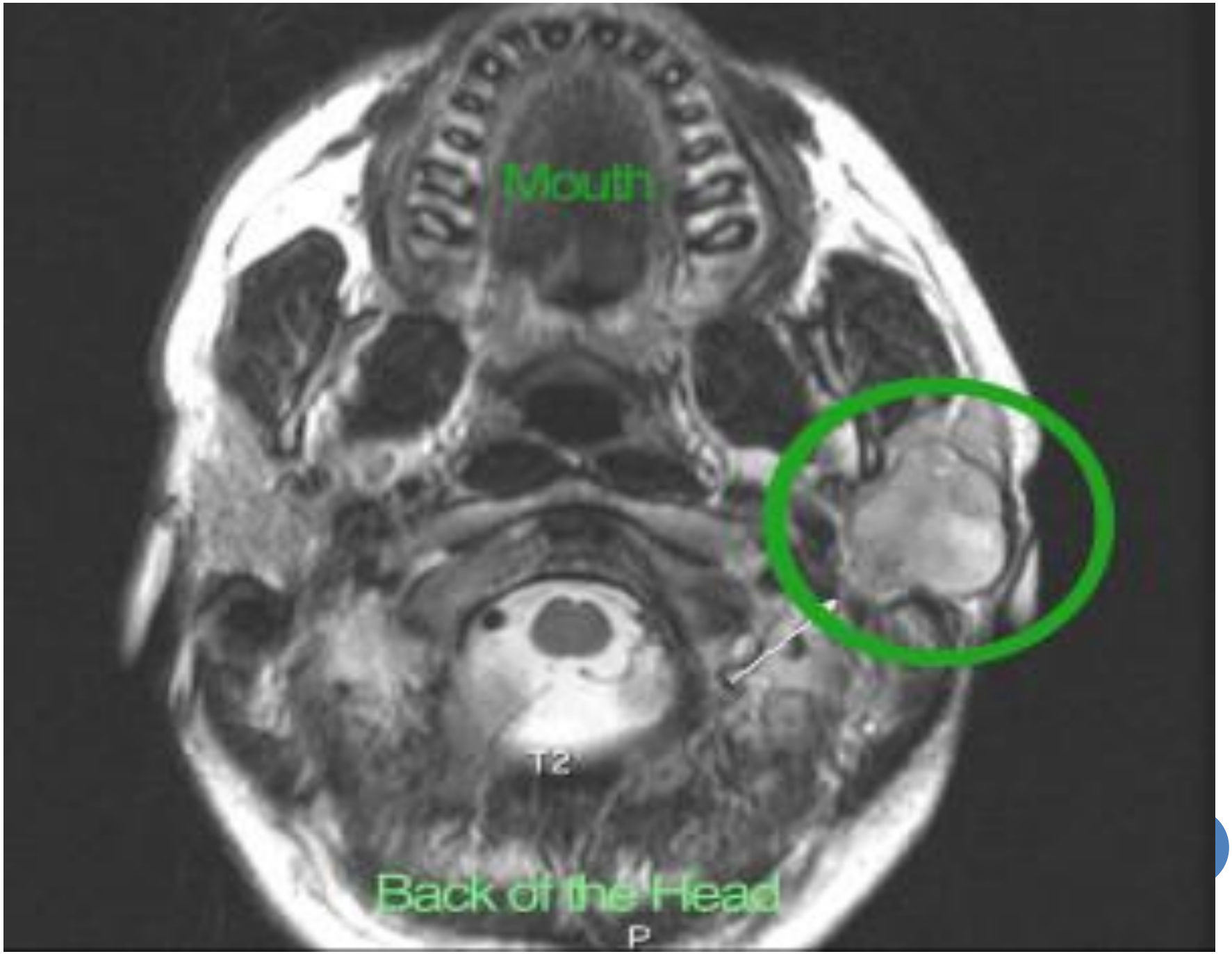
- Fine-needle aspiration. The sensitivity, specificity, and accuracy of parotid gland aspirates are approximately 92%, 100%, and 98%, respectively.

- Computed tomography (CT) scanning or magnetic resonance imaging (MRI):

- ✓ determining the extent of large tumors for evaluating extraglandular extension.
- ✓ determine the actual depth of parotid tumors
- ✓ discover other tumors in one gland or in the contralateral gland.
- ✓ distinguishing an intraparotid deep-lobe tumor from a parapharyngeal space tumor
- ✓ evaluation of cervical lymph nodes for metastasis.

- well-defined, low-signal intensity mass on the axial $T_1$-weighted MRI. Note displacement of the retromandibular vein medially by the mass compared with the normal retromandibular vein . The facial nerve branching through the normal parotid is seen.
- (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, St Louis, 2010, Mosby.)




Mouth
T2
Back of the Head
P

- F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning can be used to plan treatment of salivary gland malignancies by detecting lymph node metastases that require a neck dissection or by finding distant metastases that may not have caused abnormalities in routine blood work. This is most useful when combined with CT scanning.
- Technetium-99m (Tc-99m) pertechnetate scintigraphy with lemon juice stimulation can be used to diagnose Warthin tumors with correlation between tumor size and Tc-99m uptake.adenolymphoma and oncocytoma show as hot spots. Other salivary neoplasm shows as acold spot.
- Flow cytometry: The value of flow cytometry in salivary gland neoplasms is supporting histopathology by detecting possibly malignant tumors.
- Open biopsy: rarely indicated, feasible for tumours of minor salivary glands of the mouth cavity.
- Metastatic work up

# STAGE (TNM) ; FOR MALIGNANCIES

- $T_0$ :No evidence of primary tumor
- $T_1$ :Tumor <2 cm
- $T_2$ ;Tumor 2 to 4 cm
- $T_3$ :Tumor 4 to 6 cm
- $T_4$ :Tumor >6 cm

All subdivided into :

Without local extension.

With local extension.

- $N_0$ :No lymph node metastasis
- $N_1$ :Single ipsilateral node <3 cm
- $N_2$ :Ipsilateral, contralateral, or bilateral node <6 cm
- $N_3$ :Any node >6 cm
- $M_0$ :No distant metastasis
- $M_1$ :Distant metastasis
- Stage I :$T_{1a}$ or $_{2a}N_0M_0$
- Stage II :$T_{1b,2b,3a}N_0M_0$
- Stage III :$T_{3b,4a}N_0M_0$ or any T except $_{4b}N_1M_0$
- Stage IV :$T_{4b}$ any N any M or any T $N_{2,3}M_0$ or any T, any $N_1M_1$

# TREATMENT

- Benign tumors: complete tumor resection with safety margin.
- In general, salivary gland neoplasms respond poorly to chemotherapy, and adjuvant chemotherapy is currently indicated only for palliation.
- Carefully planned and executed surgical excision is the primary treatment for all primary salivary gland tumors. The principles of surgery vary with the site of origin.
- Superficial parotidectomy with identification and dissection of the facial nerve is the minimum operation for diagnosis and treatment of parotid masses.

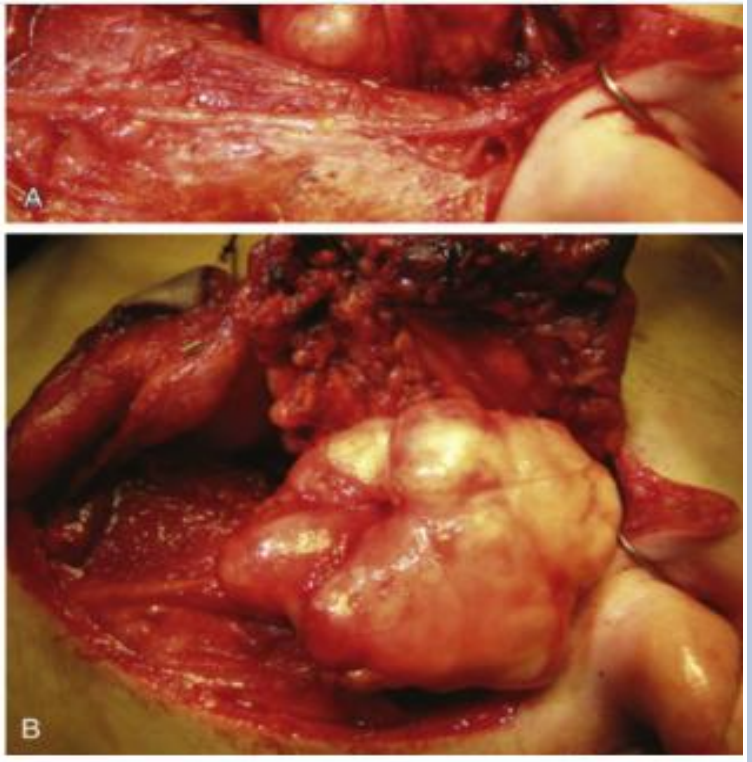
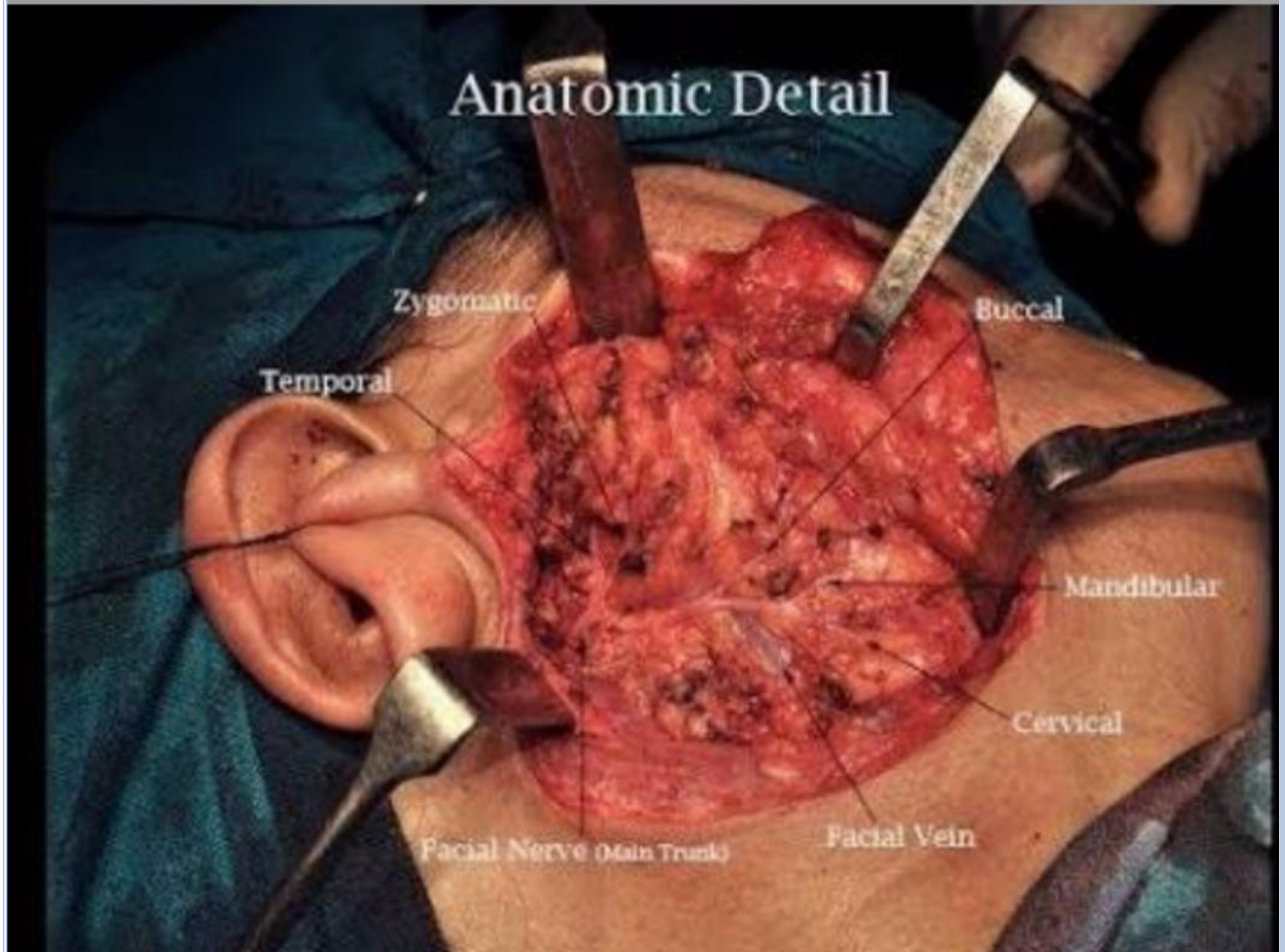



FIGURE 33-16

**A,** A 32-year-old woman with a deep parotid lobe pleomorphic adenoma. The facial nerve is displaced laterally. **B,** Once the mass is separated from the prestyloid space, it is delivered around the facial nerve, emptying the compressed parapharyngeal space and avoiding facial nerve injury.

***Malignant tumors:***

- Surgery is the mainstay of treatment; gland resection and neck dissection if lymph nodes are involved.
- lateral lobectomy with preservation of facial nerve should be considered for tumors confined to the superficial lobe of the parotid gland. Gross tumor should not be left in situ, but if the facial nerve is able to be preserved by “peeling” tumor off the nerve, it should be attempted, followed by radiation therapy for microscopic disease.
- Where malignant parotid tumors lie in close proximity to the facial nerve, there should be a low threshold for adjuvant radiotherapy


Anatomic Detail
Zygomatic
Buccal
Temporal
Mandibular
Cervical
Facial Nerve (Main Trunk)
Facial Vein

- All involved local structures should be resected in continuity with the tumor. This may include skin, masseter, mandible, temporalis, zygomatic arch, or temporal bone.
- Tumors of the deep lobe of parotid are treated by total consevative parotidectomy. Identification of the facial nerves and branches is the first and most crucial step.
- Total parotidectomy is then performed en bloc, and the fate of the facial nerve and surrounding local structures must be decided similar to superficial lobe tumors. The specimen should be sent to the pathology laboratory for immediate examination.

- Neck dissection should be performed when malignancy is detected in the lymph nodes pre- or intraoperatively.
- Other indications for neck dissection include tumors >4 cm in greatest diameter, tumors that are high-grade, tumors that have invaded local structures, recurrent tumors when no neck dissection was performed initially, and deep lobe tumors.
- Postoperative radiation is indicated for high-grade malignancies demonstrating extraglandular disease, perineural invasion, direct invasion of surrounding tissues, or regional metastases.

- No chemotherapy has been proven effective as single modality therapy. For certain histologic subtypes, some clinicians recommend combined modality chemotherapy and radiation.
- Presently, immunotherapy is in the clinical trial phase.
- A recent study demonstrated that epidermal growth factor receptor (EGFR) is expressed strongly in the cell membranes of parotid mucoepidermoid carcinomas and of the lymph node metastases. EGFR-targeting agents have potential to be used for therapy.

# Reconstruction

- The overall goal following tumor excision is to restore function and achieve the best possible aesthetic result.
- Options for wound closure in the presence of a skin or soft tissue deficit include skin grafting, cervicofacial flap, trapezius flap, pectoralis flap, deltopectoral flap, and microvascular free flap.
- Sacrifice of the facial nerve or one of its branches also must be managed appropriately. If inadvertently severed during the operation, the facial nerve should be immediately repaired under the operating microscope.

- If intentionally resected with the tumor specimen, several options for reconstruction are available to the surgeon.
- The ipsilateral or contralateral great auricular nerve may be used as an interposition graft, although this sacrifices sensation to the area normally supplied by this nerve.
- Another option is to anastomose the facial nerve to the ipsilateral hypoglossal nerve. This anastomosis may be performed end-to-side to avoid interfering with normal hypoglossal nerve function.
- During the period of waiting for facial nerve recovery, maintain corneal protection.

# Prognosis

- Poor prognostic factors include high grade, neural involvement, locally advanced disease, advanced age, associated pain, regional lymph node metastases, distant metastasis, and accumulation of p53 or c-erbB2 oncoproteins.
- Overall 5-year survival for all stages and histologic types is approximately 62%. The overall 5-year survival for recurrent disease is approximately 37%. Because of the risk of recurrence, all patients who have had a histologically proven malignant salivary gland tumor should have lifelong follow-up.

# SURVEILLANCE

- Surveillance must continue indefinitely, as local recurrence or distant metastases may become apparent many years after the initial treatment.
- Thorough physical examination every 3 months for 2 years, every 6 months for another 3 years, then annually thereafter. Liver function tests and chest radiograph should be obtained annually

# REFERENCES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