UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Salivary Glands

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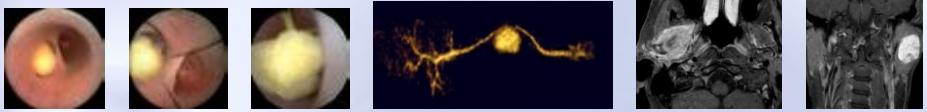


Salivary glands - objectives

Semiology of salivary gland diseases

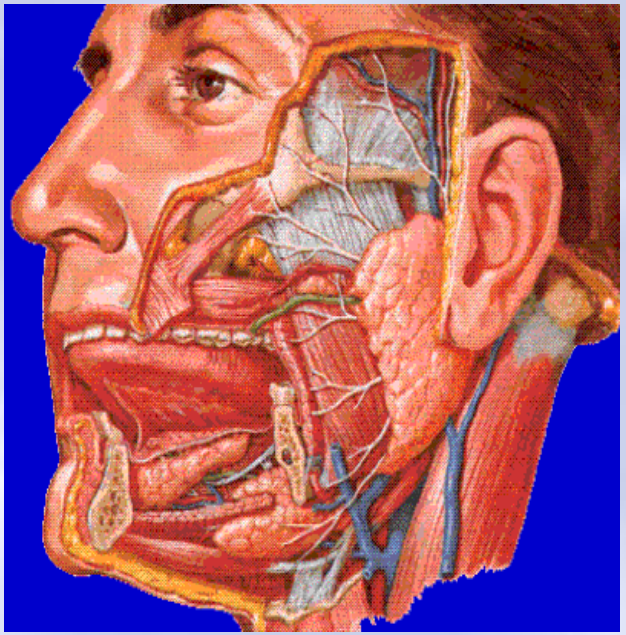
Management of salivary ductal obstruction

Salivary gland tumors

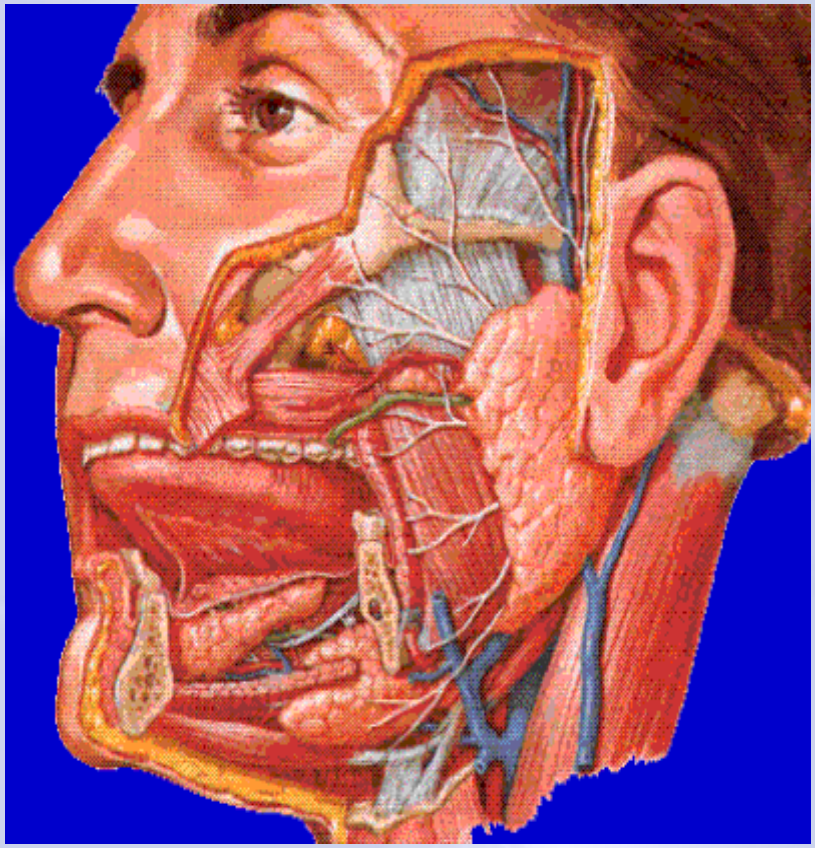
Pleomorphic adenoma

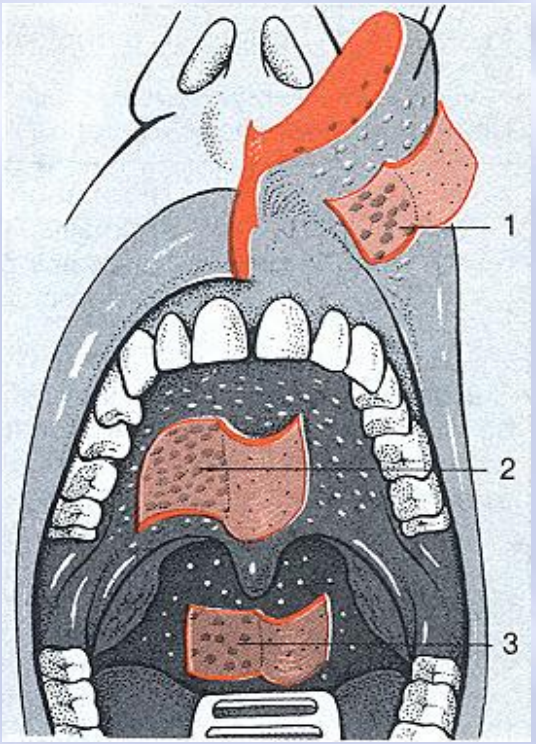
Treatment of salivary gland carcinoma

Parotidectomy



SG - anatomy



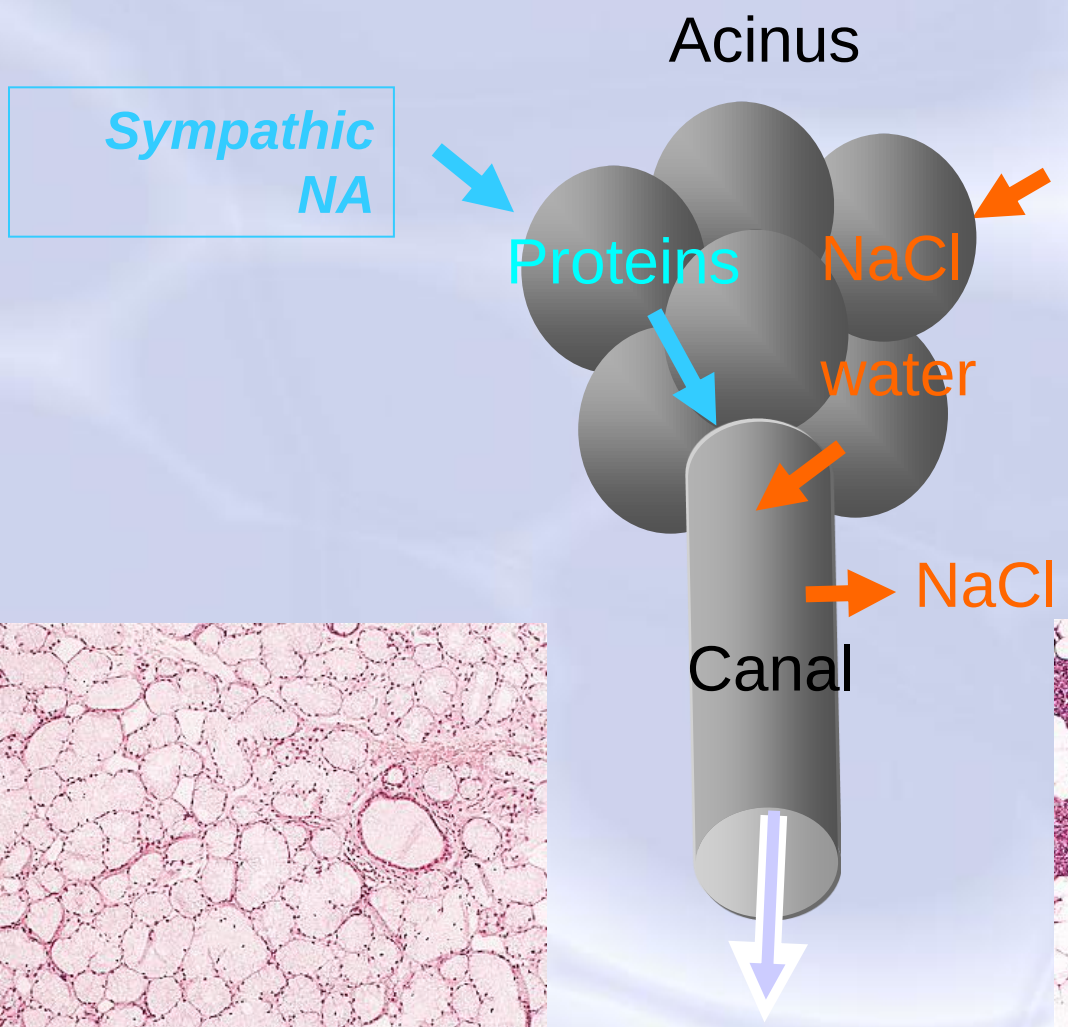


Minor glands in all upper AD tract

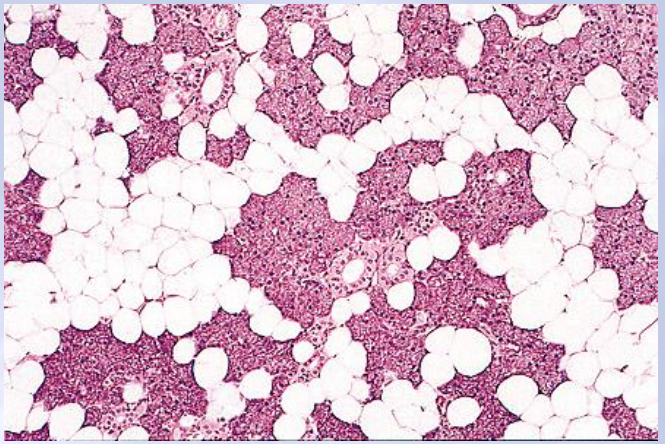
Same histology → same tumors

Netter: Interactive atlas of anatomy, Ciba.
Becker, Naumann, Pfaltz: Précis d'oto-rhino-laryngologie, Flammarion, 1986 (p551)

SG - physiology



Mucous acini (sublingual gland)



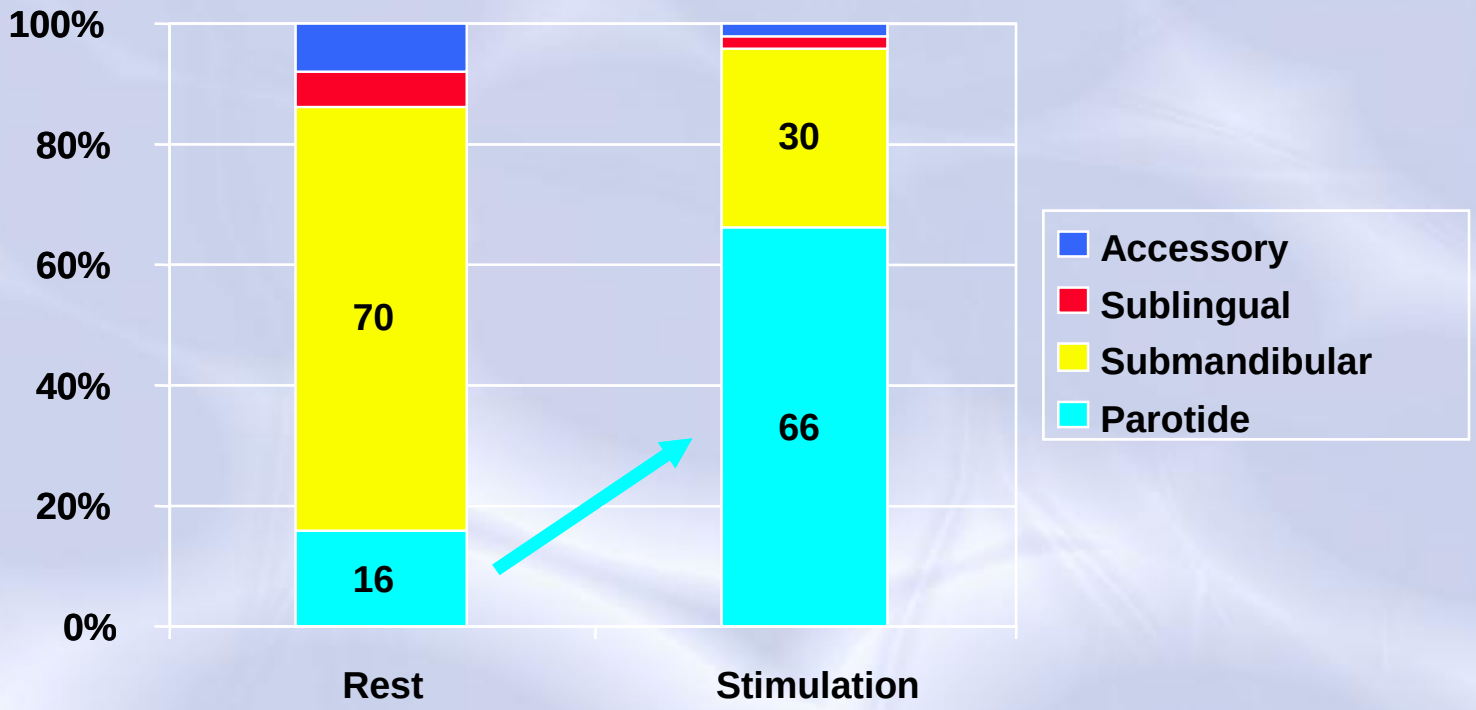
Serous acini (parotid gland)

Production of saliva:

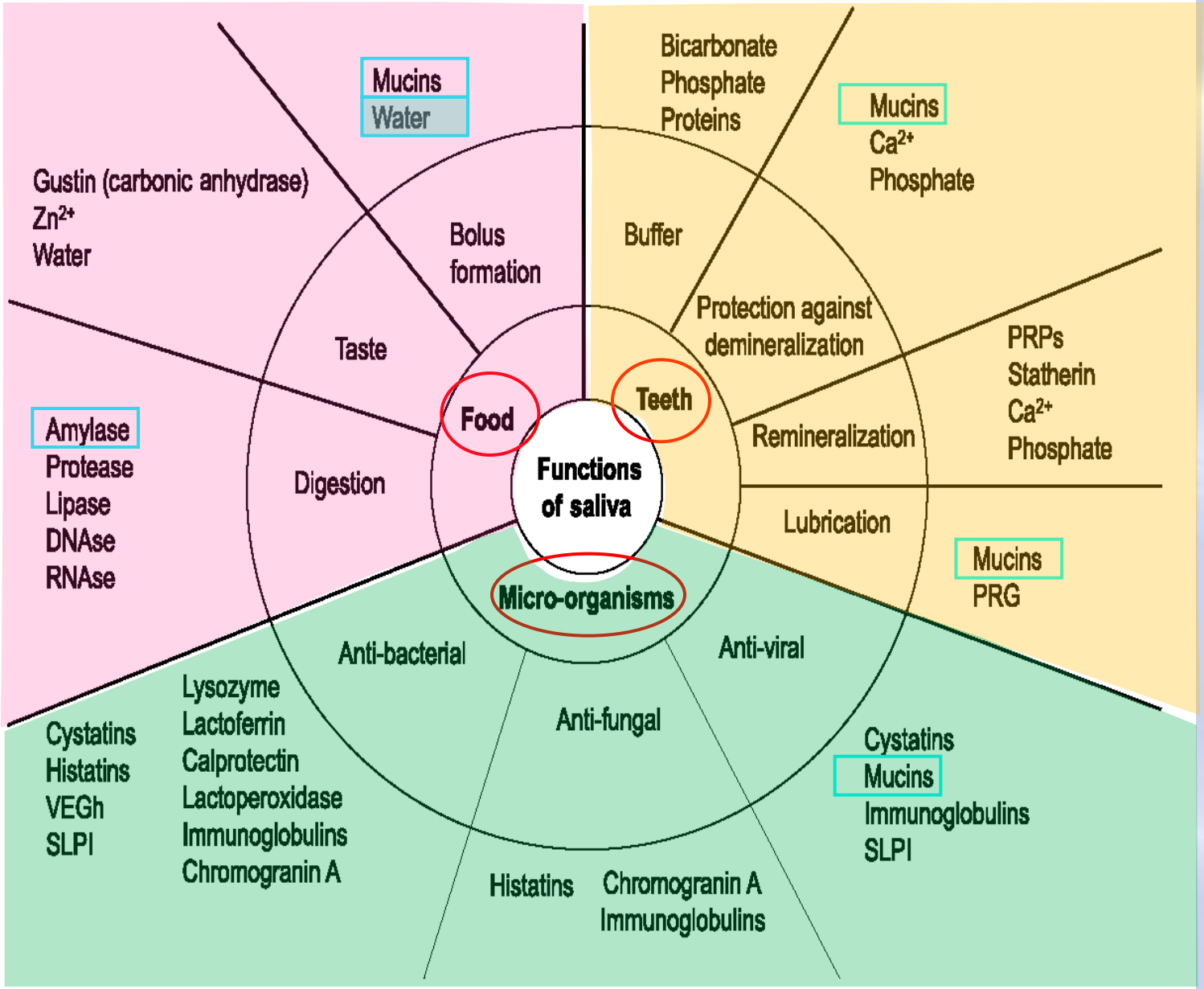
basal, continuous : 0.39 ± 0.2 ml/min (~ 600 ml/d)

upon gustatory stimulation : 4.3 ± 2.1 ml/min

composition > 99% water



Saliva – the defender of the oral cavity
AV Nieuw Amerongen and ECI Veerman



Amerongen AV, Veerman EC: Saliva--the defender of the oral cavity. Oral Dis 8:12-22,2002.

Pain ↑ meals

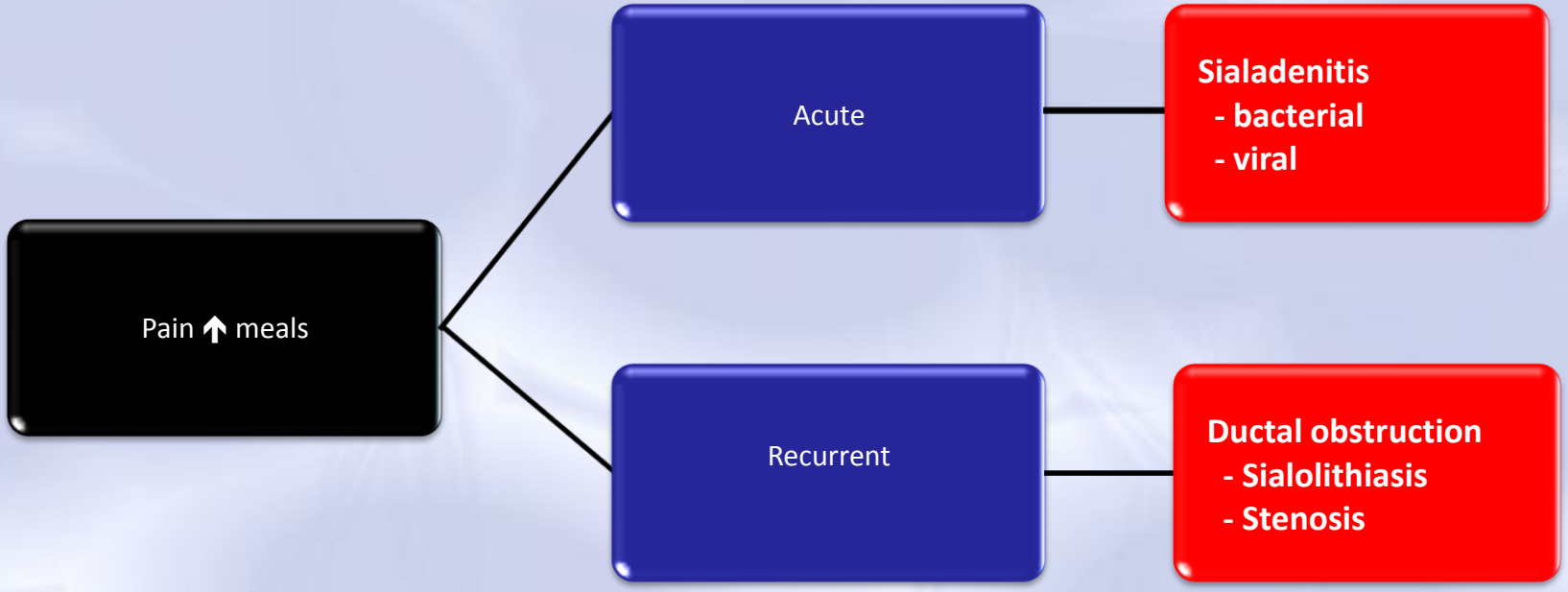
Swelling

Xerostomia

Facial paralysis

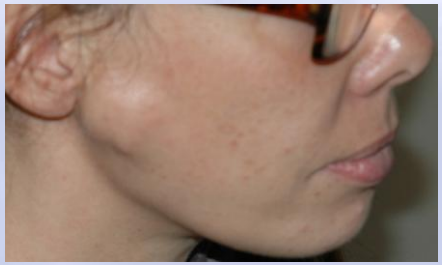
Pain ↑ meals

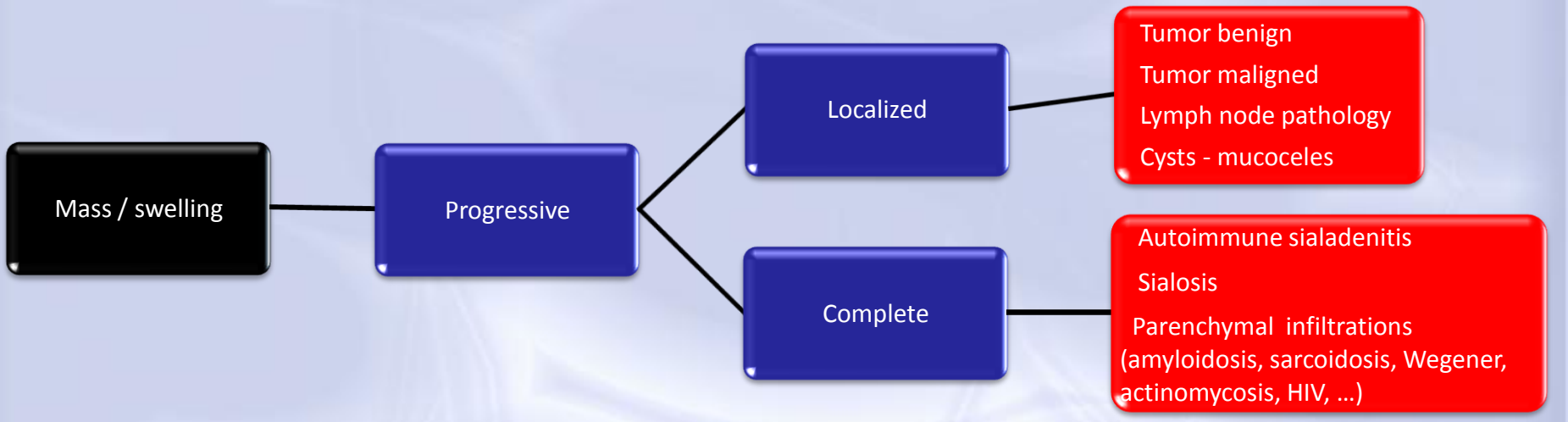
- acute: infection, sialolithiasis
- recurrent: sialolithiasis
- chronic: inflammation

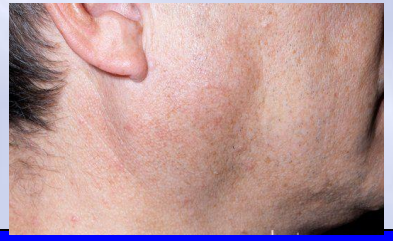


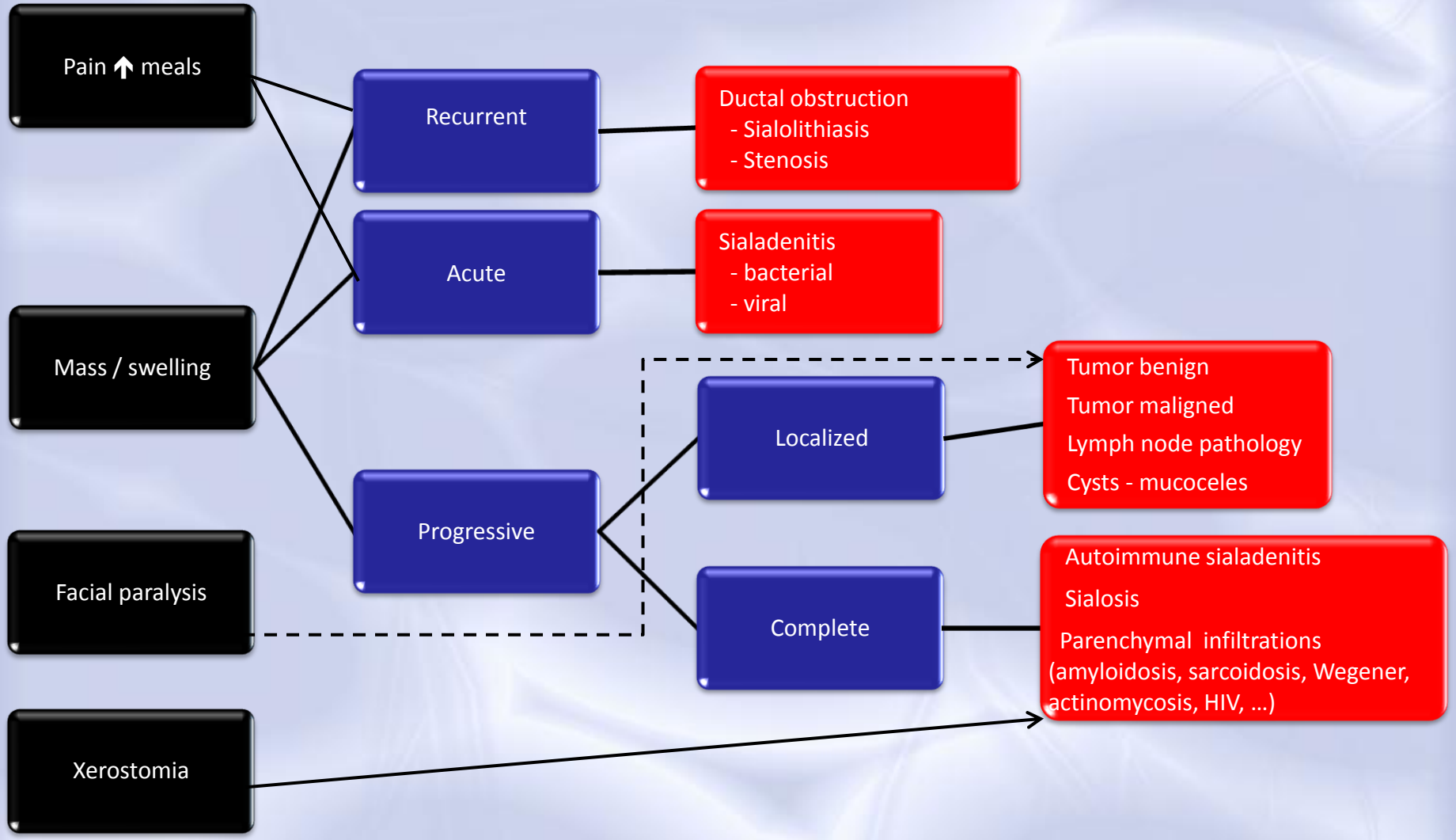
Swelling

- localized: mass, tumor
- diffuse 1 gland: infection, sialolithiasis
- diffuse >1 gland: inflammation








Pain ↑ meals
Mass / swelling
Facial paralysis
Xerostomia
Recurrent
Acute
Progressive
Localized
Complete
Ductal obstruction
- Sialolithiasis
- Stenosis
Sialadenitis
- bacterial
- viral
Tumor benign
Tumor maligned
Lymph node pathology
Cysts - mucoceles
Autoimmune sialadenitis
Sialosis
Parenchymal infiltrations
(amyloidosis, sarcoidosis, Wegener, actinomycosis, HIV, …)

SG – Infections (sialadenitis)

Viral

- Mumps (oreillons)

Bacterial acute

Chronic (specific)

- tuberculosis
- actinomycosis

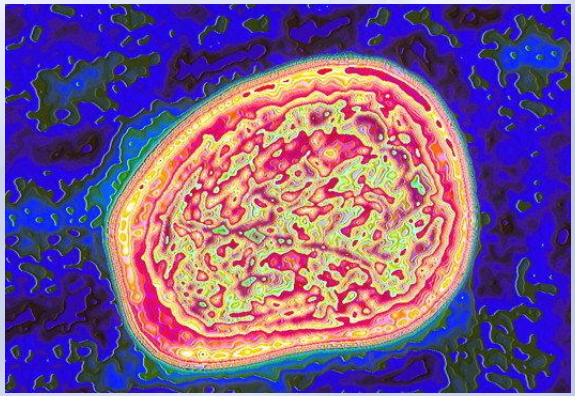
CAVE : Lymph nodes present within the parotid space (absent from the submandibular gland)

→ Any form of cervical pathology could be found in the parotid

SG - Infections - mumps

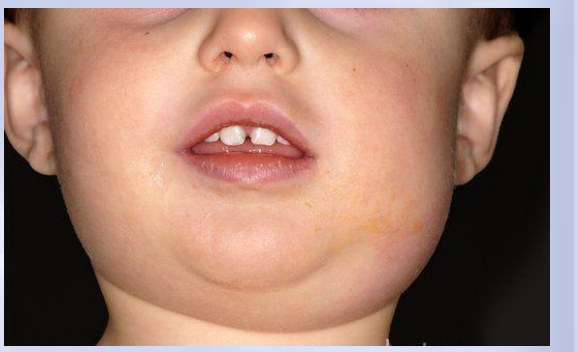
Etiology : Paramyxovirus (human parainfluenza virus types 1&3)

- transmission by air (high contagion; by 15 years > 90% antibodies)
- incubation 2-3 weeks
- viremia: 2-3 days



Clinical presentation:

- Age: 5-10 years
- Prodromal signs: headaches, myalgia, anorexia
- Symptoms: parotid pain increasing during meals, trismus
- Signs:
  - parotid swelling
  - no erythema
  - 75% bilateral parotid involvement (often sequential)
  - no or light fever



Diagnosis:

- clinical
- serology (IgM – ELISA)
  - Antibody "S" (NP protein): 2 weeks to 9 months
  - Antibody "V" (HN protein): few weeks to 5 years

"Complications":

- orchitis (25% post puberty)
- oophoritis (5% post puberty)
- aseptic meningitis (10%)
- temporary high frequency hearing loss (4%)
- rare permanent unilateral deafness (1/20'000)

Treatment:

- vaccination (since 1967)
- symptomatic

SG – Infections – Bacterial sialadenitis

Physiopathology:

- Deshydratation
- Sialolithiasis

→ **Salivary stasis**
Retrograde migration of oral bacteria

Glands : Parotids >> Submandibular

- no continuous secretion
- few anti-infectious substances in parotid saliva
- few muscular contractions to advance the saliva in the duct
- despite more sialolithiasis in Wharton's duct

Deshydratation (newborns, geriatic population, post-surgery, xerostomia post-radiation, drugs, anorexia/boulimia, Sjögren)

SG - Infections - Bacterial sialadenitis

Bacteriology:

- Staphylococcus aureus (50-90%)
- Other aerobes (rare)
- Probable role of anaerobes (50%)

Aerobic and facultative bacteria	
Streptococcus pneumoniae	3
Streptococcus pyogenes	2
Staphylococcus aureus	10 (10)*
Haemophilus influenzae	4 (2)
Escherichia coli	2 (2)
Alpha-hemolytic streptococcus	4
Subtotal	25 (14)
Anaerobic bacteria	
Peptrostreptococcus ssp.	5
Peptrostreptococcus magnus	1
Peptrostroptococcus intermedius	1
peptrostreptococcus anaerobius	1
Actinomyces israelii	2
Propionibacterium acnes	4
Eubacterium lentum	2
Fusobacterium ssp.	1
Fusobacterium nucleutum	3
Bacteroides ssp.	1
Bacterioides fragilis	1 (1)
Prevotella melaninogenica	1
Prevotella intermedia	4 (2)
Porphyromonas assacharolytica	2
Subtotal	30 (3)
Total	55 (17)

*Number in parenthesis is the number of beta-lactamase-producing bacteria. (From Brook [20]. Reproduced with permission.)

Brook, I: Acute bacterial suppurative parotitis: microbiology and management. J Craniofac Surg 14:37-40., 2003.

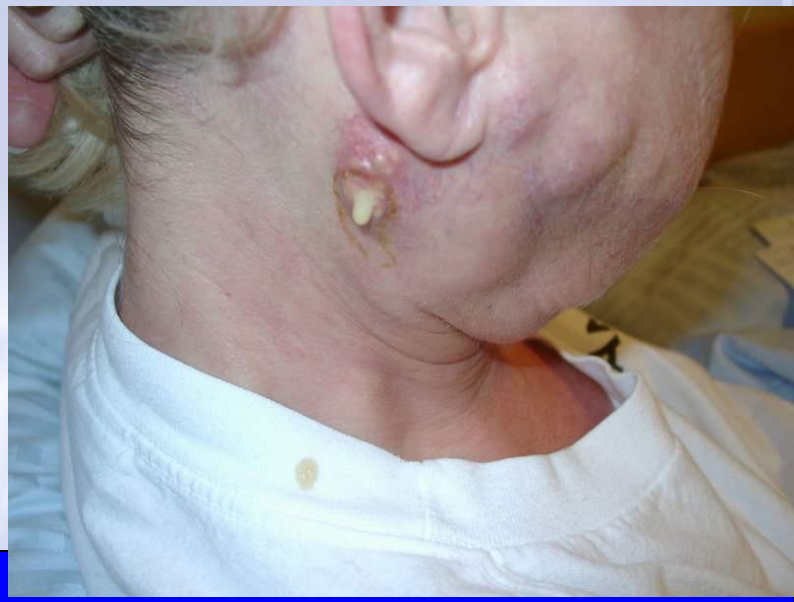
SG - Infections - Bacterial sialadenitis

Symptoms:

- acute onset (hours to few days)
- pain increased during meals
- diffuse parotid swelling (90% unilateral)

Physical exam:

- diffuse parotid swelling
- hard and painful gland
- erythema and pus of Stensen's duct orifice
- rare fluctuation (abscess)
- palpation for sialolithiasis



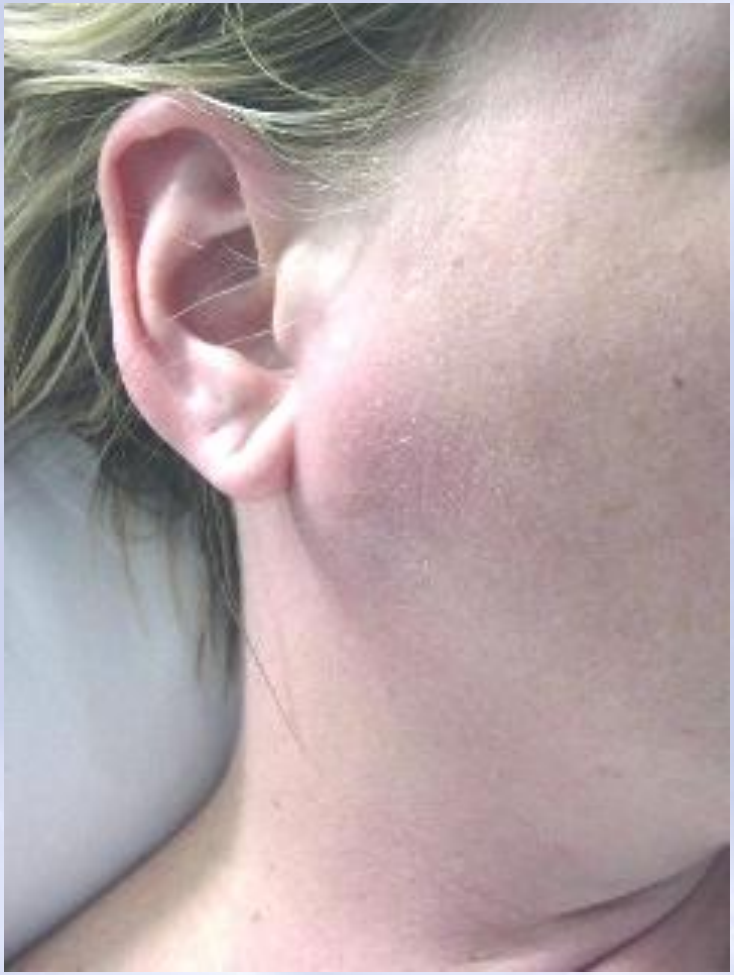
SG – Infections - Bacterial sialadenitis

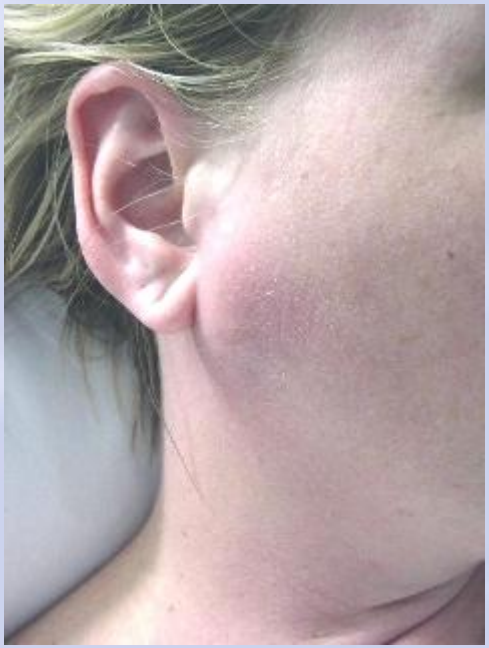
Diagnosis:

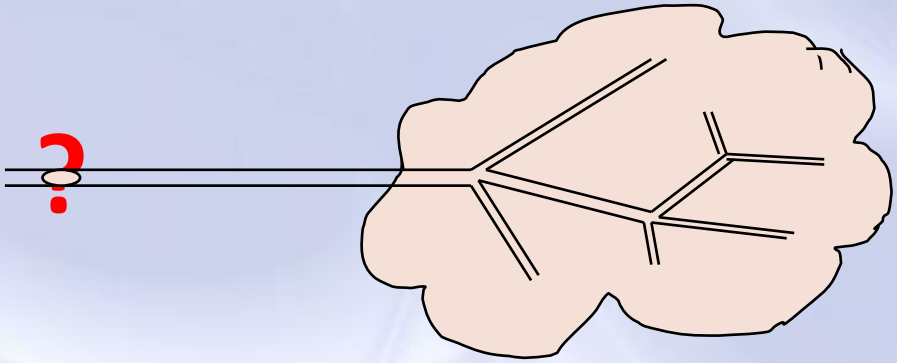
- clinical
- leucocytosis with left shift
- culture of pus (duct, aspiration of abscess)
- standard x-ray or ultrasound to rule out stone
- NO SIALOGRAPHY
- US / CT for abscess

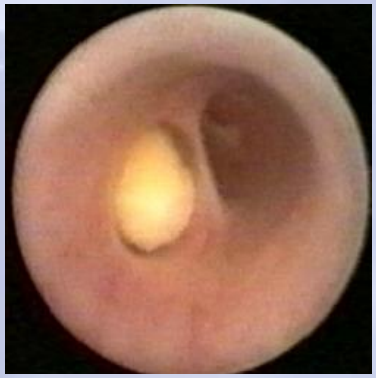
Treatment:

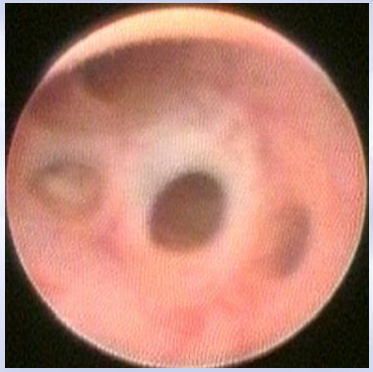
- rehydratation
- increase salivary secretion (stop medications, lemon juice, massages)
- NSAID + analgesics
- oral antibiotics: ampicilline-clavulinate, clindamycine
- if no improvement after 48 h: iv antibiotics + Gram – coverage; MRSA
- drainage of abscess

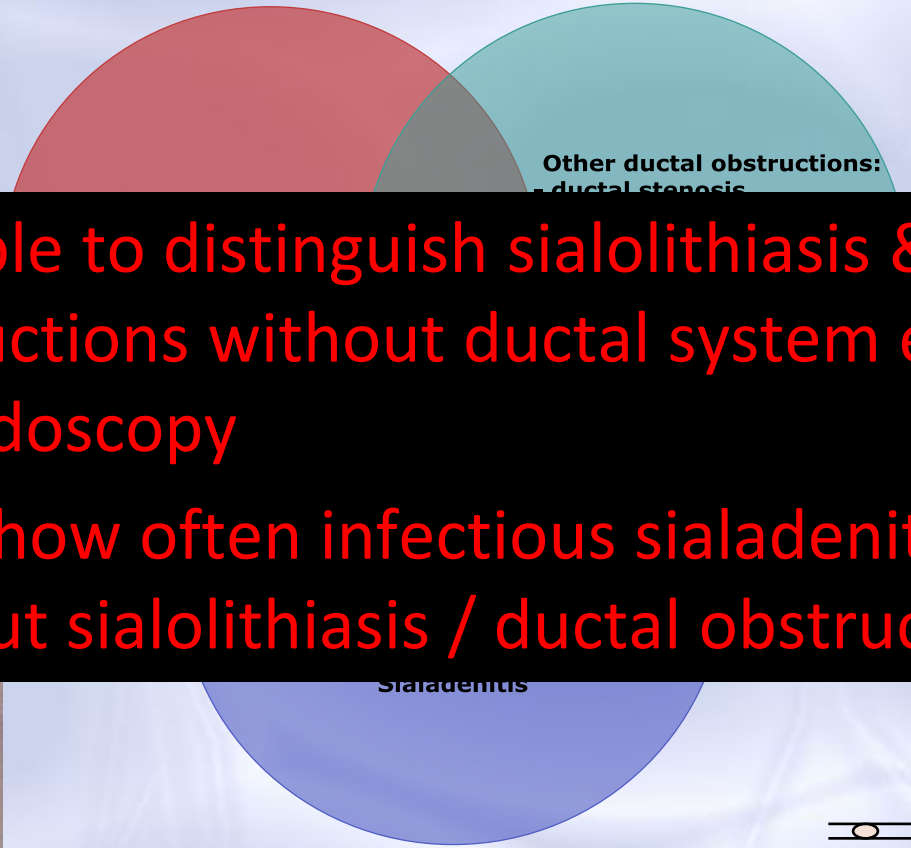






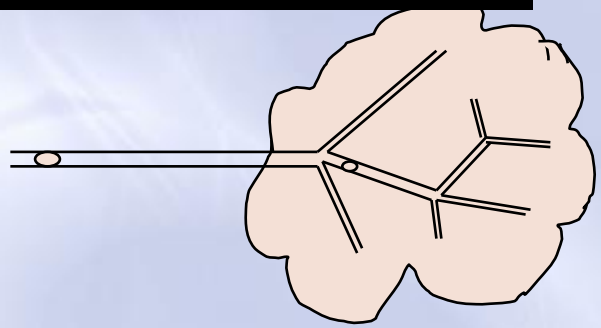






Impossible to distinguish sialolithiasis & other ductal obstructions without ductal system evaluation / sialendoscopy

Unclear how often infectious sialadenitis exists without sialolithiasis / ductal obstruction



SG – Sialolithiasis

Incidence : 200 / 1’000’000

Age : 42y

Etiology: ???

- no relation with dietary calcium
- no relation with kidney or gallbladder stones

Physiopathology:

- nidus (bacteria, micro-calcifications, cellular debris, foreign body)
- growth
  - hypersaturation with calcium / phosphorus
  - decrease of crystallization inhibitors
  - interaction crystal – canal cells
  - decrease in salivary flow

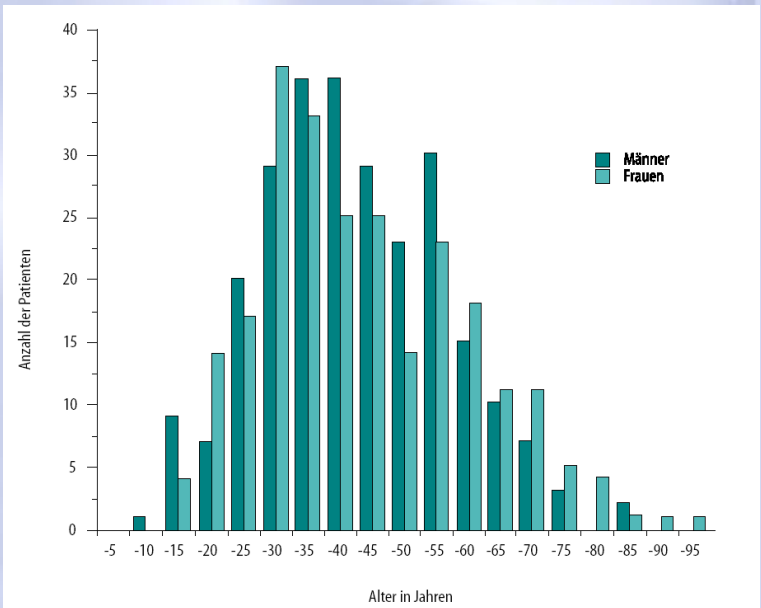
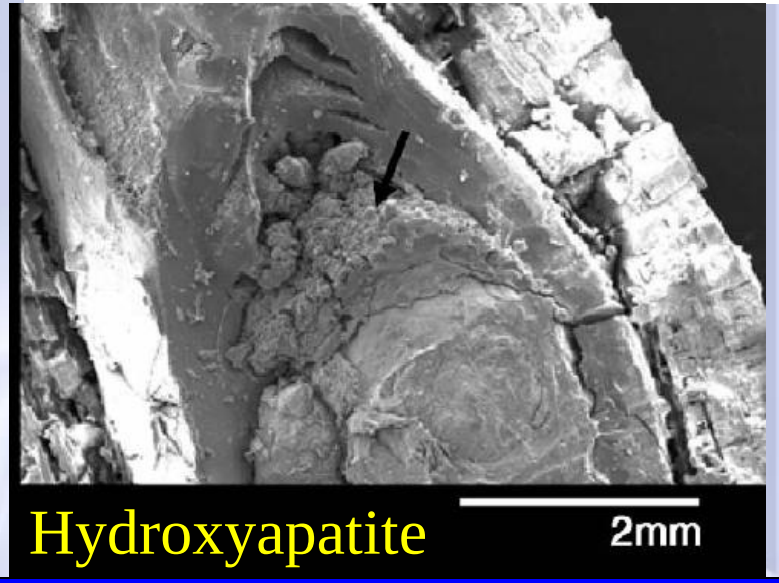


Abb. 1 ▲ **Auftreten der Sialolithiasis in der Glandula submandibularis in Abhängigkeit von Geschlecht und Alter**



Sialolithiasis present with pain and swelling

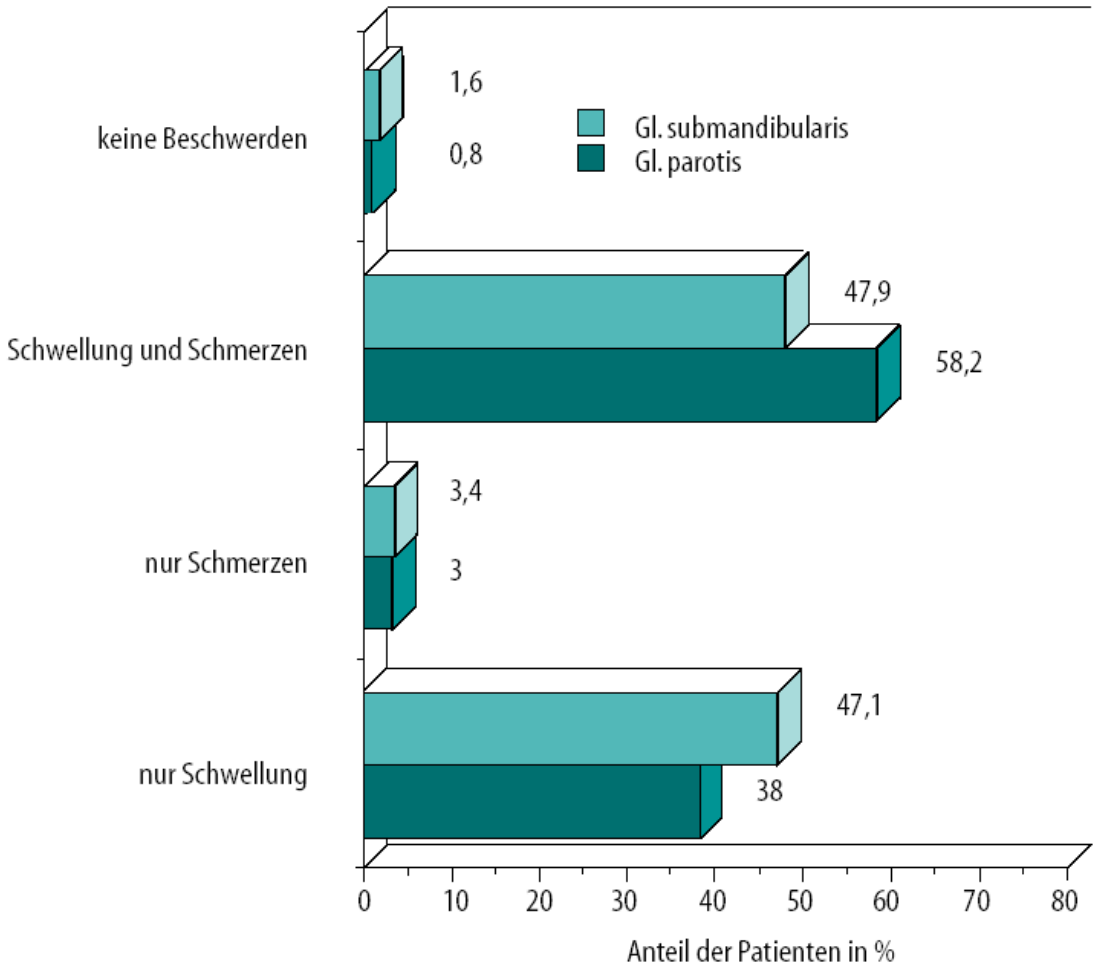


Abb. 3 ▲ **Symptomatik der Sialolithiasis in Abhängigkeit vom erkrankten Organ**

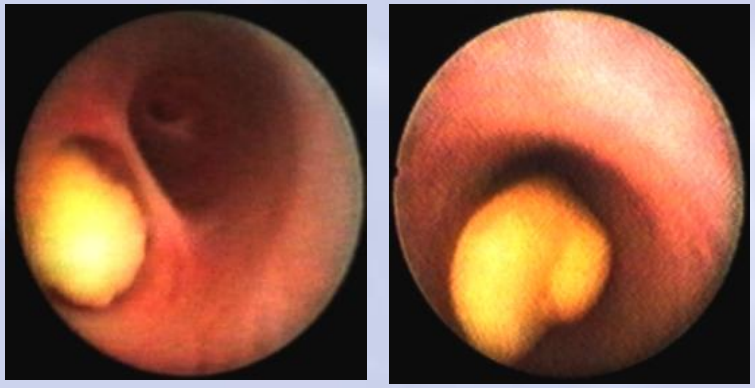
Zenk, Constantinidis, Kydles, Hornung, Iro - HNO 47:963, 1999.

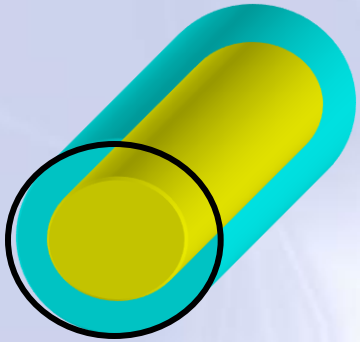
SG – Sialolithiasis - treatment

- Acute phase : antibiotics, NSAID, corticosteroids
- Definitive treatment – classic :
  - spontaneous passage
  - anterior stones: sialodochoplastie (Wharton)
  - posterior stones: open surgery
- Definitive treatment – 1990's:
  - external lithotripsy
    - numerous sessions, pain
    - fragments left in the duct
    - limited by the size of the stone
    - success: 75% (parotid) et 40% (submandibular)
  - internal lithotripsy
  - external lithotripsy with endoscopic retrieval

SG – Sialendoscopy

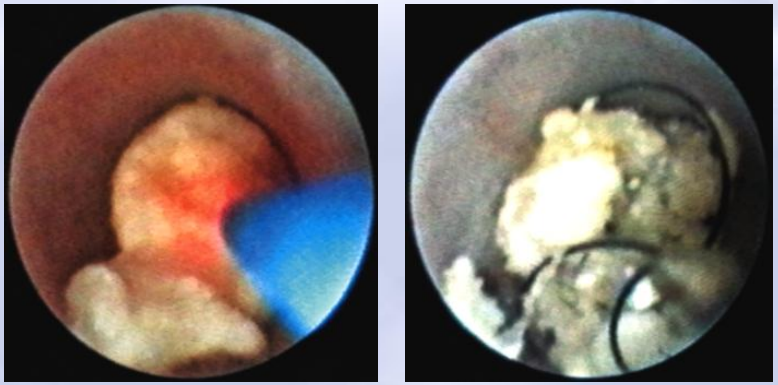
Diagnostic sialendoscopy

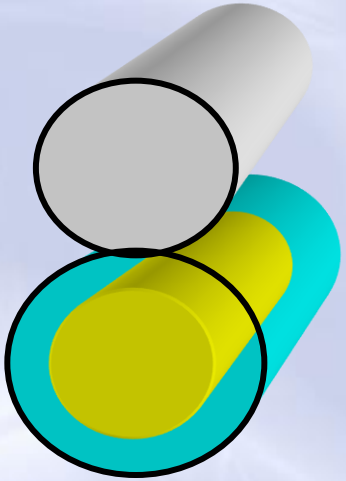




One channel endoscope for vision
Rinsing

Interventional sialendoscopy





Two channels: vision + work
Rinsing

Marchal F, Dulguerov P. Sialendoscopy - the state of the art. Arch Otolaryngol Head Neck Surgery 2003.

SG – Diagnostic sialendoscopy

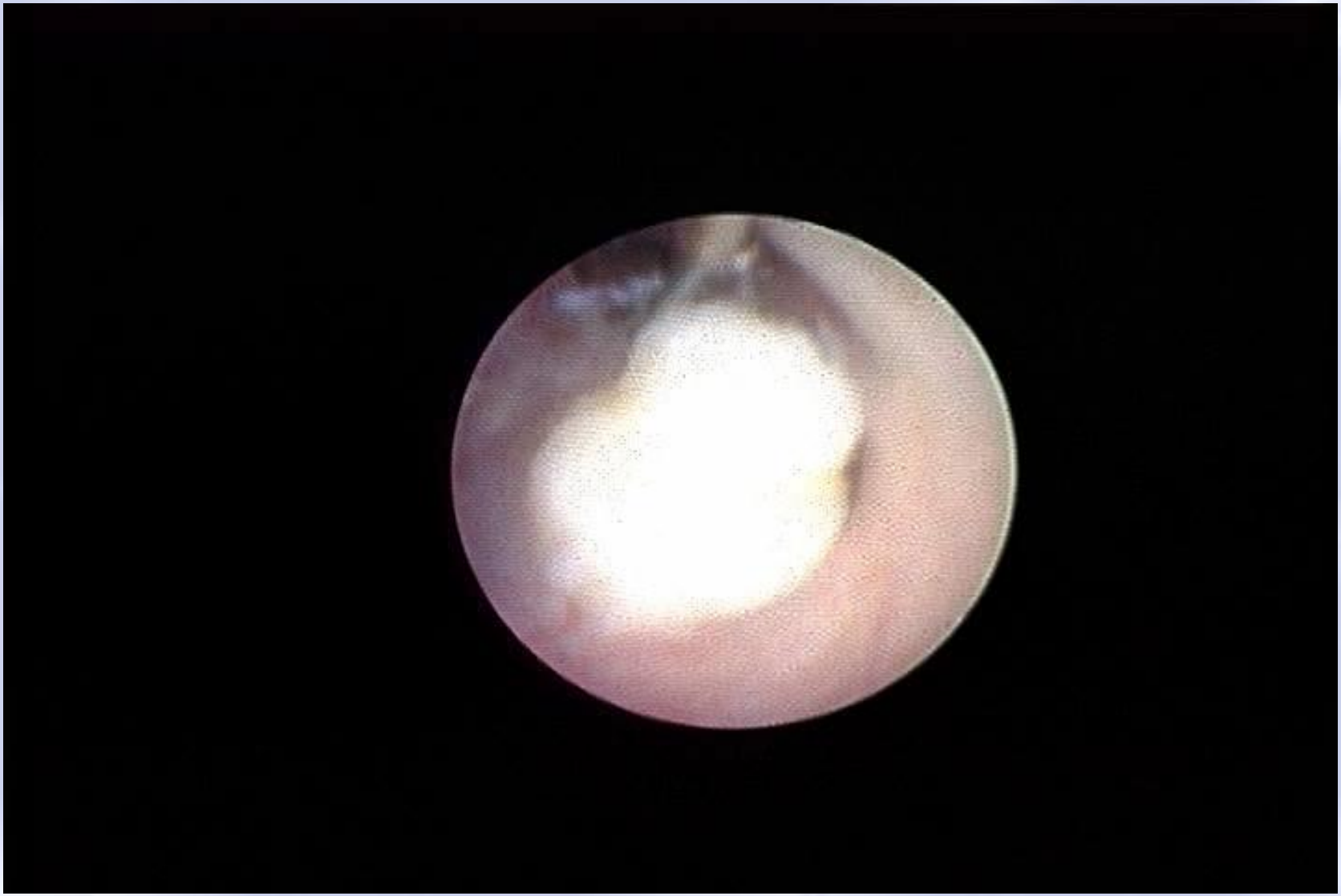
SG – Diagnostic sialendoscopy

Diagnostic sialendoscopy possible in 98% of cases

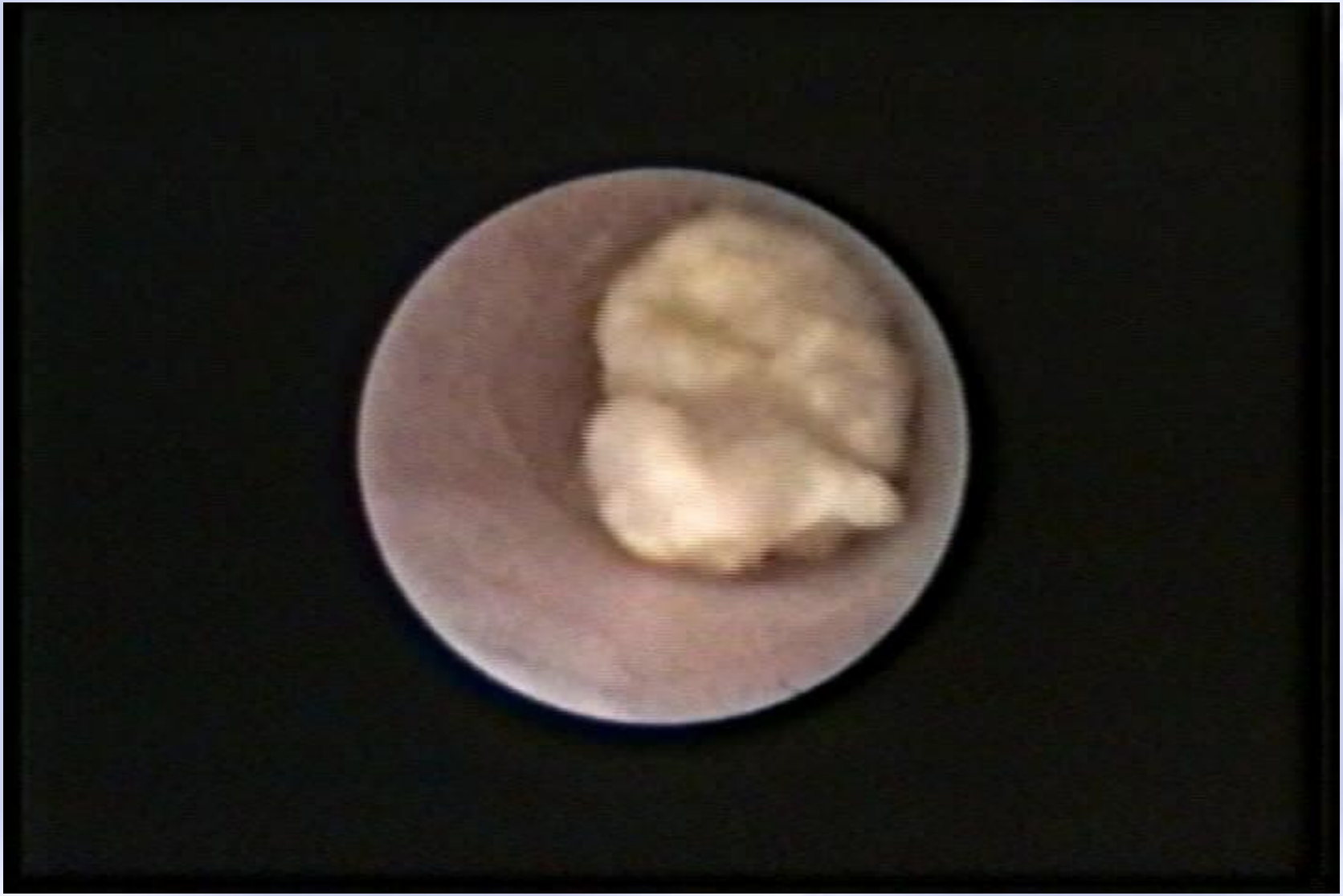
Diagnosis	Sialolithiasis Stenosis Sialodochitis Normal	58% 11% 37% 32%
Duration	22 min	(100 last cases: 11 min)
Pain	2.2 ± 1.4	(scale 0-10)
Limitations	Fibrosis, angulations, mouth opening and prominent teeth	
Complications	0	

Marchal F, Dulguerov P, Becker M, Barki G, Disant F, Lehmann W. Specificity of parotid sialendoscopy. Laryngoscope 111:264-71,2001.
Marchal F, Dulguerov P, Becker M, Barki G, Disant F, Lehmann W. Submandibular diagnostic and interventional sialendoscopy: new procedure for ductal disorders. Ann Otol Rhinol Laryngol 111:27-35,2002.

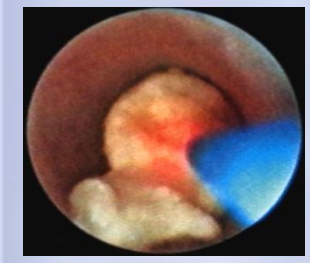
SG – Interventional sialendoscopy

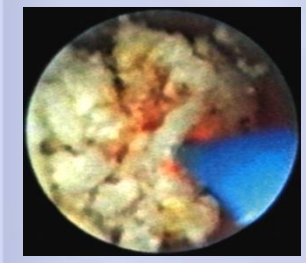


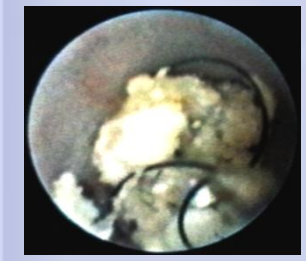
SG – Interventional sialendoscopy

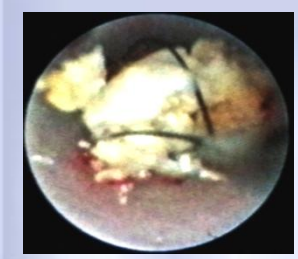


SG – Interventional sialendoscopy



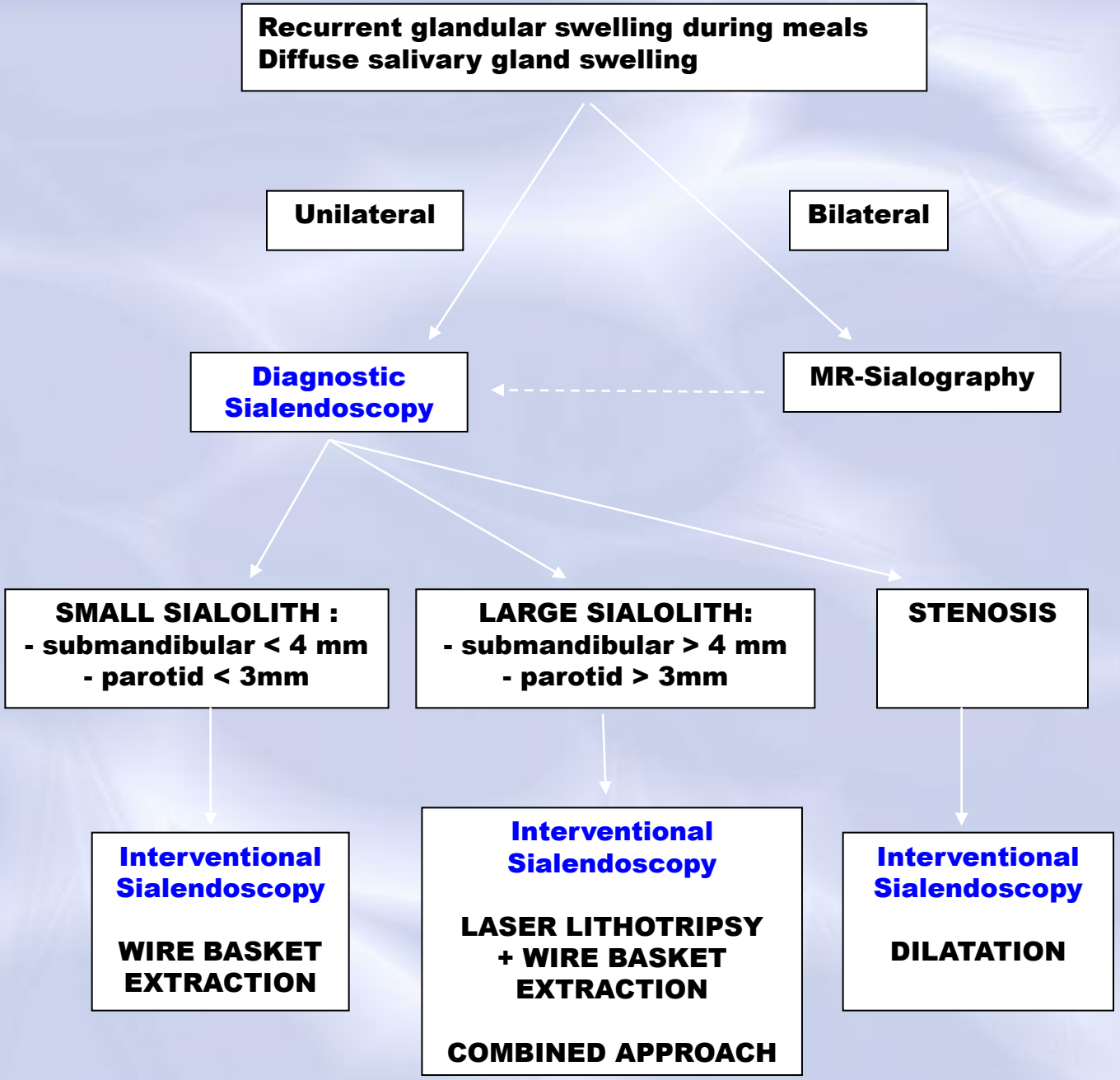






Success	356 (79%)	Stones removed (1 session) Stones removed (>1 sessions) Stenosis dilated	235 121 38
Failures	94 (21%)	Incomplete fragmentation / extraction Embedded stones Recurrent stenosis Submandibular gland resection Parotidectomies	56 11 7 19 1
Complications	43 (10%)	Perforations Blocked wires Brocken wire baskets Bleeding Nerve damage	18 25 3 0 0
Duration	71 ± 41 minutes		

Marchal F, Dulguerov P. Sialendoscopy - the state of the art. Arch Otolaryngol Head Neck Surgery 2003.



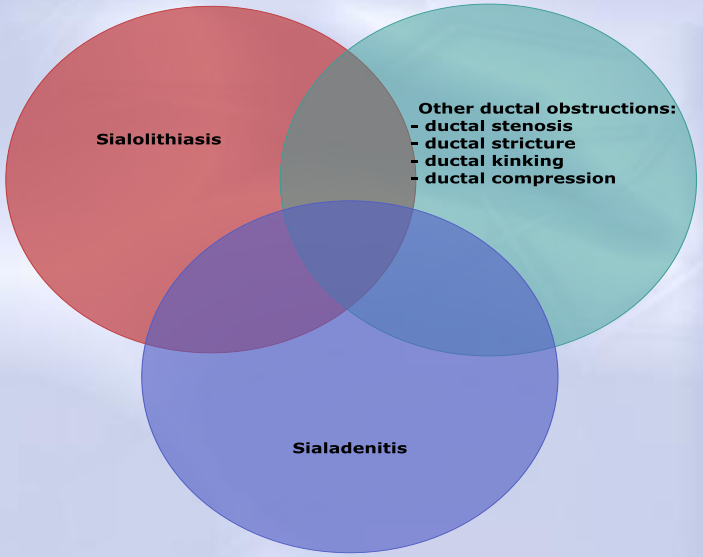
Marchal F, Dulguerov P. Sialendoscopy - the state of the art. Arch Otolaryngol Head Neck Surgery 2003.

US has low sensitivity

True positive	34
True negative	36
False positive	2
False negative	10
Sensitivity	34/44 (77%) CI [63 - 87]
Specificity	36/38 (95%) CI [82 - 99]
Positive predictive value	34/36 (94%) CI [81 - 99]
Negative predictive value	36/46 (78%) CI [64 - 87]
Accuracy	70/82 (85%) CI [76 - 92]

Becker M et al: HOW RELIABLE IS ULTRASONOGRAPHY IN THE ASSESSMENT OF SIALOLITHIASIS? AJR, In press

Salivary glands – ductal pathologies



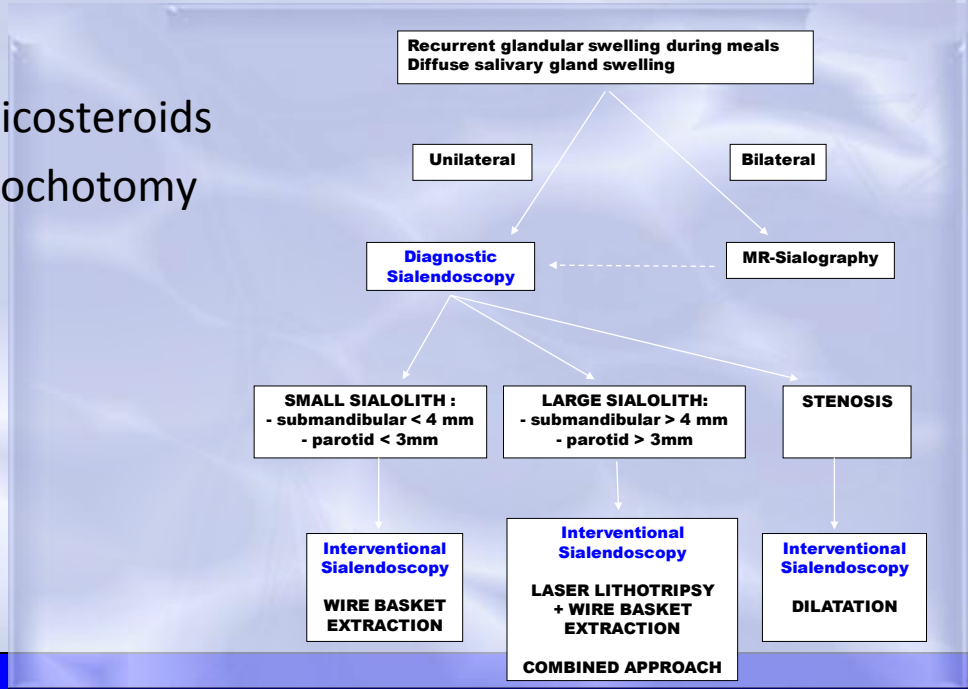
Impossible to distinguish sialolithiasis & other ductal obstructions without ductal system evaluation / sialendoscopy

Ductal pathologies & sialolithiasis present with pain and diffuse gland swelling

Diagnosis is clinical / diagnostic sialendoscopy

Management:

- Acute phase : antibiotics, NSAID, corticosteroids
- Submandibular anterior stone: sialodochotomy
- Else: sialendoscopy



Marchal F, Dulguerov P. Sialendoscopy - the state of the art. Arch Otolaryngol Head Neck Surgery 2003.

Salivary glands - outline

Physiology

Semiology

Infections

Sialolithiasis

sialendoscopy

..... Inflammations

Tumors

benign

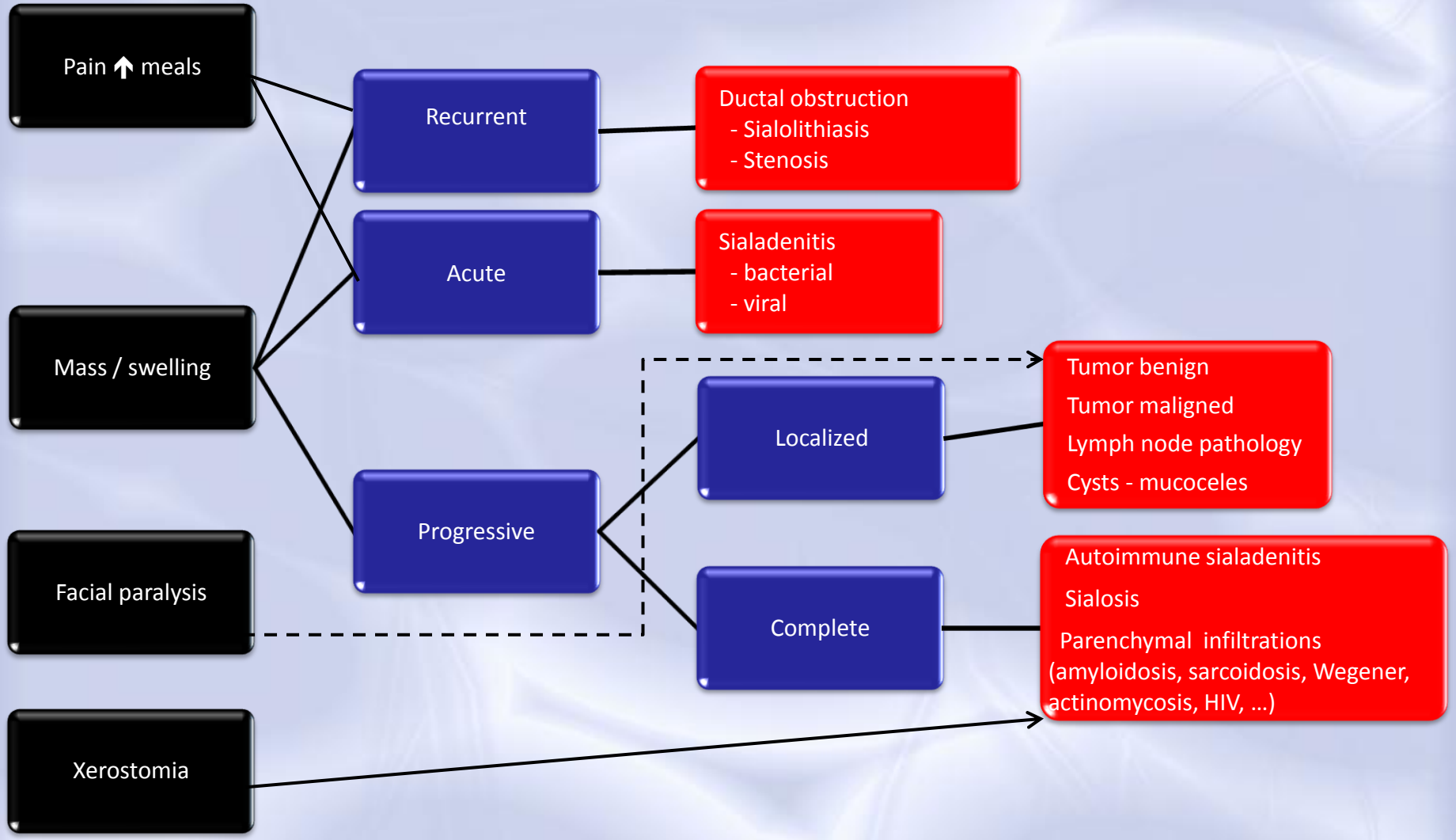
pleomorphic adenoma

cancers

Surgery

..... Anatomy

parotidectomy

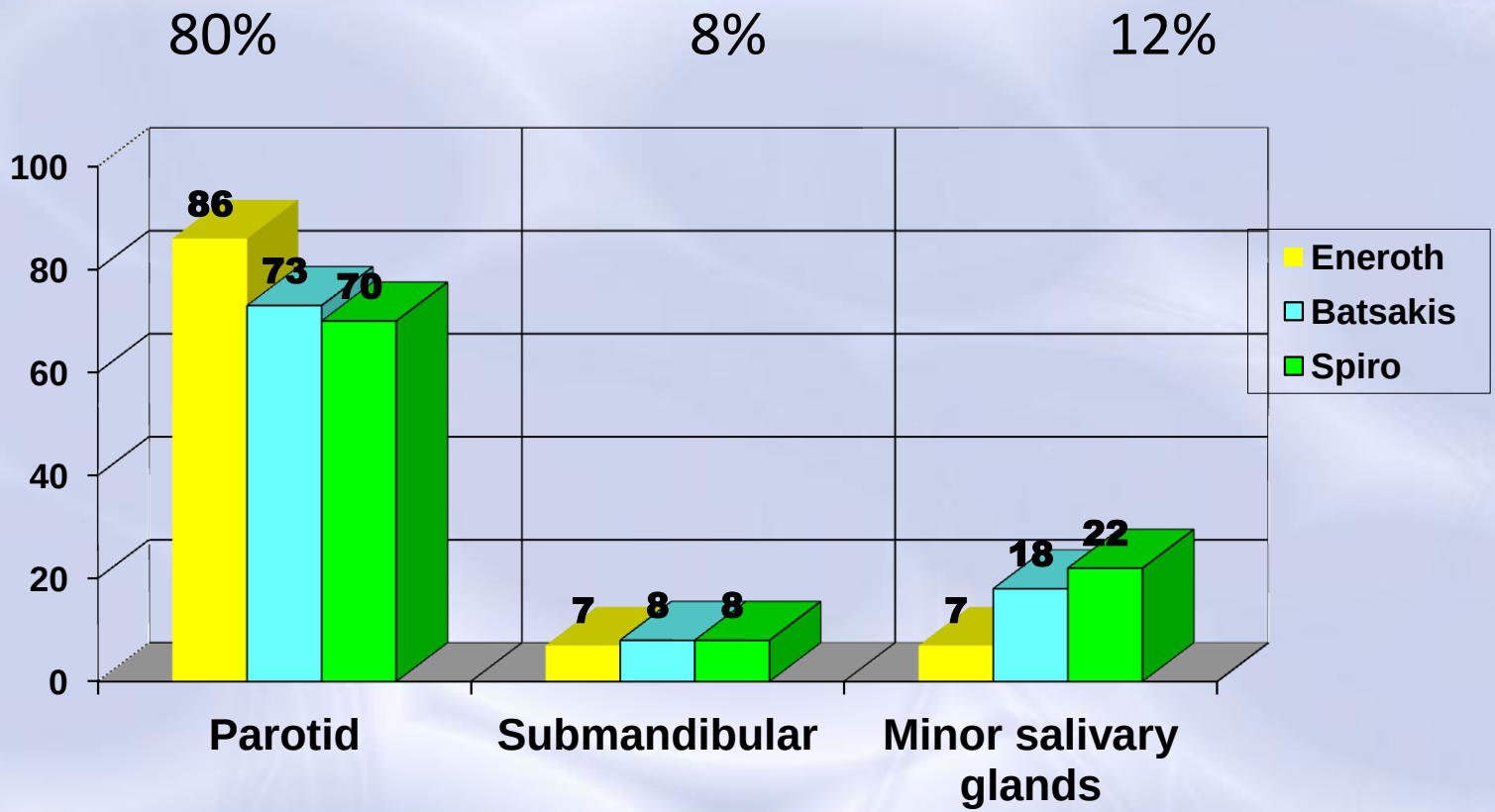

Pain ↑ meals
Mass / swelling
Facial paralysis
Xerostomia
Recurrent
Acute
Progressive
Localized
Complete
Ductal obstruction
- Sialolithiasis
- Stenosis
Sialadenitis
- bacterial
- viral
Tumor benign
Tumor maligned
Lymph node pathology
Cysts - mucoceles
Autoimmune sialadenitis
Sialosis
Parenchymal infiltrations
(amyloidosis, sarcoidosis, Wegener, actinomycosis, HIV, …)

SG - inflammations

- Sjögren syndrome
- Sarcoidosis
- Melkersson-Rosenthal syndrome
- Recurrent parotitis of childhood
- Post-radiation sialadenitis
- Cysts
  - Mucoceles
  - Lympho-epithelial parotid cyst
  - HIV-associated parotid pseudocysts
- Sialo(adeno)sis
- Necrotisis sialometaplasia

Most salivary gland tumors are in the parotid

Salivary glands tumors: ~ 5/100'000



Eneroth CM. Salivary gland tumors in the parotid gland, submandibular gland, and the palate region. Cancer 27:1415-8, 1971.

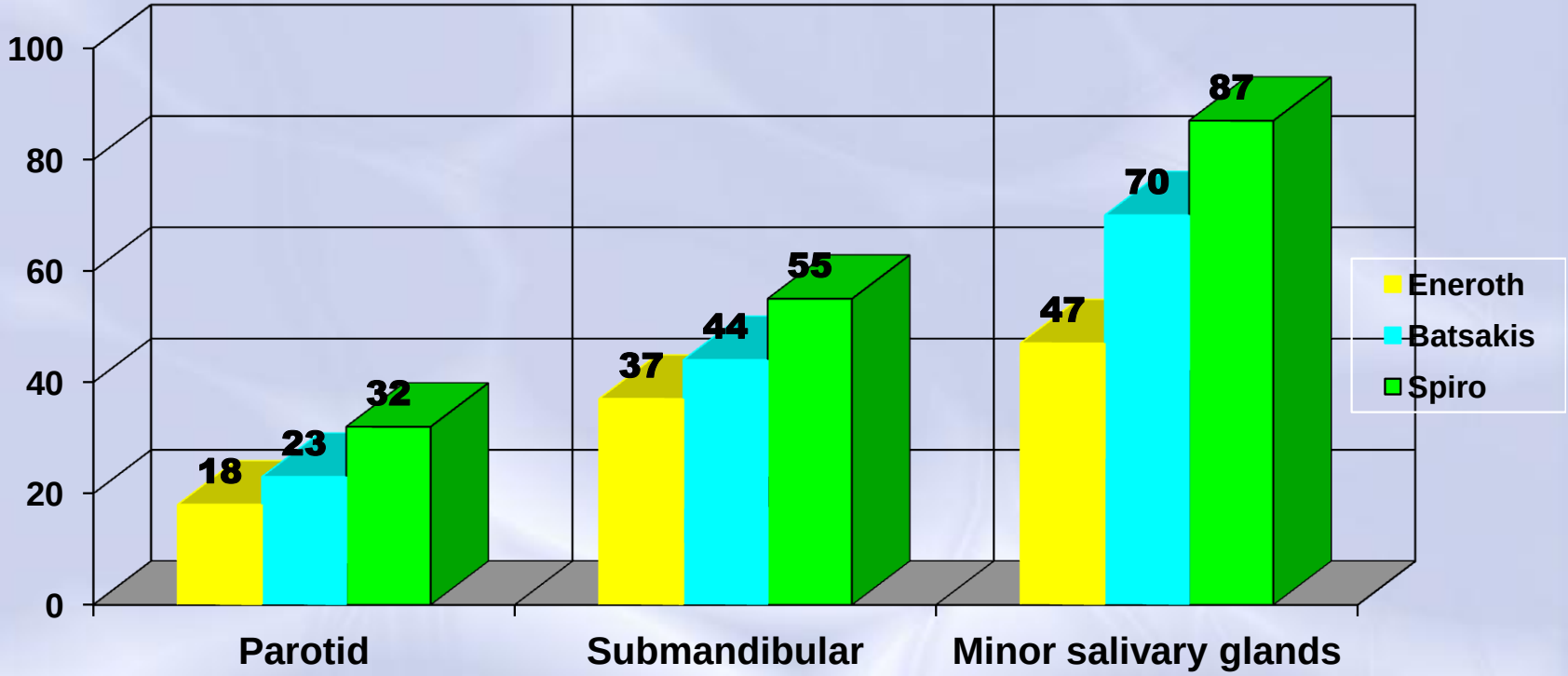
Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Pathol 146:51-8, 1985.

Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg 8:177-84, 1986.

The incidence of carcinoma varies with the gland involved

Salivary glands cancers: ~ 1/100'000

%cancer 20% 50% 75%



Eneroth CM. Salivary gland tumors in the parotid gland, submandibular gland, and the palate region. Cancer 27:1415-8, 1971.
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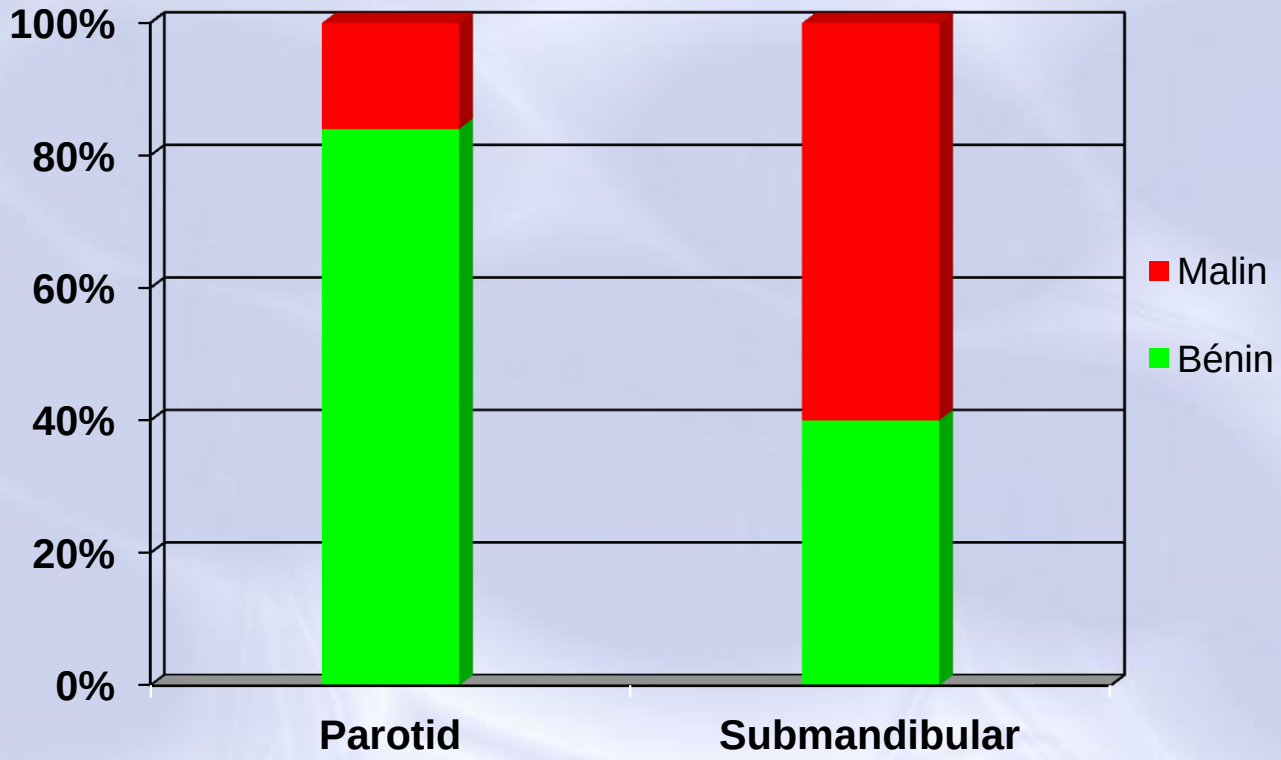
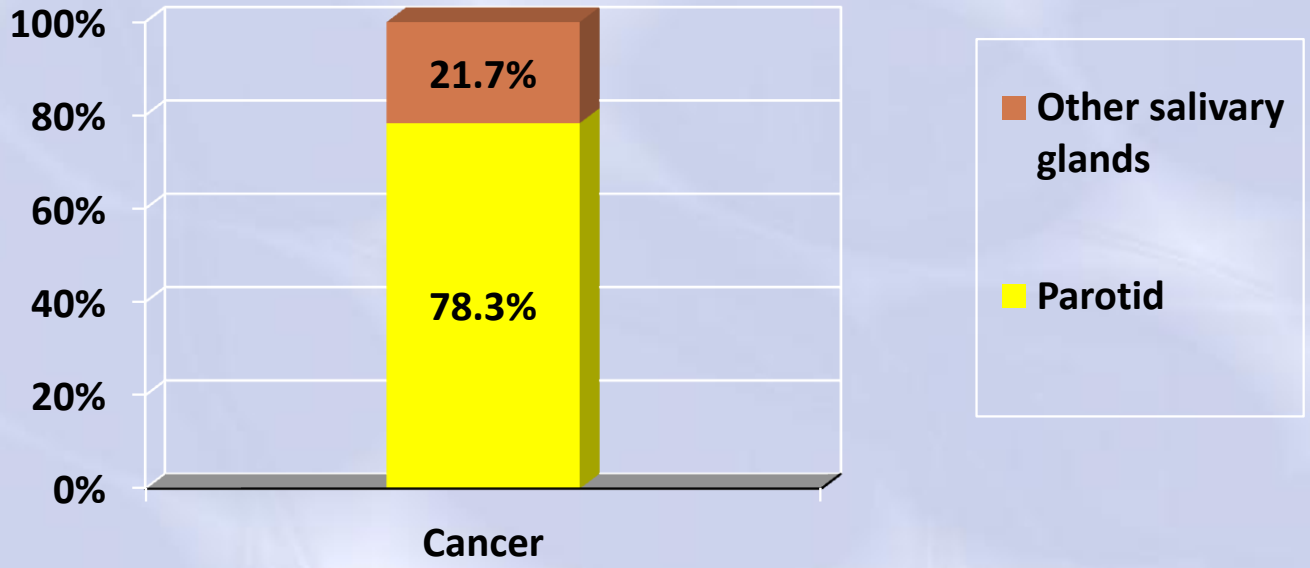
Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg 8:177-84, 1986.

Most parotid tumors are benign



Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

80% of salivary gland cancers are in the parotid gland



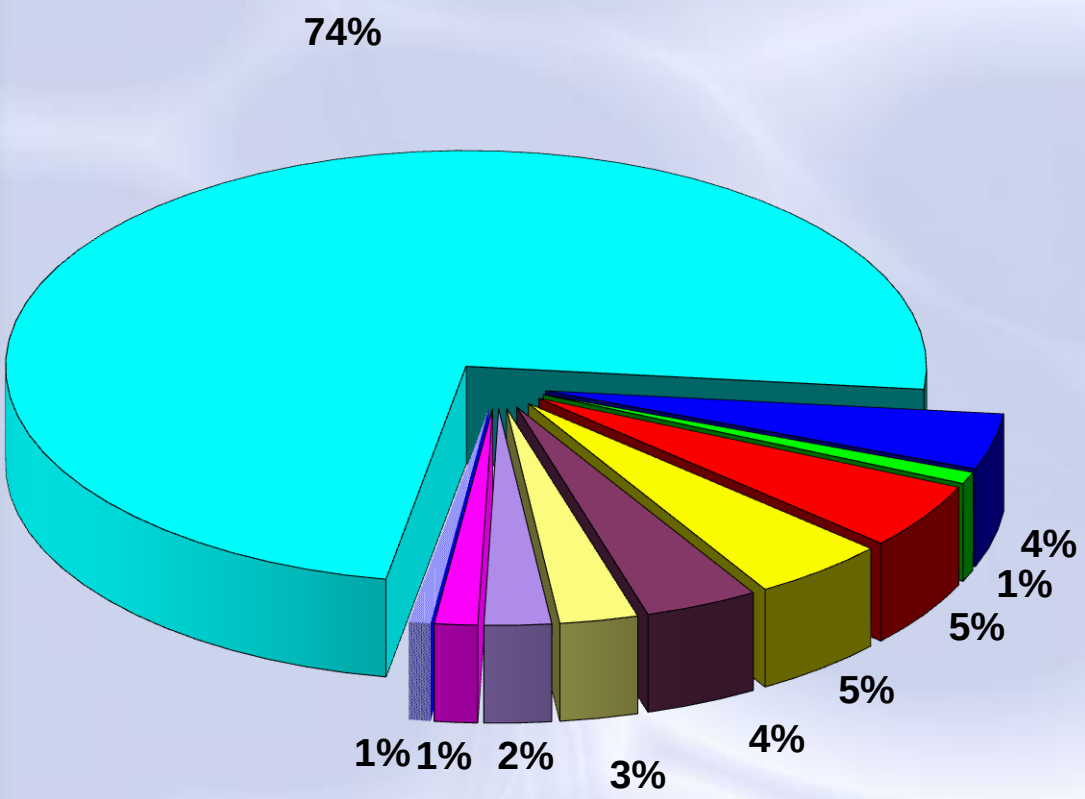
de Ridder M, Balm AJ, Smeele LE et al. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989-2010). *Cancer Epidemiol* 39:14-20,2015.

SG tumors histology

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	

Barnes L, Eveson JW, Reichart P, and Sidransky D: WHO Classification of Tumours – Pathology and Genetics. Tumours of the Head and Neck, IARC Press, Lyon, 2005.

Pleomorphic adenoma is the most frequent SG tumor



- Pleomorphic adenoma
- Whartin
- Other monorphic adenoma
- Mucoepidermoid ca
- Adenoid cystic ca
- Undifferentiated ca
- Acinic cell ca
- Adenocarcinoma
- Ex pleomorphic adenoma ca
- Squamous cell ca

Eneroth, C. M.: Salivary gland tumors in the parotid gland, submandibular gland, and the palate region. Cancer 27: 1415-1418,1971.

The etiology of most salivary gland tumors is unknown

No relation to smoking, infections ...

Irradiation :

- Japan – atomic bomb
- Irradiation for benign pathologies in childhood; dental X-rays; I^{131}
- Delay : 15 year
- Carcinoma (RR=11): muco-epidermoid, squamous cell carcinoma,
- Benign tumors (RR=3): Whartin, pleomorphic adenoma

Pleomorphic adenoma >>> cancer

Smoking >>> Whartin tumor

SG tumors present with an isolated mass

Age : 55-60 years (4 to 98 years)

M/F ratio : 1 / 0.5

Semiology : isolated asymptomatic mass

Signs of malignancy:

- fixation: 2-13%
- trismus: 4%
- facial paralysis: 12-24%
- neck mass: 6-20%

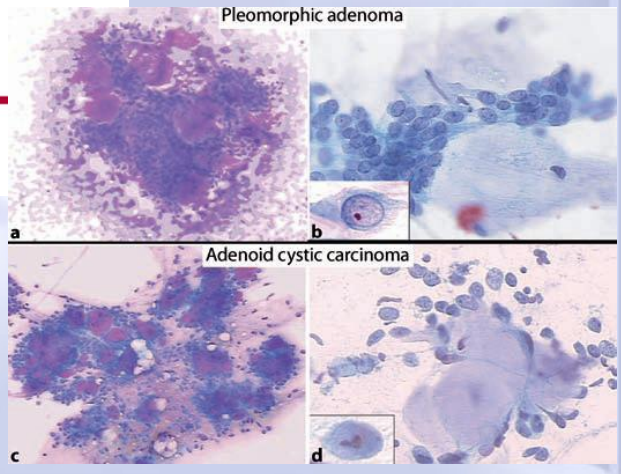
No prognostic role: rapid growth, pain

FNA is false negative in about 20%

Comparison of American Studies With Non-American Studies for Malignant vs Benign Lesions*

	American Studies (n = 9)	Non-American Studies (n = 55)
Area under the curve	0.94 (0.91-0.96)	0.97 (0.95-0.98)
Inconsistency, I^2 (%)	<1 (not determined)	97 (95-99)
Log rank Q, df, *P*	0.05, 2, .49	65.9, 2, .00
Sensitivity	0.83 (0.77-0.88)	0.79 (0.74-0.83)
Specificity	0.93 (0.87-0.93)	0.97 (0.97-0.98)
Positive likelihood ratio	8.8 (6.3-12.3)	33.7 (23.4-48.4)
Negative likelihood ratio	0.19 (0.13-0.26)	0.22 (0.18-0.27)
Disease prevalence	0.43	0.23
Positive predictive value	0.90	0.89
Negative predictive value	0.89	0.94

* Values in parentheses are 95% confidence intervals.



Schmidt, R. L., Hall, B. J., Wilson, A. R.Layfield, L. J.: A Systematic Review and Meta-Analysis of the Diagnostic Accuracy of Fine-Needle Aspiration Cytology for Parotid Gland Lesions. Am J Clin Pathol 136: 45-59,2011.

Frozen sections is false negative in 10%

Table 2
Summary of Accuracy Estimates for Frozen Section and Comparison With FNAC

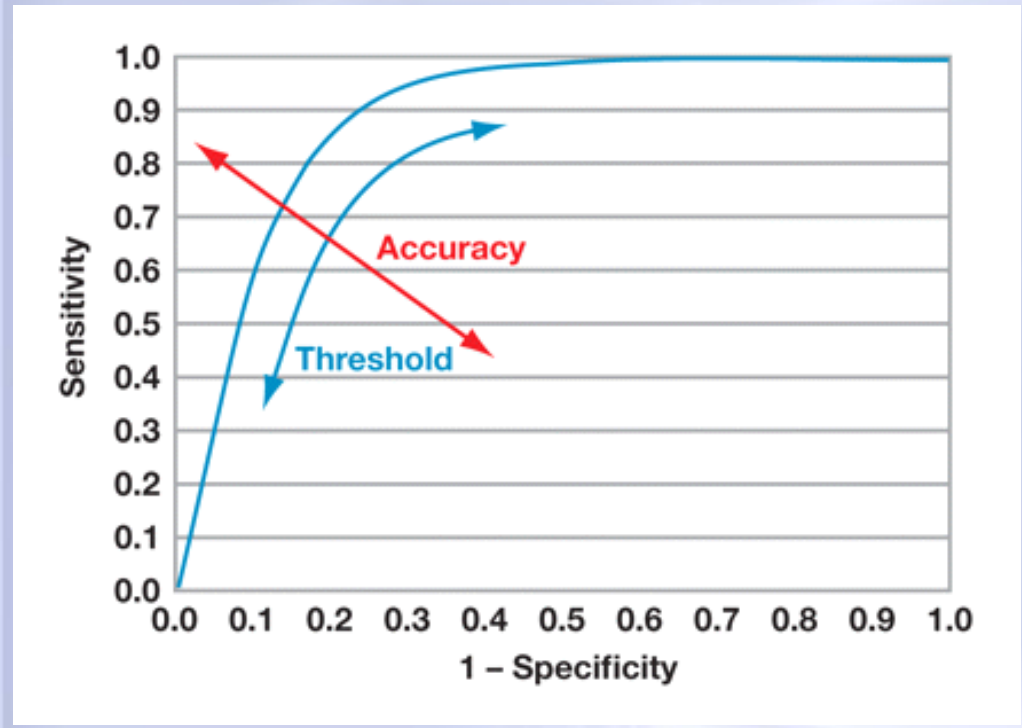
	Frozen Section		FNAC*	
Parameter	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Sensitivity	0.90	0.81-0.94	0.80	0.76-0.83
Specificity	0.99	0.98-0.99	0.97	0.96-0.98
Positive likelihood ratio	80.6	47.5-137.0	28.6	20.7-42.0
Negative likelihood ratio	0.11	0.06-0.19	0.21	0.17-0.26
Area under summary receiver operating characteristic curve	0.99	0.98-1.00	0.96	0.94-0.97
Inconsistency, I^2	53	0-100	98	97-99

CI, confidence interval; FNAC, fine-needle aspiration cytology.
* Data from Schmidt et al.[1]

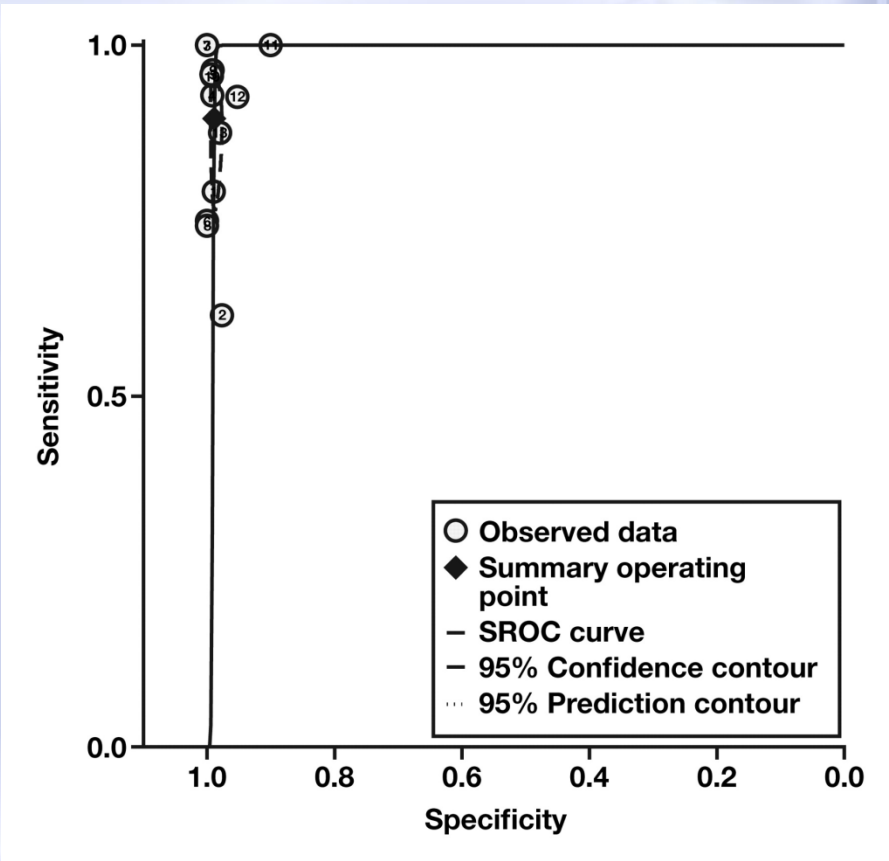
Schmidt, R. L., Hunt, J. P., Hall, B. J., Wilson, A. R.Layfield, L. J.: A systematic review and meta-analysis of the diagnostic accuracy of frozen section for parotid gland lesions. Am J Clin Pathol 136: 729-738,2011.

Frozen section is better than FNA

FNA



Frozen sections



Schmidt, R. L., Hunt, J. P., Hall, B. J., Wilson, A. R.Layfield, L. J.: A systematic review and meta-analysis of the diagnostic accuracy of frozen section for parotid gland lesions. Am J Clin Pathol 136: 729-738,2011.

Core needle biopsy is very accurate

Study	TP	FP	FN	TN	ND	UV	Total	Sens	Spec	Tissue-Specific Accuracy	Included
Breeze 2009[15]	50	0	1	147	2	0	200	0.96	1.00	NR	Yes
Huang 2012[17]	16	0	1	47	0	0	64	0.94	1.00	32/33	Yes
Naqvi 2008[22]	25	0	1	83	1	0	109	0.96	1.00	108/108	Yes
Pfeiffer & Ridder 2012[16]	34	0	0	37	5	0	76	1.00	1.00	30/32	Yes
Taki 2005[23]	6	1	2	28	0	0	37	0.71	0.91	12/18	Yes
Buckland 1999[27]	3	0	0	5	0	8	8	1.00	1.00	7/7	No
Bowyer 2012[28]	NR	NR	NR	NR	NR	NR	4	NR	NR	NR	No
Howlett 2007[26]	21	0	0	55	0	0	76	1.00	1.00	74/76	No
Kesse 2002[14]	10	0	0	18	0	26	54	1.00	1.00	27/28	No
Pratap 2009[25]	NR	NR	NR	NR	3	NR	63	0.89	1.00	NR	No
Wan 2004[21]	12	0	1	40	0	0	53	0.83	1.00	30/31	No
Yamashita 2002[24]	0	0	0	0	0	0	6	NR	1.00	6/6	No

FN = false negative; FP = false positive; ND = nondiagnostic; NR = not reported; Sens = sensitivity; Spec = specificity; TN = true negative; TP = true positive; UV = unverified.

Sensibility: 96%

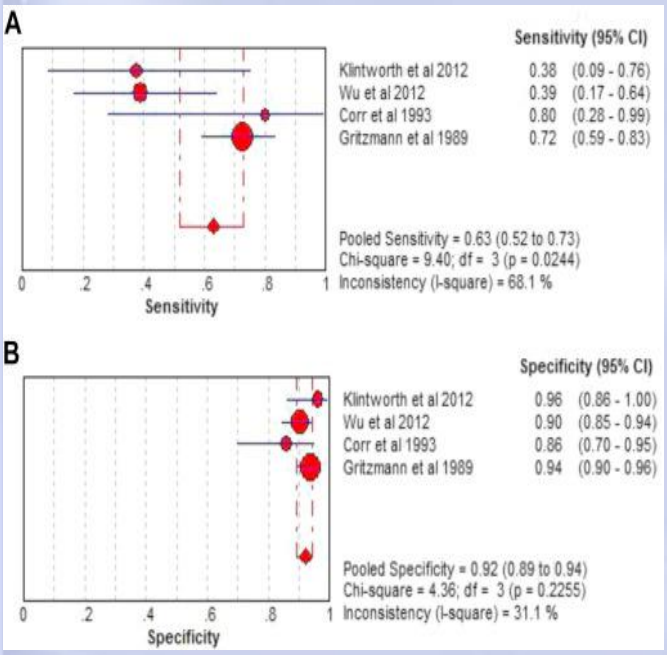
Specificity: 100%

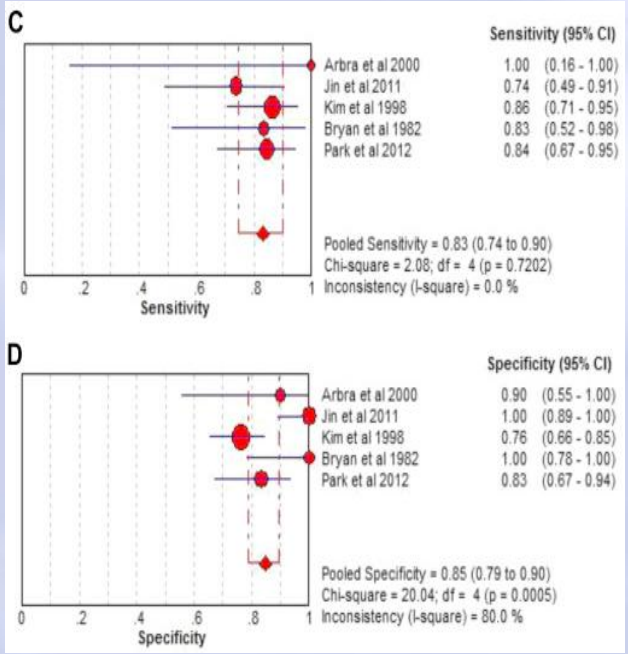
Complications:

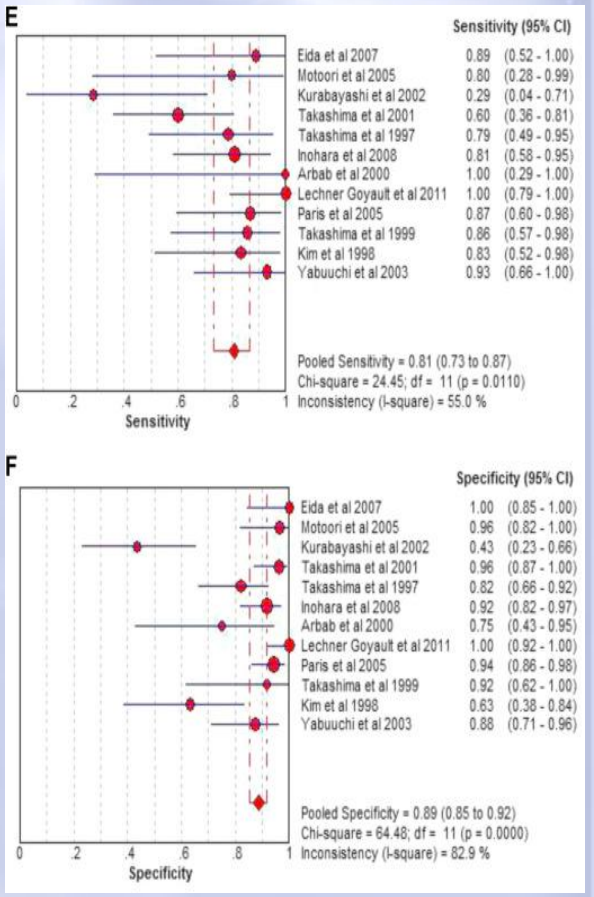
- 1.6% hematoma
- 0.4% anesthesia-related 7N temporary paresis

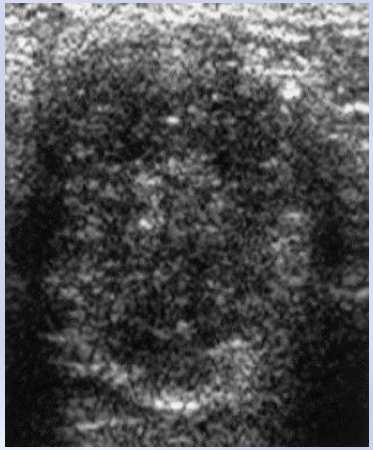
Witt BL, Schmidt RL. Ultrasound-guided core needle biopsy of salivary gland lesions: A systematic review and meta-analysis. *Laryngoscope* 124:695-700,2014.

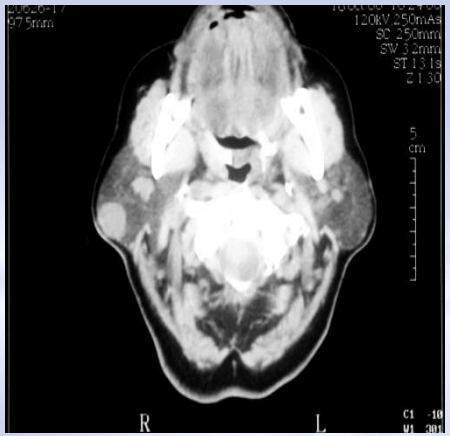
MRI is probably the best imaging modality

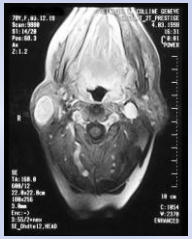












Liu Y, Li J, Tan Y-r, Xiong P, Zhong L-p. Accuracy of diagnosis of salivary gland tumors with the use of ultrasonography, computed tomography, and magnetic resonance imaging: a meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 119:238-45, 2015.

SG Tumors - evaluation

NO preoperative open biopsy

FNA: false negatives for malignancy ~ 20%

Frozen sections: false negatives for malignancy ~ 10%

Role of core needle biopsy ?

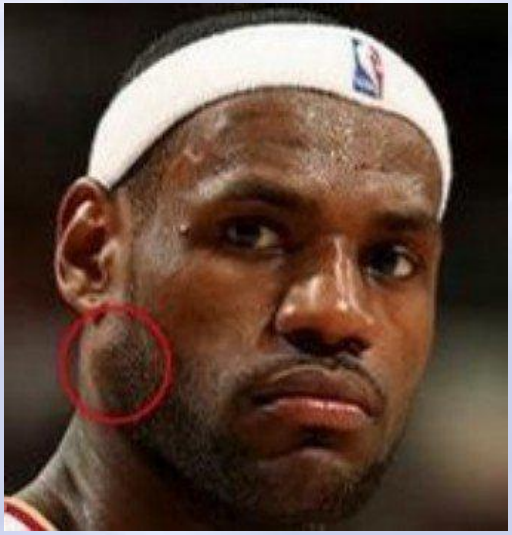
Imaging:

cannot differentiate benign vs. malignant

useful if:

1) **the presence of mass in uncertain**
2) **the location (superficial or deep lobe) is unclear**
3) **an extension outside the parotid gland is suspected**
4) **recurrence**
5) **malignancy suspected**

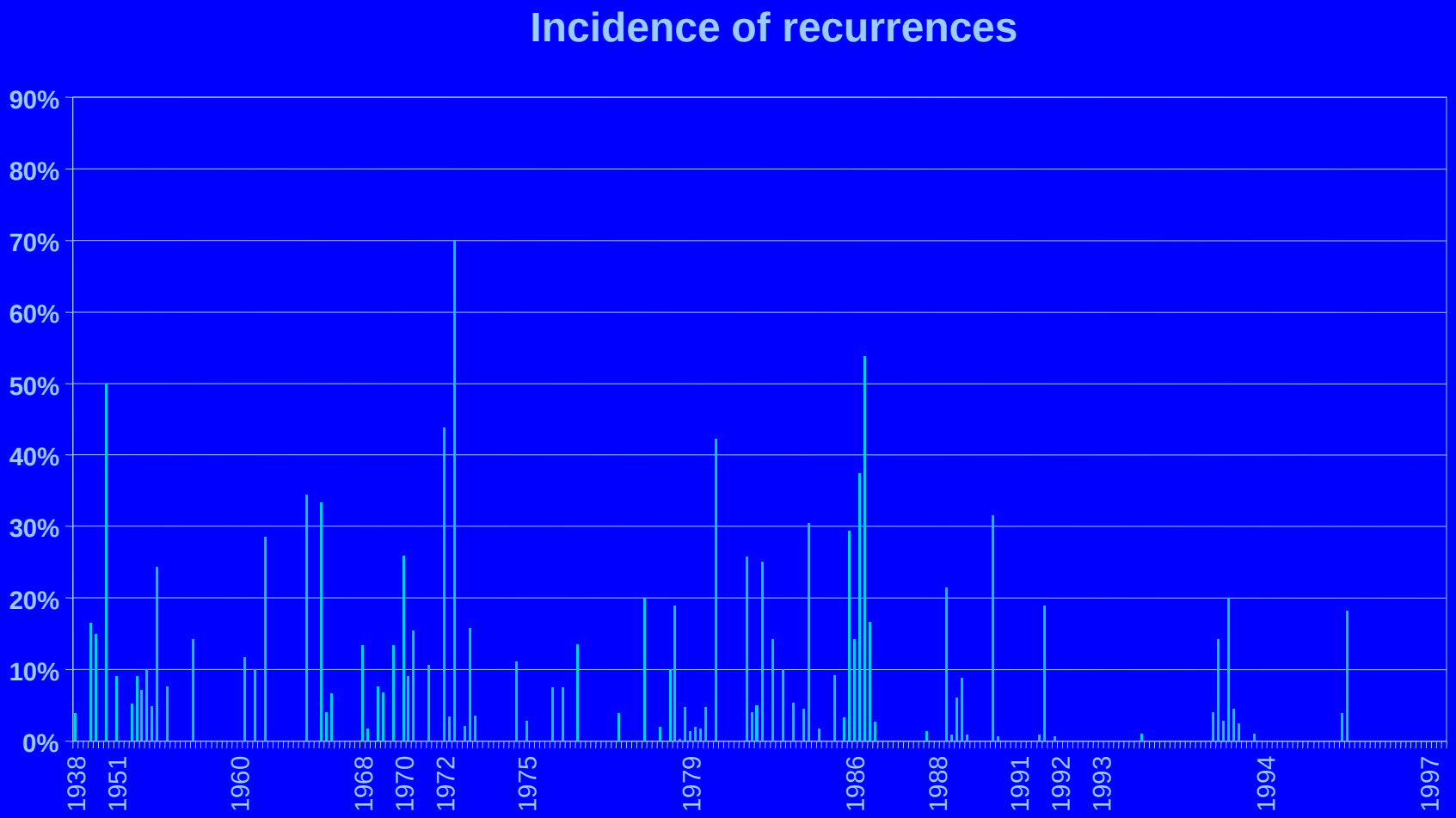
Most SG masses require surgery



EXCEPTIONS:

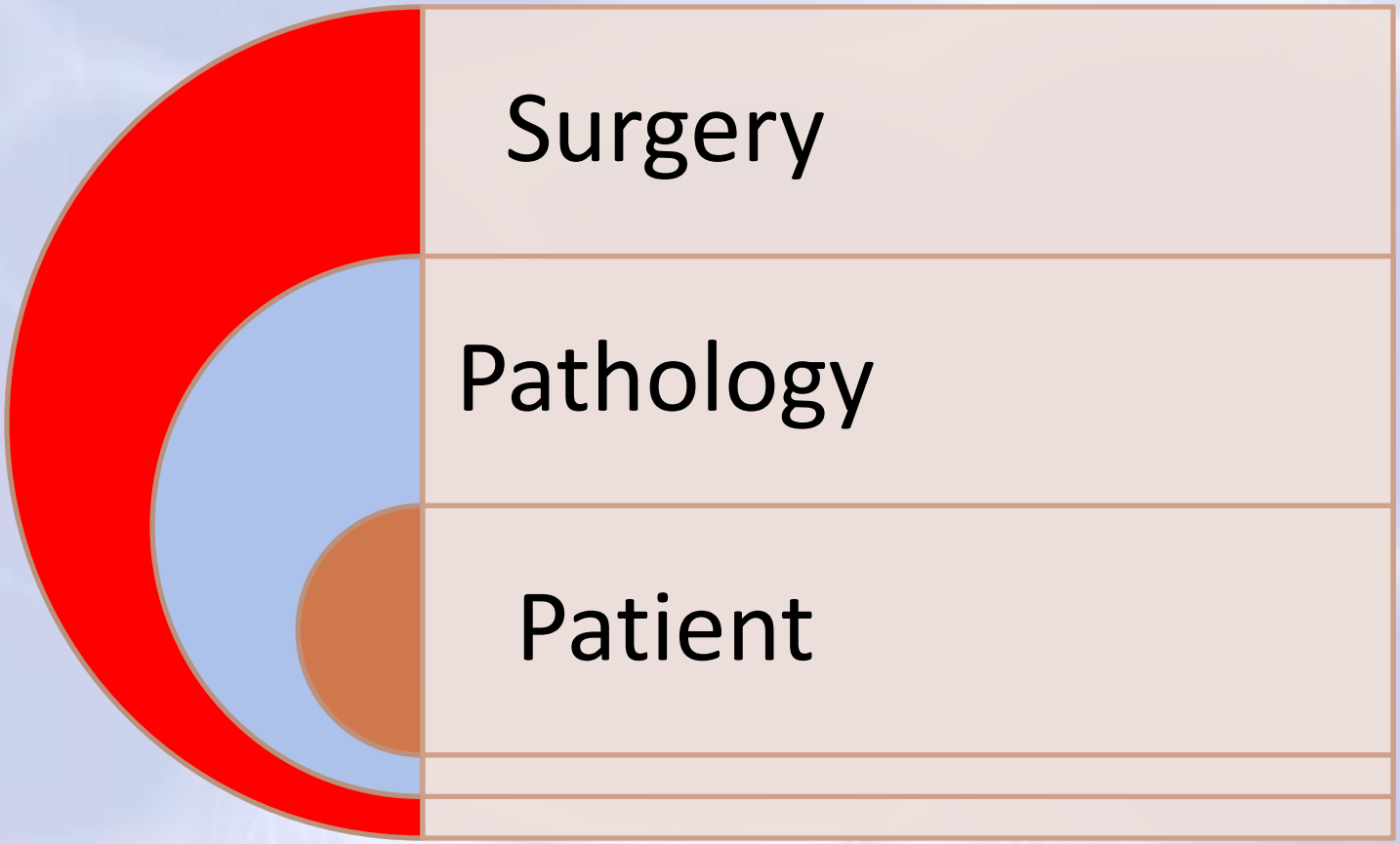
1. Pathology
   - Infection / inflammation / systemic disease
   - Lymphoma
   - Metastasis
   - Pediatric hemangioma
   - Benign: Whartin tumor in a old patient
2. Patient not fit for surgery

The recurrences of pleomorphic adenoma is highly variable

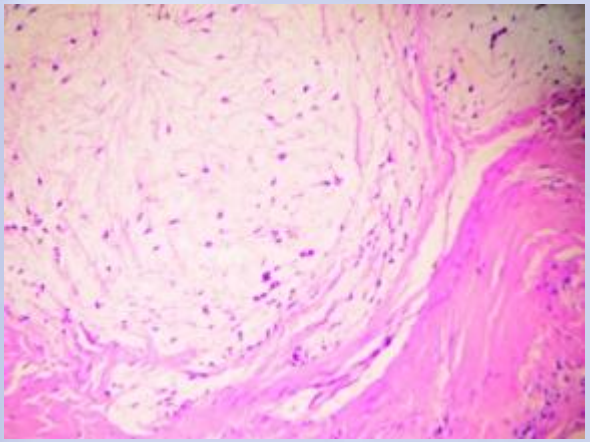


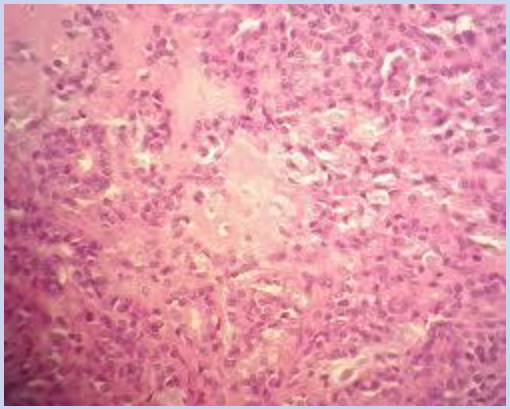
Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

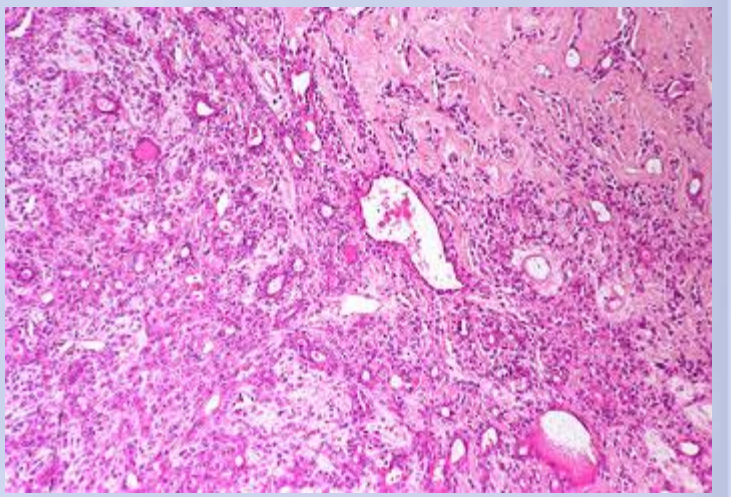
The type of parotidectomy is not the only factor in PA recurrence



Dulguerov P, Todic J, Pusztaszeri M, Alotaibi NH (2017) Why Do Parotid Pleomorphic Adenomas Recur? A Systematic Review of Pathological and Surgical Variables. Front. Surg. 4:26. doi: 10.3389/fsurg.2017.00026



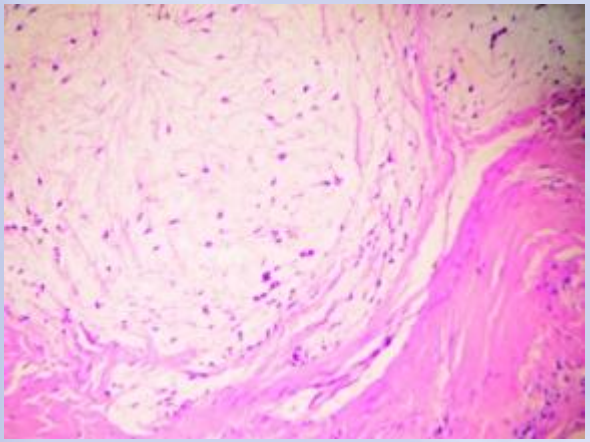




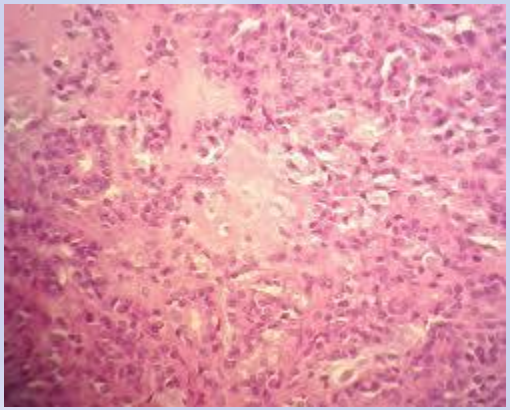
Seifert G, Langrock I, Donath K. Pathomorphologische Subklassifikation der pleomorphen Speicheldrusenadenome. Analyse von 310 pleomorphen Parotisadenomen. HNO 1976;24:415-26.

There are subtypes of pleomorphic adenoma

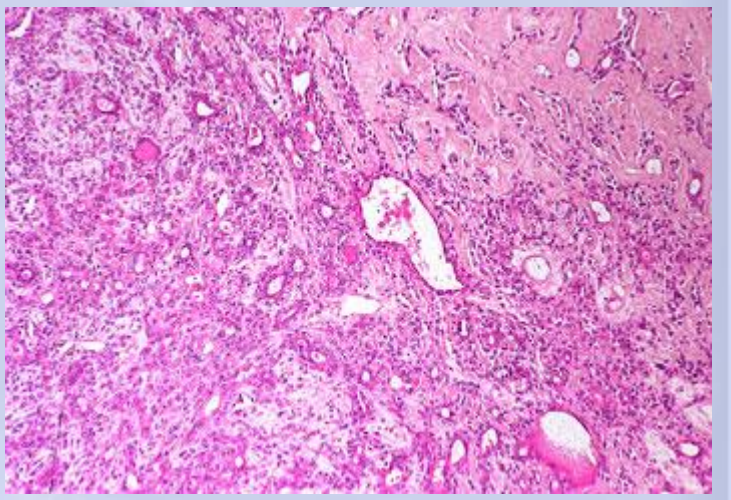
Hypocellular
50-80% stroma



Classical
30-50% stroma



Hypercellular
< 30% stroma



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The capsule of pleomorphic adenoma is often thin or absent

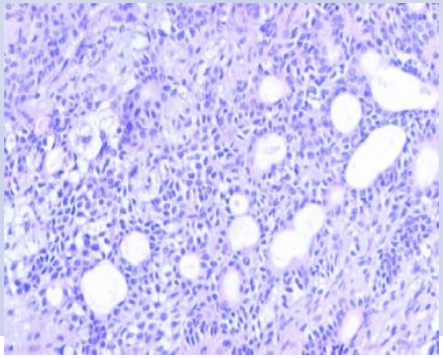
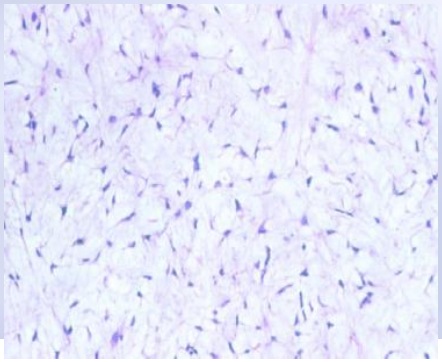
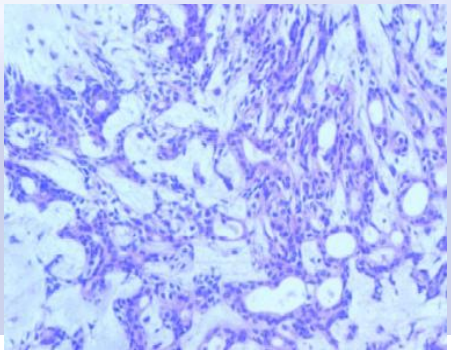




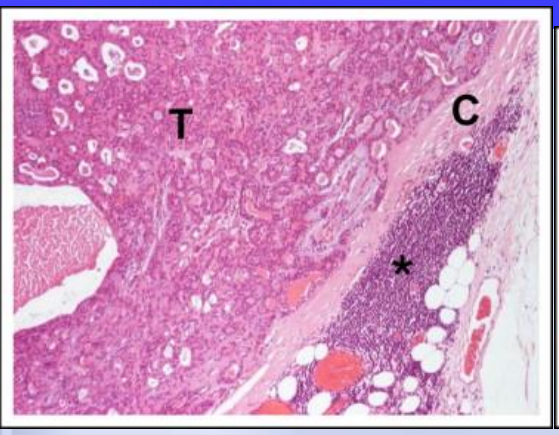
TABLE II.
Capsular Features of the Pleomorphic Adenomas.

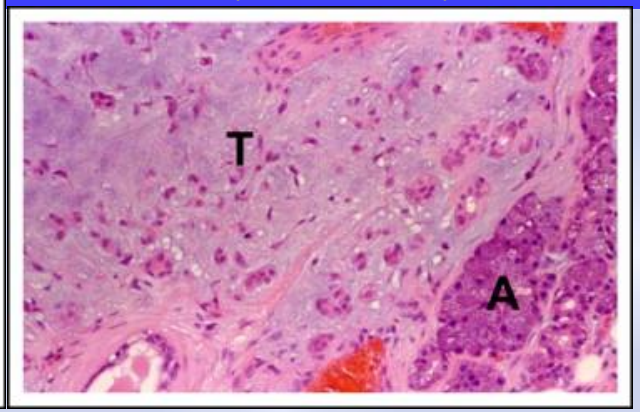
	All	Cellular Type	Myxoid Type	Classic Type
No. of patients	100	35	51	14
Focally very thin capsules	97	34 (97%)	49 (96%)	14 (100%)
Focal absence of encapsulation	46	4 (11%)	36* (71%)	6 (43%)
Pseudopodia and satellite nodules	28	8 (23%)	17 (33%)	3 (21%)

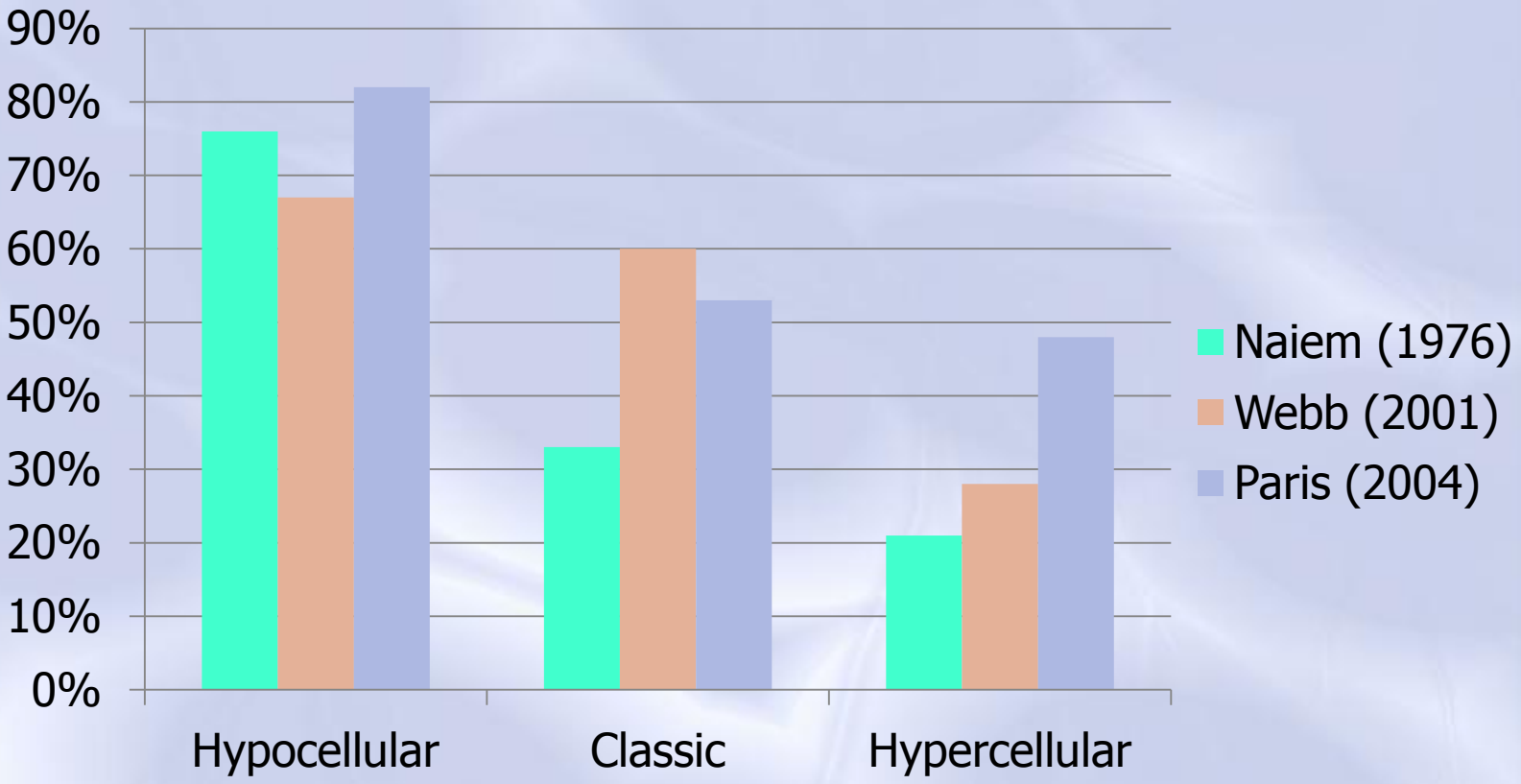
*Significantly different from other subtypes (Pearson's Chi-Square Test; $P \leq .01$).

Stennert E, Guntinas-Lichius O, Klussmann JP Arnold G (2001): Histopathology of pleomorphic adenoma in the parotid gland: a prospective unselected series of 100 cases. *Laryngoscope 111: 2195-200.*

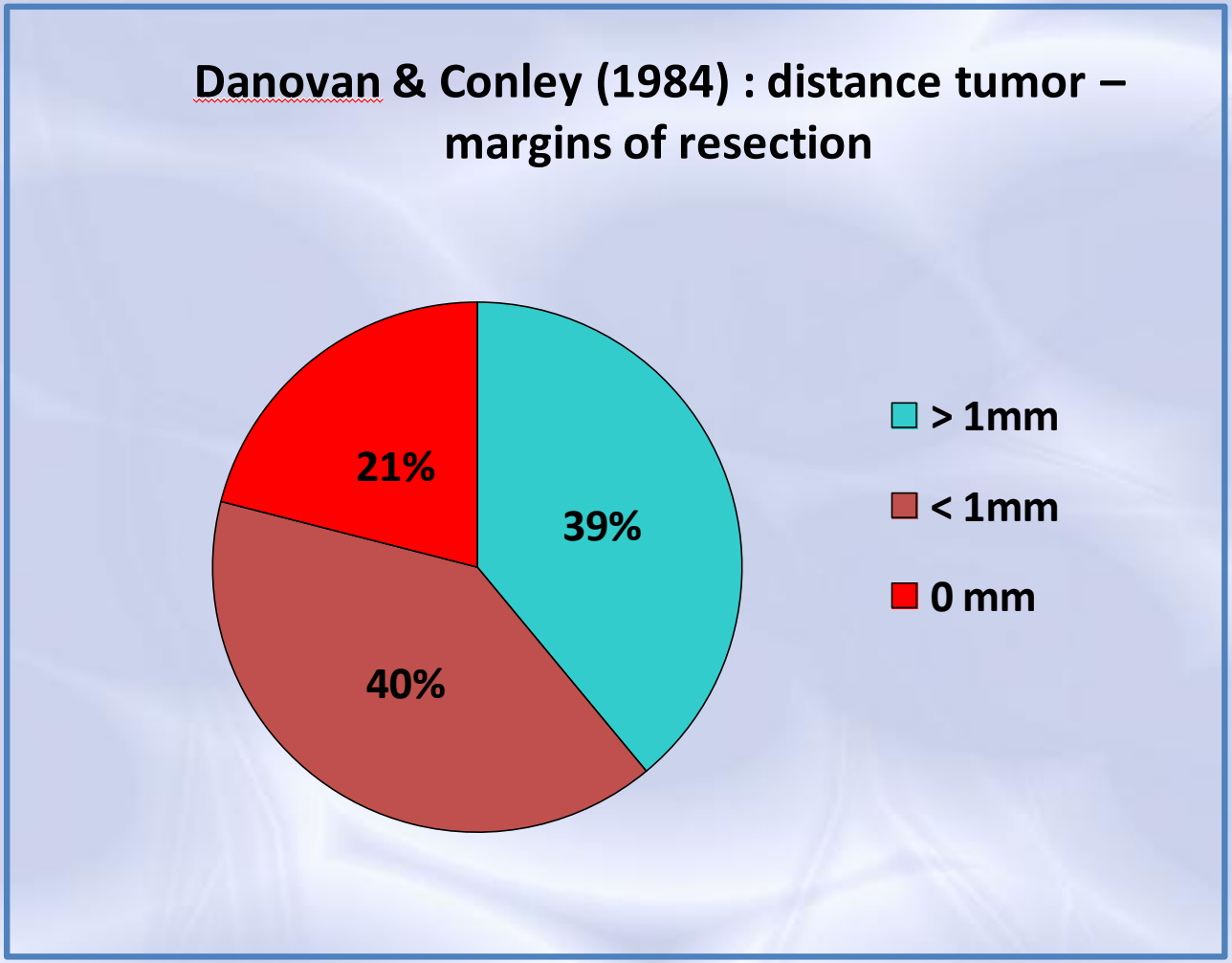
Incomplete capsule more often in hypocellular PA





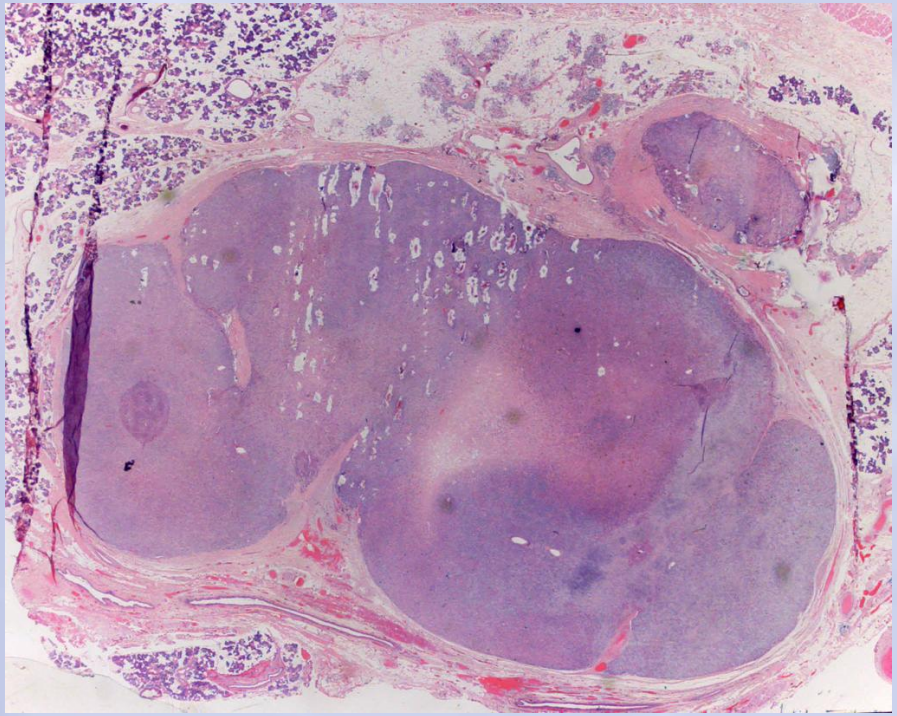


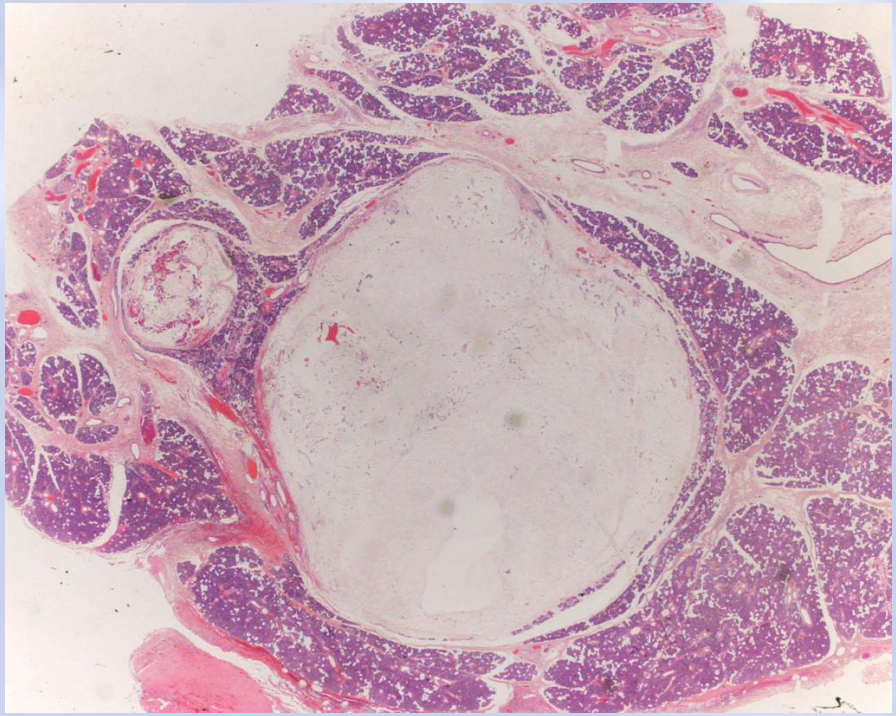
Obtaining adequate normal tissue margin is often impossible



Danovan DT Conley JJ (1984): Capsular significance in parotid tumor surgery: reality and myths of lateral lobectomy. *Laryngoscope 94: 324-329.*

Pleomorphic adenoma often exhibit pseudopodia





Author	Reference	Incidence of pseudopodia or satellite nodules
Stennert et al.	*Laryngoscope 2001*	72%
Paris et al.	*Ann Otolaryngol Chir Cervicofac 2004*	28%
Zbaeren et al.	*Head Neck 2007*	48%

Pathologic and surgical factors related to PA recurrence

Reference	Lack of capsule[a] (%)	Pseudopodia[a] (%)	Satellite nodules[a] (%)	Multi-centricity[a] (%)	Exposed capsule[a] (%)	Gross specimen damage (%)	Tumor puncture[a] (%)	Tumor spillage[a] (%)	Margins[a]
Danovan and Conley (8)	21				40	27			
Goudot et al. (79)	4/14								
Lam et al. (14)	33			0	100	27			
Natvig and Soberg (81)					36			2/33	
Henriksson et al. (13)		8/55					4/7	12/22	
Stennert et al. (18, 77)	46/66	28	28						
Webb and Eveson (19)		12		0	81	5.5			
Ghosh et al. (11)								5/11	1.8%/18%[b]
Paris et al. (82)		53/60		0					
Zbären and Stauffer (74)	33	40	13	0	80				
Orita et al. (83)			3	1					
Riad et al. (84)				0			11/100	1/57	1.3/6 mm[c]
Park et al. (75)	58/70	53/60	10/60				4/30	4/30	11%/50%

[a]*Incidence of characteristic in non-recurrent PA/recurrent PA.*

[b]*>1/<1 mm.*

[c]*Average margin in non-recurrent PA/recurrent PA.*

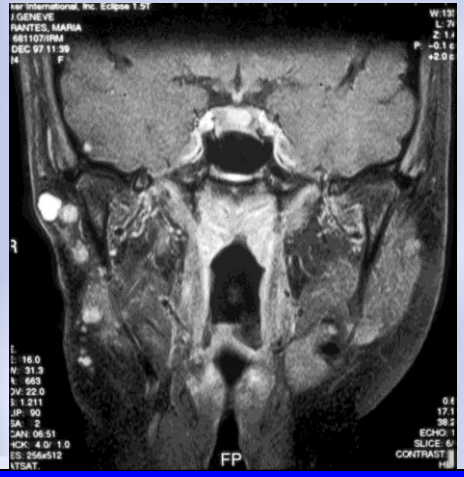
Dulguerov P, Todic J, Pusztaszeri M, Alotaibi NH (2017) Why Do Parotid Pleomorphic Adenomas Recur? A Systematic Review of Pathological and Surgical Variables. Front. Surg. 4:26. doi: 10.3389/fsurg.2017.00026

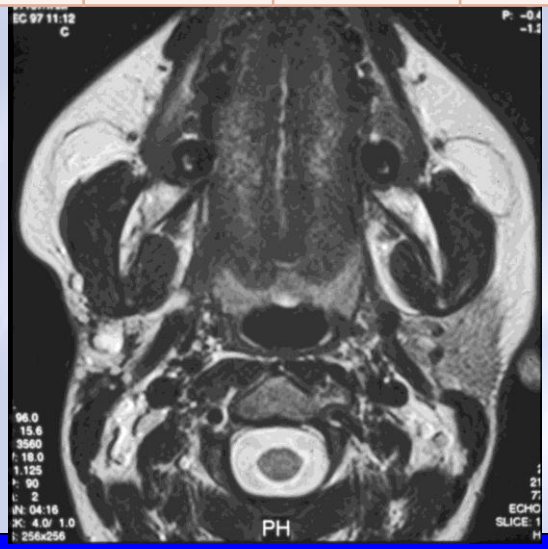
Recurrences after pleomorphic adenoma surgery occur years after the initial surgery

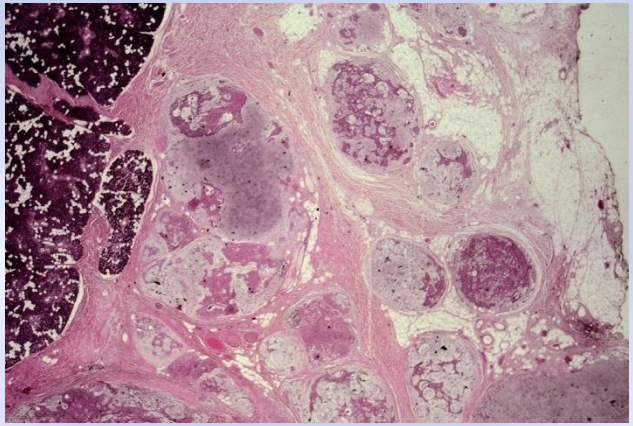
		N	Mean interval
Renehan	1996	114	8 y
Leverstein	1997	29	10 y
Yugueros	1998	39	14 y
Carew	1999	31	9 y
Glas	2001	52	3 y
Maxwell	2004	35	5 y
Leonetti	2005	42	5 y
Zbären	2005	33	12 y

Recurrences after pleomorphic adenoma surgery are multicentric

		N	First recurrence		First and subsequent recurrence	
Phillips	1995	126			85	(67%)
Renehan	1996	114	52	(46%)		
Maxwell	2004	35	20	(57%)		
Stennert	2004	31			28	(90%)
Leonetti	2005	42			42	(100%)
Zbären	2005	33	24	(73%)		







Patients with recurrent pleomorphic adenoma are younger at first presentation by 15-20 years

		with recurrent pleomorphic adenoma		without recurrent pleomorphic adenoma	
		No of patients	mean age	No of patients	mean age
Maran	1984	19	27	64	51
Mc Gregor	1988	31	30	143	47
Renehan	1996	114	32	551	47
Zbären	2007	42	36	294	46

more aggressive tumors in young patients ?

less extensive surgery in young patients ?

Pleomorphic adenoma recurrences are associated with further recurrences

		No of patients	Re - recurrence
O'Dwyer	1986	32	31%
Renehan	1996	114	15%
Yugueros	1998	39	21%
Maxwell	2004	35	24%
Zbären	2007	42	19%

- **Second recurrences more frequent ~ 15-30%**

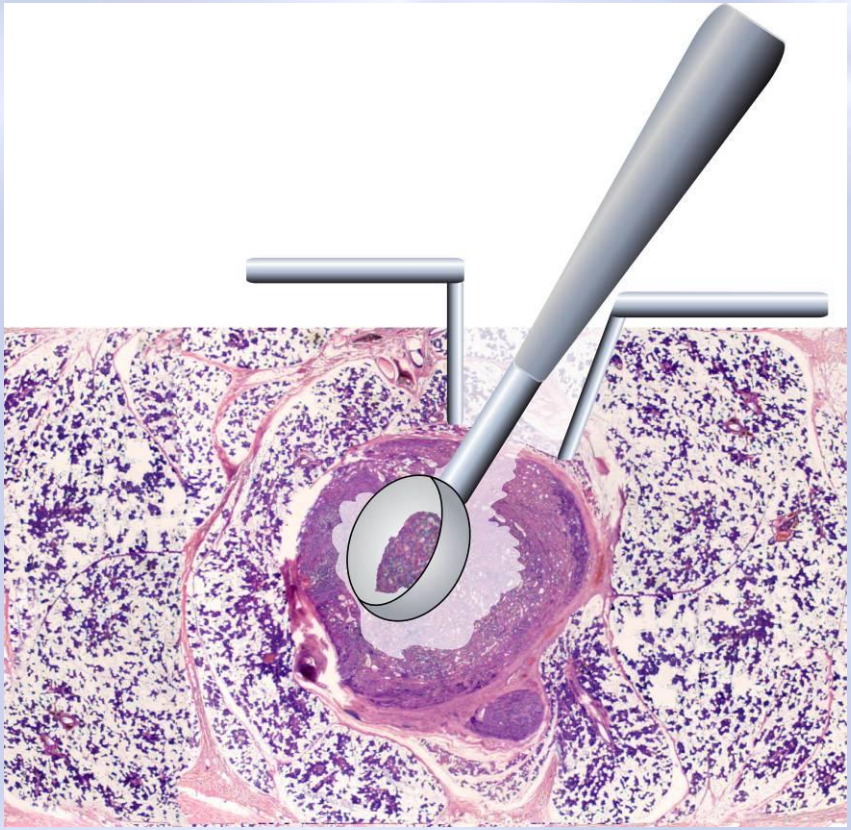
Surgery for pleomorphic adenoma recurrences are associated with more facial nerve complications

		No of patients	Facial nerve paresis
Maran	1984	19	31%
O'Dwyer	1986	32	15%
Renehan	1996	114	24%
Zbären	2005	42	19%

Type of parotid surgery - Enucleation intracapsular

"There are three possible planes in which a parotid tumor may be removed.

In the first place, the rather delicate capsule may be opened and the contained tumor tissue expressed. After this has been done an attempt may be made to remove the capsule."

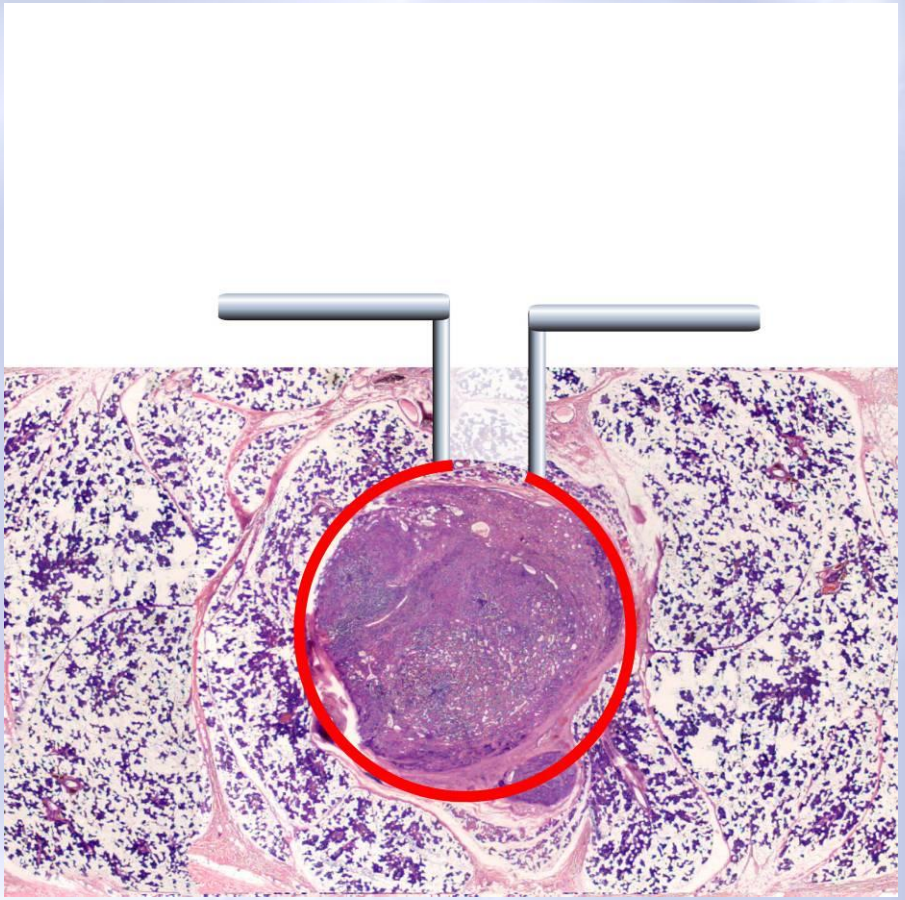


"curretage"
"shelling out"

Patey DH (1940): The treatment of mixed tumours of the parotid gland. Brit J Surg 28: 29-38.

Type of parotid surgery: Enucleation extracapsular

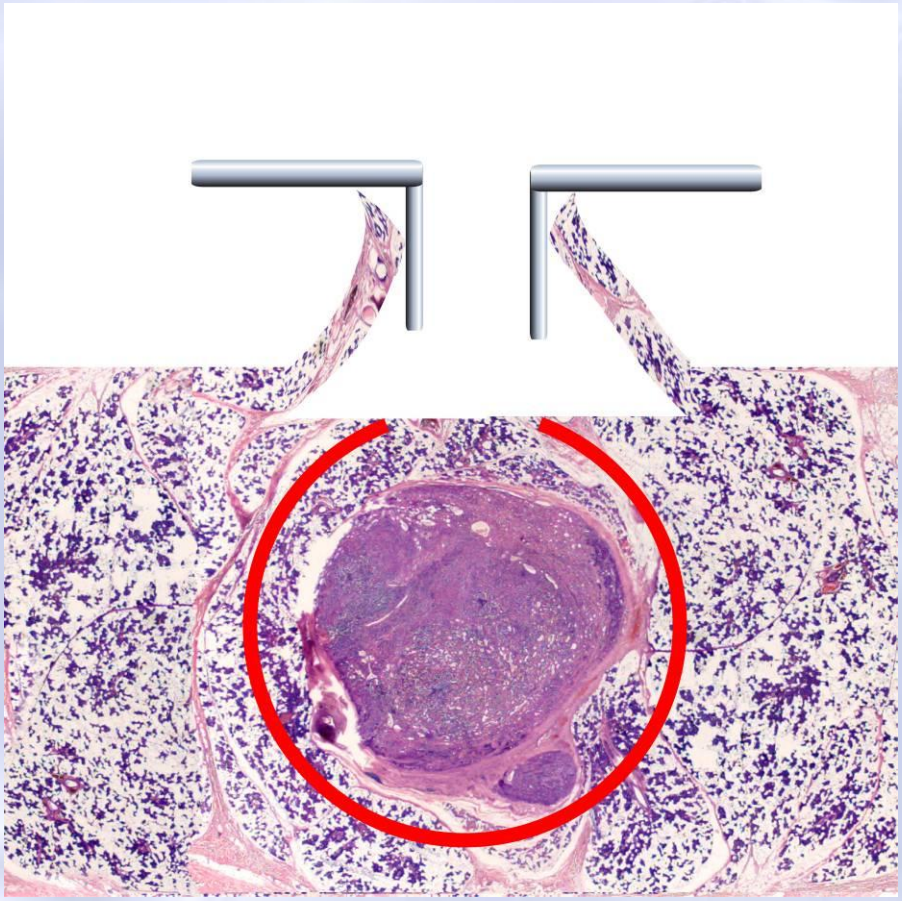
"Secondly the tumor may be enucleated in the layer of loose alveolar tissue which lies between it and the surrounding normal salivary glandular tissue…"



Patey DH (1940): The treatment of mixed tumours of the parotid gland. Brit J Surg 28: 29-38.

Type of parotid surgery: Extracapsular dissection

"Finally the tumor may be removed with a margin of surrounding salivary glandular tissue…"



Patey DH (1940): The treatment of mixed tumours of the parotid gland. Brit J Surg 28: 29-38.

ESGS parotidectomy classification

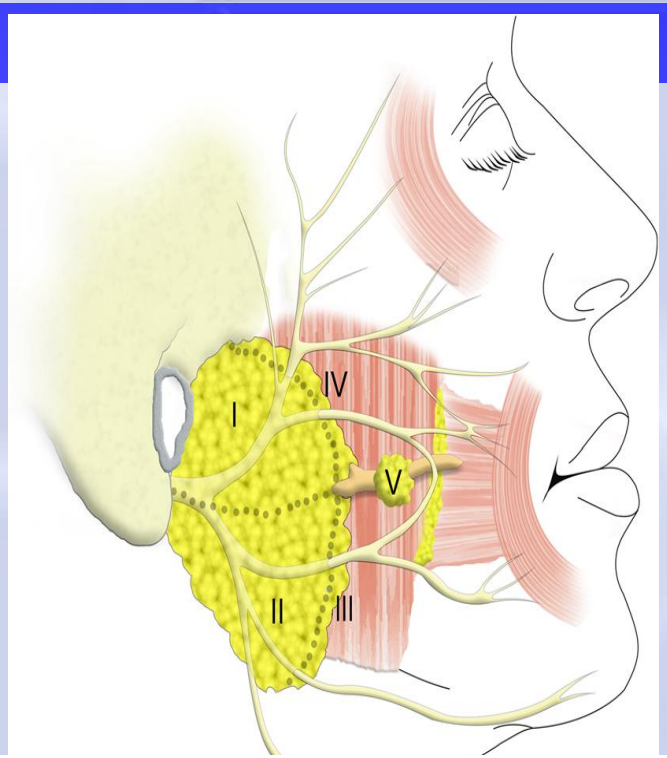


Table 4 ESGS definitions of resections

Term	ESGS definition
Parotidectomy	Two conditions needed
	Dissection of the facial nerve (at least the main trunk and one the two major divisions—temporofacialis, cervicofacialis)
	At least one level is removed
Extracapsular dissection (ECD)	At least one condition
	No facial nerve dissection performed and/or
	Less than one level removed

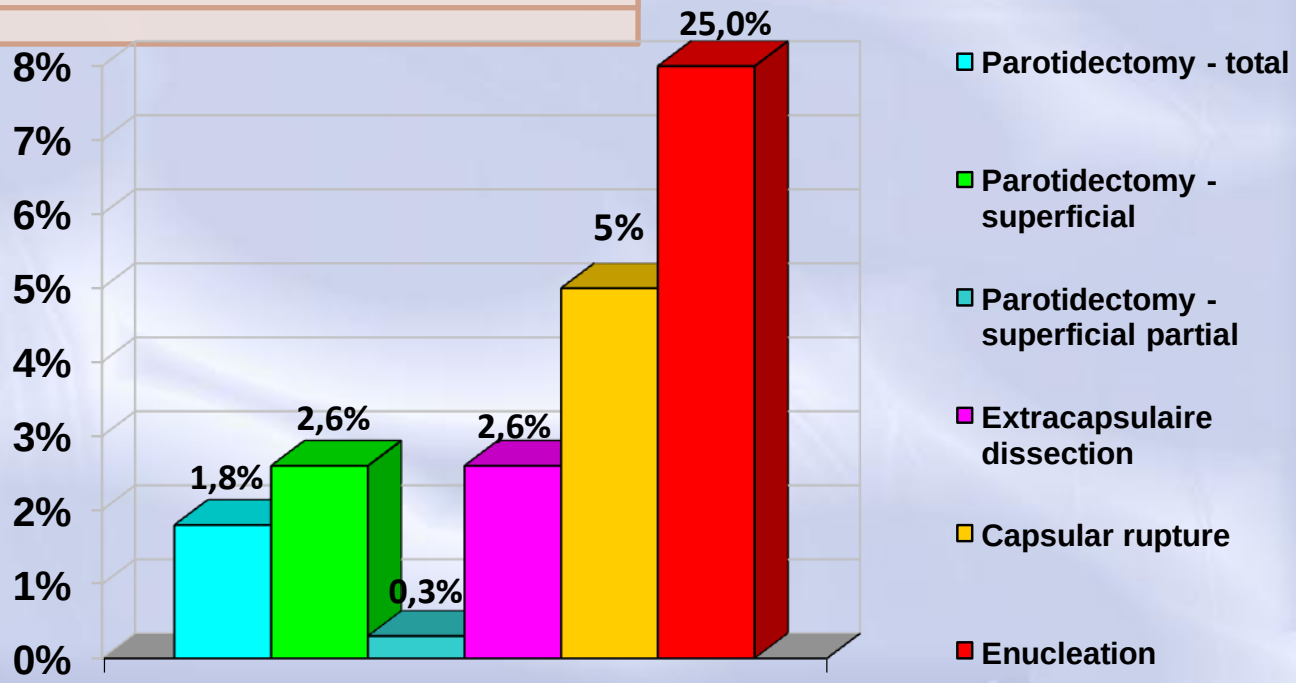
Table 5 Non-parotid structures that could be removed

Symbol	Definition
CN VII	Facial nerve trunk and/or all the main branches (*)
CN VII t-z-b-m-c	Facial nerve branches (*)
ECA	External carotid artery
GAN	Greater auricular nerve
LTB	Lateral temporal resection
MB	Mastoid bone
MM	Masseter muscle
S	Skin
Others to be defined	

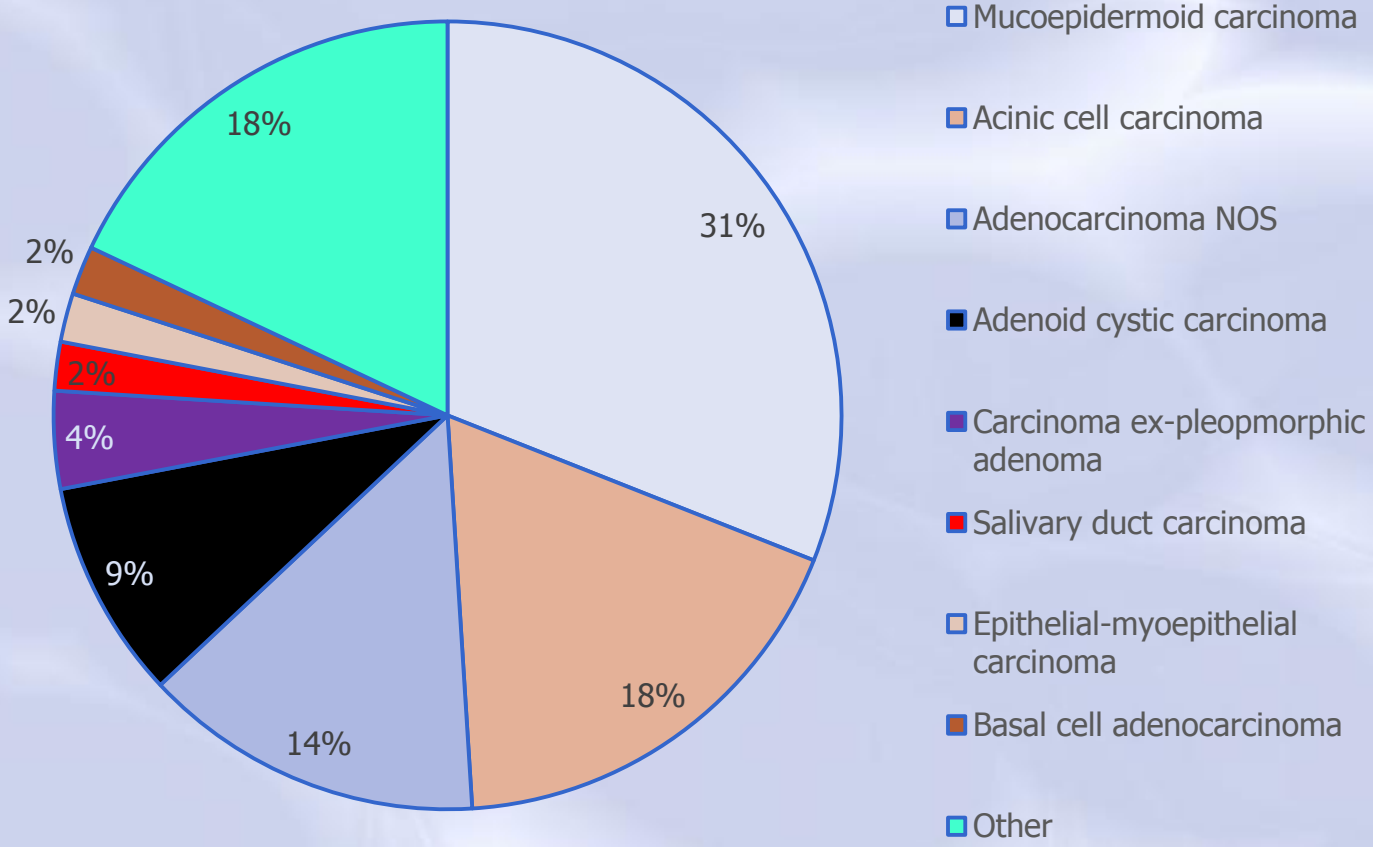
* In the case of facial nerve, when all the nerve has been sacrificed just use CN VII, but when the surgeon has sacrificed just some branches then CN VII z for example means the surgeon has removed only the zygomatic branches

Quer M, Guntinas-Lichius O, Marchal F, Vander Poorten V, Chevalier D, Leon X, Eisele, D, Dulguerov, P. Classification of parotidectomies: a proposal of the European Salivary Gland Society. *Eur Arch Otorhinolaryngol* 273:3307-12, 2016.

Surgery	• Exposed capsule • Tumor puncture • Tumor spillage
Pathology	• Lack of capsule • Pseudopodia • Nodules
Patient	• Age • Size



Parotid carcinoma histologies



National Cancer Data Base (70% US)

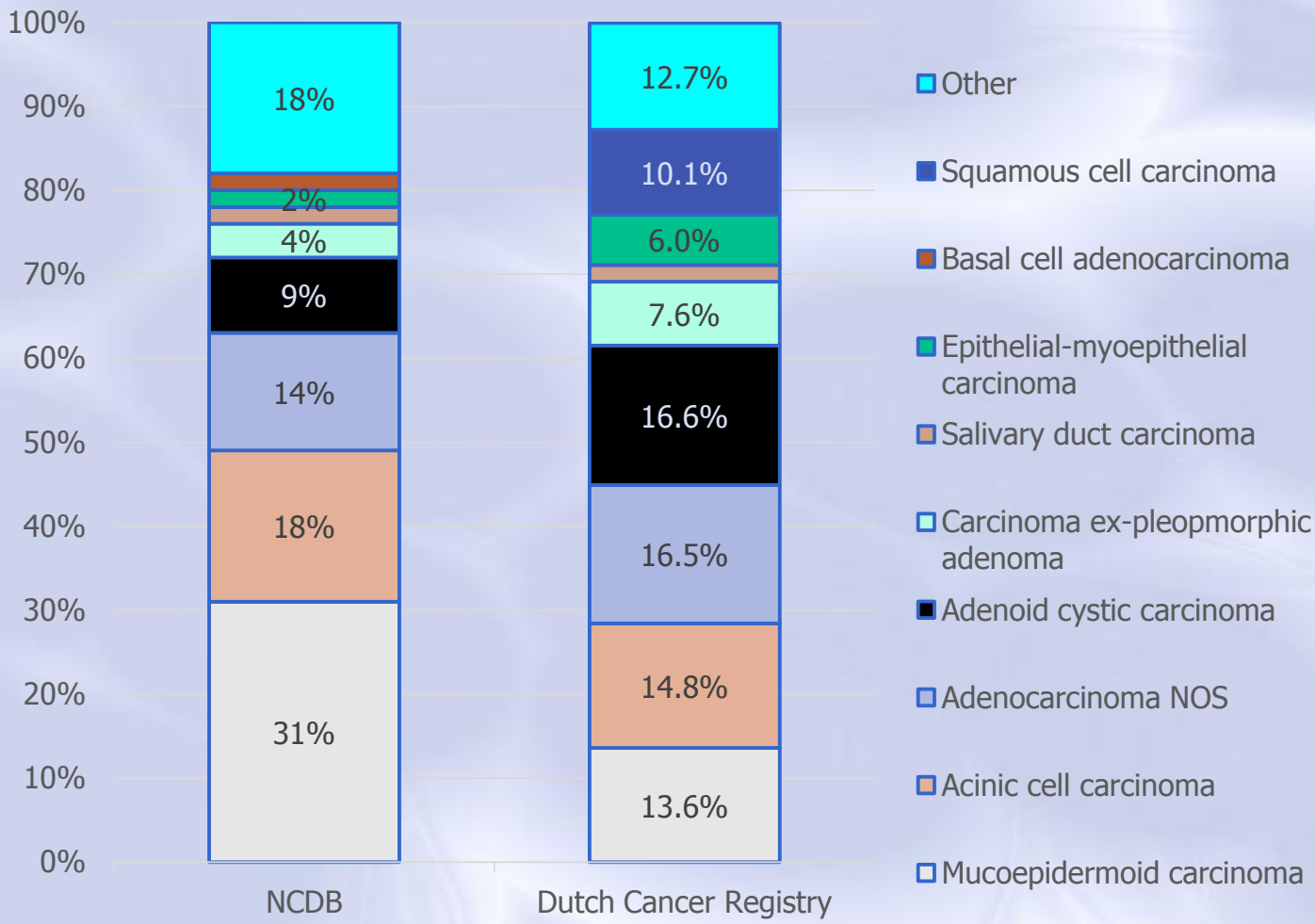
1998-2012 - 22'653 patients

Squamous cell carcinoma excluded (14% of total)

Other (18%) – 90 different histologies !!!

Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients. *Otolaryngol Head Neck Surg* 154:121-30, 2016.

Parotid carcinoma histologies



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de Ridder M, Balm AJ, Smeele LE, Wouters MW, van Dijk BA. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989-2010). *Cancer Epidemiol* 39:14-20,2015.

WHO histological classification of tumors of the salivary glands

1992 #18

2 Carcinomas
2.1 Acinic cell carcinoma
2.2 Mucoepidermoid carcinoma
2.3 Adenoid cystic carcinoma
2.4 Polymorphous low-grade adenocarcinoma (terminal duct adenocarcinoma)
2.5 Epithelial-myoepithelial carcinoma
2.6 Basal cell adenocarcinoma
2.7 Sebaceous carcinoma
2.8 Papillary cystadenocarcinoma
2.9 Mucinous adenocarcinoma
2.10 Oncocytic carcinoma
2.11 Salivary duct carcinoma
2.12 Adenocarcinoma
2.13 Malignant myoepthelioma (myoepithelial carcinoma)
2.14 Carcinoma in pleomorphic adenoma (malignant mixed tumor)
2.15 Squamous cell carcinoma
2.16 Small cell carcinoma
2.17 Undifferentiated carcinoma
2.18 Other carcinomas

2004 #24

Malignant epithelial tumours

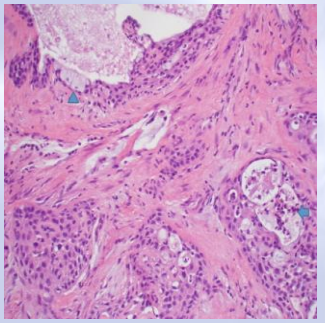
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial-myoepithelial carcinoma
* Clear cell carcinoma, not otherwise specified
Basal cell adenocarcinoma
Sebaceous carcinoma
Sebaceous lymphadenocarcinoma
Cystadenocarcinoma
* Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma, not otherwise specified
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
* Carcinosarcoma
* Metastasizing pleomorphic adenoma
Squamous cell carcinoma
Small cell carcinoma
Large cell carcinoma
* Lymphoepithelial carcinoma
* Sialoblastoma

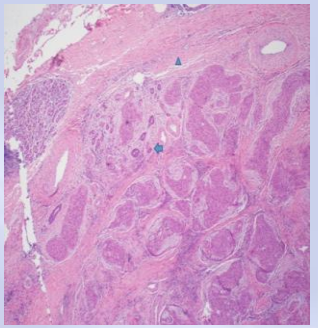
New

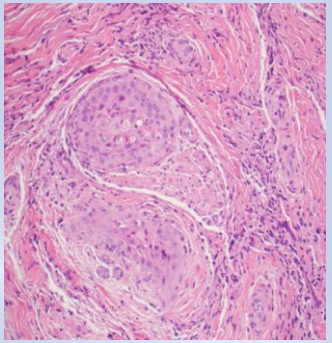
Frequent

Mucoepidermoid carcinoma

% in parotid carcinoma		31
% T1 / T2 / T3 / T4		48 / 28 / 12 / 12
% grade: Low / High		68 / 32
Histologie		various grading systems
%N+ / % occult N		20 / 10
% 5-y overall survival	Stage I	84
	Stage II	72
	Stage III	58
	Stage IV	26
Genetics		t(11;19)(q21;p13)
		MECT1-MAML2 fusion (better prognosis)
		Specific, better prognosis
		30-80%
Pathway involved		*NOTCH*
Molecular markers		MUC1: high grade; M+; low survival
		MUC4: low grade; M-; good survival
		EGFR: high grade; M+; low survival
		HER: high grade; M+; low survival
Comments		**Fusion lacking, high grade MEC = different entity?**







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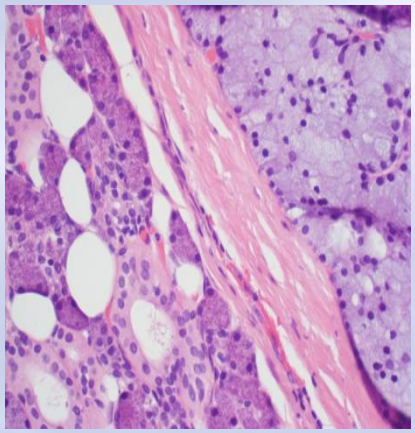
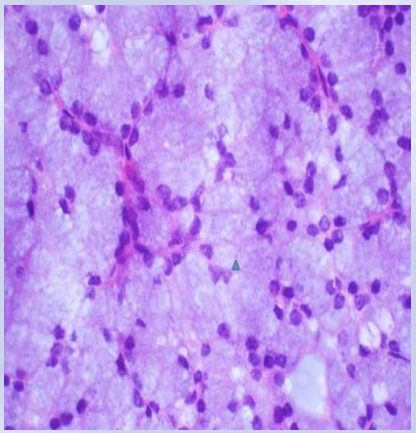
Yin LX, Ha PK. Genetic alterations in salivary gland cancers. *Cancer* 122:1822-31, 2016.

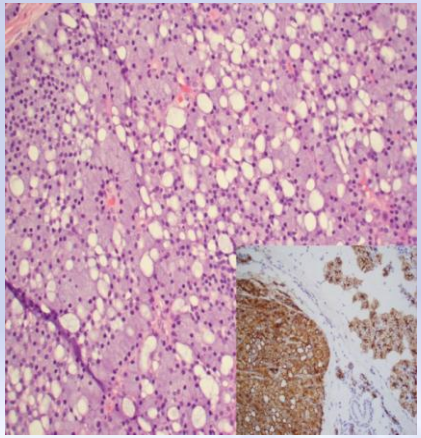
Lewis AG, Tong T, Maghami E. Diagnosis and Management of Malignant Salivary Gland Tumors of the Parotid Gland. *Otolaryngol Clin North Am* 49:343-80, 2016.

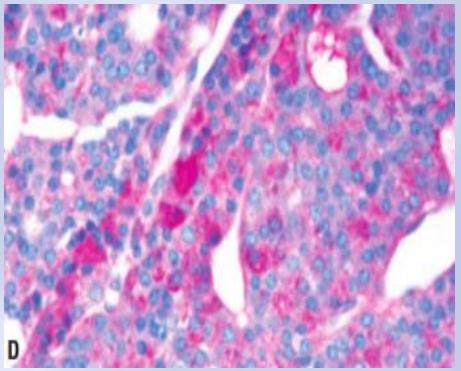
Acinic cell carcinoma

% in parotid carcinoma		18
% T1 / T2 / T3 / T4		45 / 38 / 11 / 7
% grade: Low / High		85 / 15
Histologie		NA
%N+ / % occult N		10 / 5
% 5-y overall survival	Stage I	89
	Stage II	87
	Stage III	70
	Stage IV	40
Genetics		none, really
Pathway involved		*mTOR ??*
Molecular markers		DOG1
Comments		**t(12,15)(p13;q25) ETV6–NTRK3 translocation is recognized as mammary analogue secretory carcinoma (MASC) of salivary glands**









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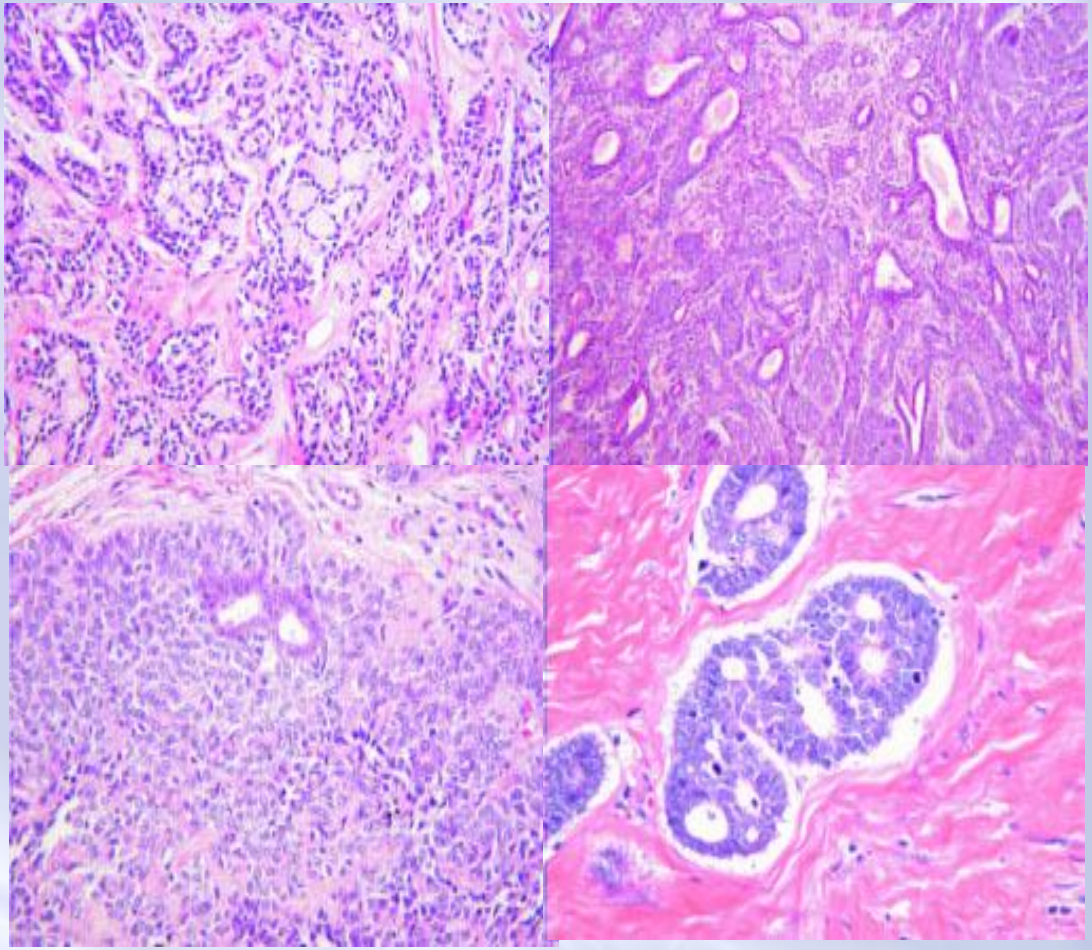
Skalova A, Vanecek T, Sima R, Laco J, Weinreb I, Perez-Ordonez B, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol* 34:599-608, 2010.

Adenocarcinoma NOS

% in parotid carcinoma		14
% T1 / T2 / T3 / T4		27 / 30 / 18 / 25
% grade: Low / High		33 / 67
Histologie		waste basket - should be classified as more specific adenocarcinoma; grading on glandular differentiation
%N+ / % occult N		45 / 20
% 5-y overall survival	Stage I	66
	Stage II	52
	Stage III	41
	Stage IV	18
Genetics		none
		0
		0
		0
Pathway involved		*none*
Molecular markers		none
		0
		0
		0
Comments		none



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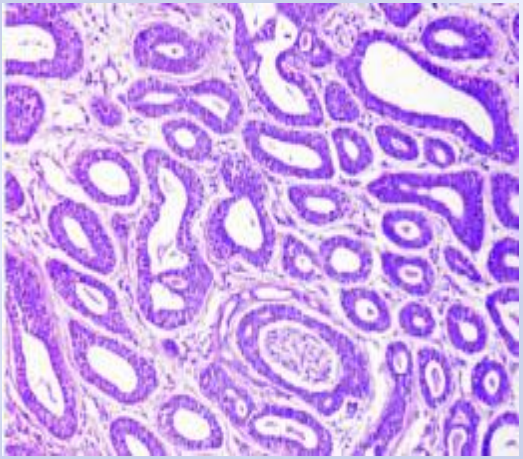
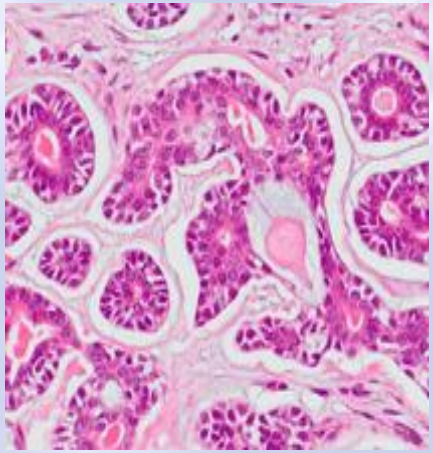
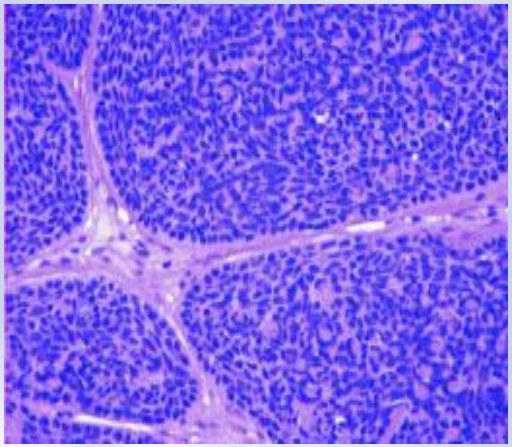
Adenoid cystic carcinoma

% in parotid carcinoma		9
% T1 / T2 / T3 / T4		30 / 28 / 17 / 25
% grade: Low / High		65 / 35
Histologie		Grading based on solid component
%N+ / % occult N		14/7
% 5-y overall survival	Stage I	86
	Stage II	77
	Stage III	84
	Stage IV	47
Genetics		t(6;9)(q22-23;p23-24)
		MYB-NFIB fusion
		specific
		33-50%
Pathway involved		*none*
Molecular markers		MYB-NFIB fusion not linked to prognosis
		EGFR: high grade; no survival difference
		MIB-1 prognostic for survival
		NCAM related to perineural spread
Comments		Delayed metastasis responsible for deaths; perineural spread responsible for local recurrences







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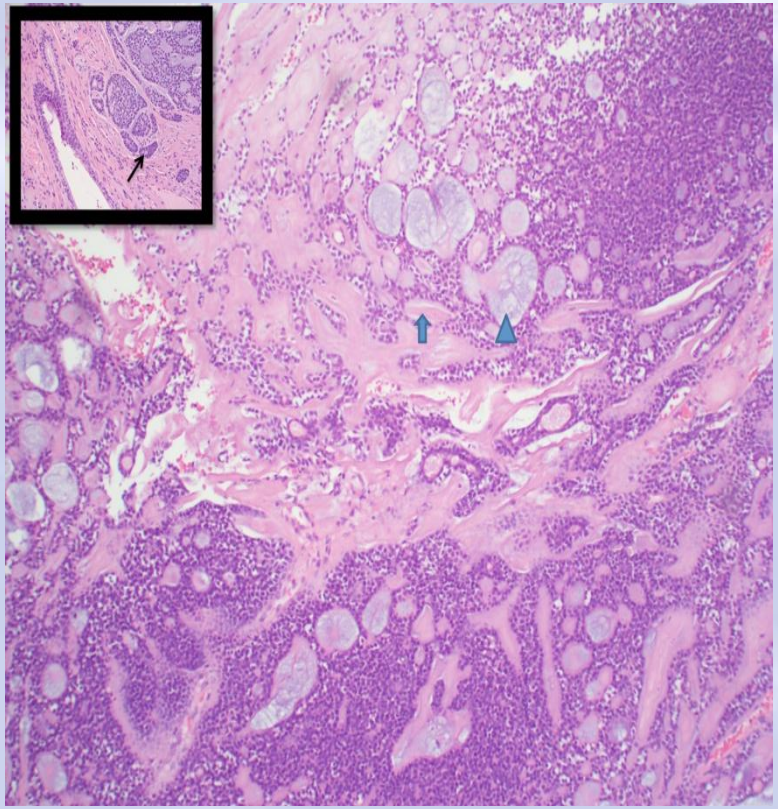
Carcinoma ex-pleomorphic adenoma

% in parotid carcinoma		4
% T1 / T2 / T3 / T4		25 / 33 / 24 / 18
% grade: Low / High		31 / 69
Histologie		Non-, minimally-, and full invasive clasification
%N+ / % occult N		24 / 12
% 5-y overall survival	Stage I	91
	Stage II	69
	Stage III	69
	Stage IV	34
Genetics		none
		0
		0
		0
Pathway involved		*PLAG1, HMGA2*
Molecular markers		none
		0
		0
		0
Comments		none



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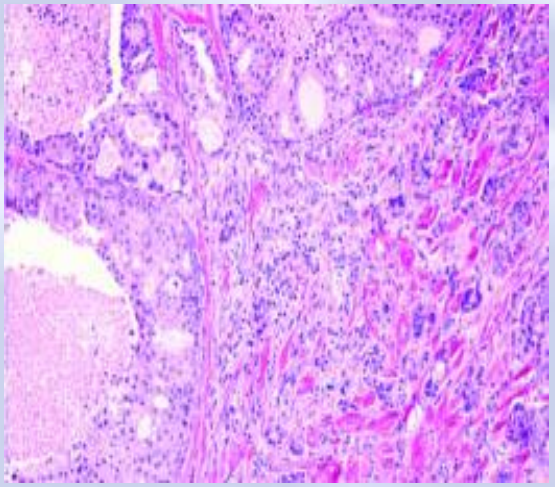
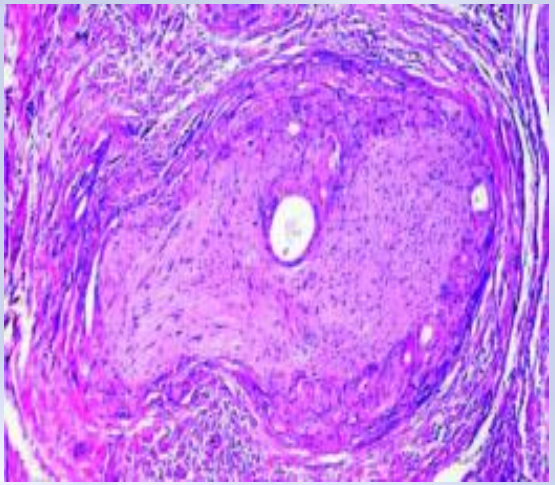
Salivary duct carcinoma

% in parotid carcinoma		2
% T1 / T2 / T3 / T4		30 / 30 / 19 / 21
% grade: Low / High		21 / 79
Histologie		0
%N+ / % occult N		54 / 24
% 5-y overall survival	Stage I	82
	Stage II	61
	Stage III	55
	Stage IV	28
Genetics		none
		0
		0
		0
Pathway involved		*HER2, BRAF*
Molecular markers		HER2 expression related to poor survival
		p53 overexpression related to poor survival
		Androgene receptors
		0
Comments		Frequent perineural spread





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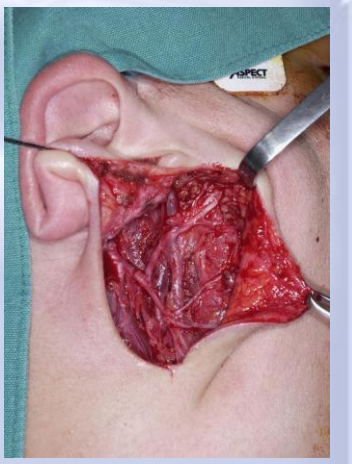
Lewis AG, Tong T, Maghami E. Diagnosis and Management of Malignant Salivary Gland Tumors of the Parotid Gland. *Otolaryngol Clin North Am* 49:343-80, 2016.

INFO NEEDED

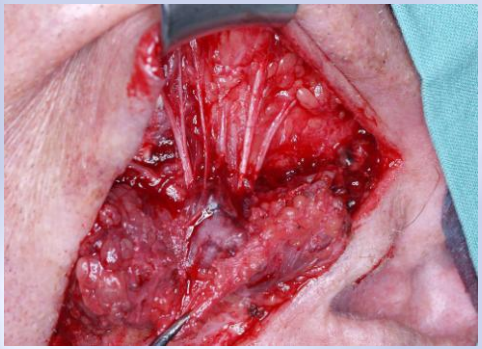


	% used	Locoregional control	Overall survival
Parotidectomy I-IV (VII) *Radical parotidectomy*	?	?	?
Parotidectomy I-IV *Total parotidectomy*	?	?	?
Parotidectomy I-II *Superficial parotidectomy*	?	?	?
Extracapsular dissection	?	?	?

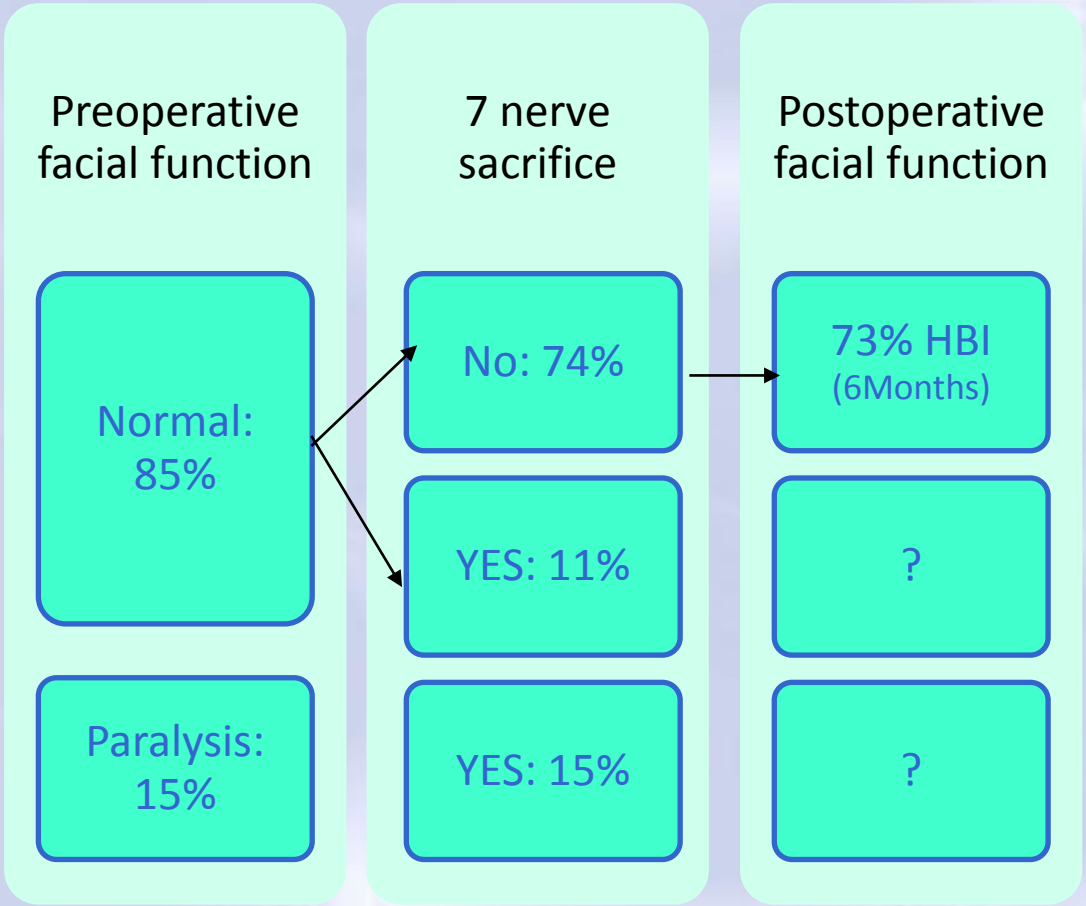
T1/T2 low grade	Superficial parotidectomy
Others	Total parotidectomy

INFO NEEDED

Preoperative facial function	7 nerve sacrifice	Postoperative facial function
Normal	None	%
Partial paralysis	Partial (branches)	%
Total paralysis	Total (trunc)	%



Facial nerve: to sacrifice or not



Facial nerve branches should not be sacrificed unless the tumor is adherent

Guntinas-Lichius O, Klussmann JP, Schroeder U, Quante G, Jungehuelsing M, Stennert E. Primary parotid malignoma surgery in patients with normal preoperative facial nerve function: outcome and long-term postoperative facial nerve function. *Laryngoscope* 114:949-56, 2004.

Table 2. Overall Incidence of Nodal and Occult Disease by Histology (in Percentages).

Histology	N+	Occult Nodes
Mucoepidermoid carcinoma	20.2	9.3
Acinar cell carcinoma	10	4.4
Adenocarcinoma not otherwise specified	45.2	19.9
Adenoid cystic carcinoma	14.2	7
Carcinoma ex pleomorphic adenoma	23.9	11.8
Salivary ductal carcinoma	53.5	23.6
Epithelial-myoepithelial carcinoma	4.8	1.5
Basal cell adenocarcinoma	9.4	6.3
Total	24.4	10.2

National Cancer Data Base (70% US)

1998-2012

22'653 patients

Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients. *Otolaryngol Head Neck Surg* 154:121-30, 2016.

Neck metastasis decreases 5y survival by 40%

Table 4. Overall Survival by Nodal Status and Grade.

Histology: Overall Survival	N0, %	N+, %	$P_{log\text{-}rank}$	Low Grade, %	High Grade, %	$P_{log\text{-}rank}$
Mucoepidermoid carcinoma						
2 y	91	66	<.001	96	67	<.001
5 y	82	43		88	47	
Acinar cell carcinoma						
2 y	97	78	<.001	98	70	<.001
5 y	90	54		91	40	
Adenocarcinoma not otherwise specified						
2 y	83	57	<.001	87	63	<.001
5 y	65	29		71	38	
Adenoid cystic carcinoma						
2 y	91	76	<.001	93	71	<.001
5 y	79	53		84	47	
Carcinoma ex-pleomorphic adenoma						
2 y	91	61	<.001	92	73	<.001
5 y	78	38		80	53	
Salivary ductal carcinoma						
2 y	88	69	<.001	89	71	<.001
5 y	73	35		74	42	
Epithelial-myoepithelial carcinoma						
2 y	93	81	.005	93	81	.07
5 y	80	56		77	56	
Basal cell adenocarcinoma						
2 y	94	95	.686	94	100	.377
5 y	79	82		88	69	
All histologies						
2 y	91	64	<.001	94	66	<.001
5 y	79	40		85	44	

National Cancer Data Base (70% US)

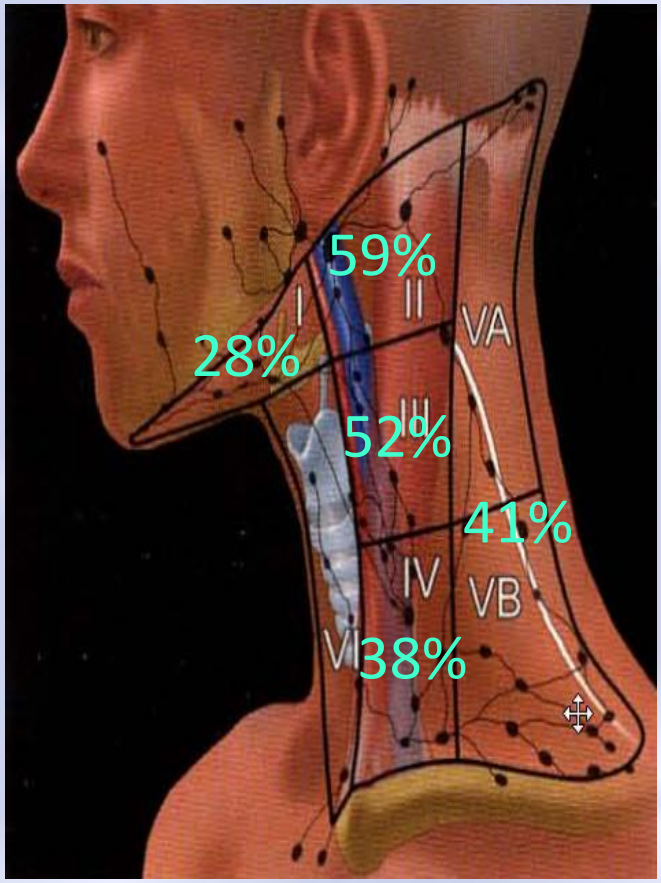
1998-2012

22'653 patients

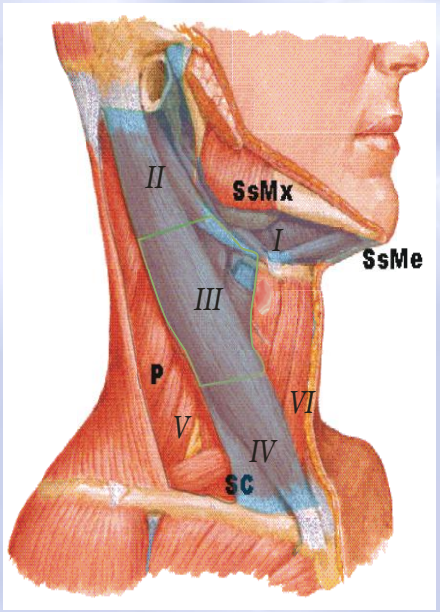
Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients. *Otolaryngol Head Neck Surg* 154:121-30, 2016.

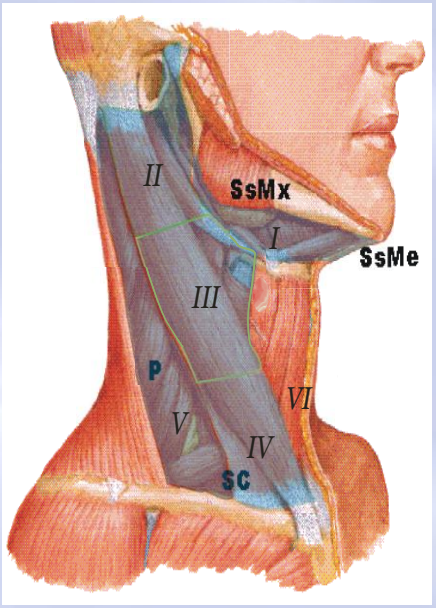
INFO NEEDED

N+ neck → neck dissection



N=66





Chisholm EJ, Elmiyeh B, Dwivedi RC, Fisher C, Thway K, Kerawala C, et al. Anatomic distribution of cervical lymph node spread in parotid carcinoma. *Head Neck* 33:513-5,2011. + Armstrong, *Cancer* 1992 + Klussmann, *Eur J Surg Oncol* 2008

Do a total parotidectomy prior to ND

Table 1

Clinicopathological data of 70 patients diagnosed with parotid gland cancer

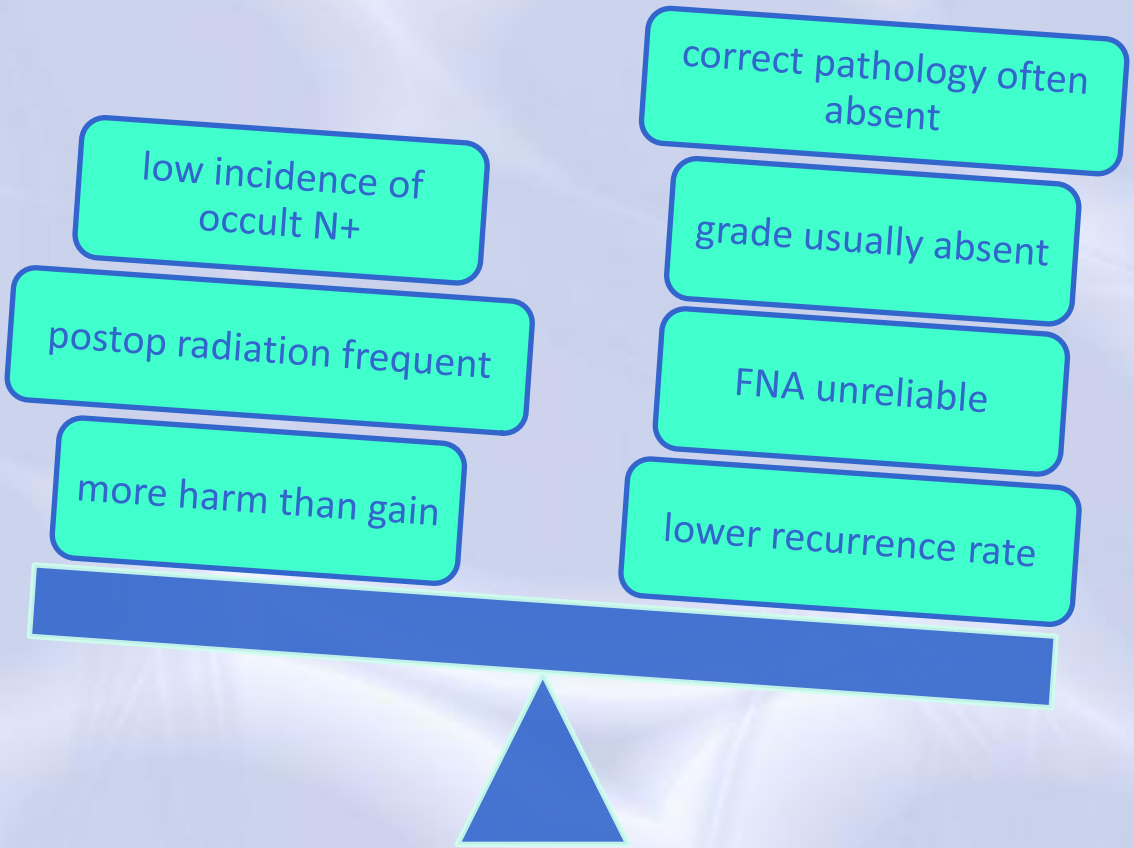
	Total		pN−		pN+		*p*
	n	**%**	***n***	**%**	***n***	**%**	
n	70	100	55	100	15	100	
Patients being pN + in							
Level I					0	0.0	
Level II					3	20.0	
Level III					2	13.3	
Level IV					0	0.0	
Level V					0	0.0	
Extraparotideal					5	33.3	
Intraparotideal					11	73.3	

Stenner M, Molls C, Luers JC, Beutner D, Klussmann JP, Huettenbrink KB. Occurrence of lymph node metastasis in early-stage parotid gland cancer. *Eur Arch Otorhinolaryngol* 269:643-8,2012.

N0 neck: to treat or not to treat

No neck dissection

ND in all cN0



Predictors of neck metastasis: HISTOLOGY

Table 2. Overall Incidence of Nodal and Occult Disease by Histology (in Percentages).

Histology	N+	Occult Nodes
Mucoepidermoid carcinoma	20.2	9.3
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Predictors of neck metastasis: HIGH GRADE / T stage

Table 6. Predictors of Nodal Metastasis.

Histology: Univariate	OR (95% CI)	*P*	Multivariate	OR (95% CI)	*P*
MEC					
Age > 62 y	1.789 (1.584-2.022)	<.001	Age > 62 y	0.697 (0.555-0.874)	.002
African American	0.7 (0.578-0.847)	<.001	T2	2.445 (1.846-3.238)	<.001
Other	0.706 (0.516-0.965)	.029	T3	4.477 (3.247-6.173)	<.001
Male	2.324 (2.05-2.635)	<.001	T4	5.701 (4.104-7.919)	<.001
T2	3.662 (2.887-4.644)	<.001	High grade	6.388 (5.01-8.147)	<.001
T3	7.491 (5.722-9.807)	<.001			
T4	13.623 (10.455-17.75)	<.001			
High grade	9.526 (8.216-11.044)	<.001			
AC CA					
Age > 62 y	1.704 (1.368-2.123)	<.001	T4	4.53 (2.098-9.781)	<.001
Other	0.37 (0.15-0.911)	.031	High grade	10.621 (6.367-17.717)	<.001
Male	1.42 (1.146-1.758)	.001			
T2	1.636 (1.141-2.346)	.007			
T3	3.77 (2.452-5.797)	<.001			
T4	8.003 (5.152-12.434)	<.001			
High grade	14.103 (9.957-19.975)	<.001			
ANOS					
Age > 62 y	1.165 (1-1.358)	.05	Male	1.329 (1.009-1.75)	.043
Other	0.59 (0.363-0.959)	.033	T2	1.836 (1.274-2.645)	.001
Male	1.854 (1.588-2.165)	<.001	T3	2.991 (1.993-4.49)	<.001
T2	2.154 (1.609-2.883)	<.001	T4	3.35 (2.284-4.914)	<.001
T3	4.04 (2.924-5.582)	<.001	High grade	5.145 (3.765-7.031)	<.001
T4	5.29 (3.904-7.167)	<.001			
High grade	6.092 (4.947-7.501)	<.001			
Ad Cy CA					
Male	1.319 (1.016-1.712)	.037	T4	3.102 (1.342-7.169)	.008
T2	2.419 (1.256-4.656)	.008	High grade	2.395 (1.292-4.439)	.006
T3	4.688 (2.42-9.082)	<.001			
T4	6.798 (3.706-12.47)	<.001			
High grade	2.93 (1.896-4.527)	<.001			
CA EPA					
T3	3.015 (1.472-6.176)	.003	T4	4.225 (1.531-11.655)	.005
T4	5.863 (2.832-12.141)	<.001	High grade	7.663 (2.84-20.672)	<.001
High grade	9.752 (4.772-19.93)	<.001			
SDC					
T3	2.28 (1.012-5.139)	.047	T4	9.857 (3.109-31.246)	<.001
T4	8.035 (3.295-19.595)	<.001	High grade	4.993 (2.102-11.859)	<.001
High grade	6.54 (3.457-12.371)	<.001			
EMC					
Age > 62 y	0.296 (0.125-0.699)	.005			
Male	2.348 (1.018-5.417)	.045			
High grade	4.476 (1.334-15.02)	.015			
BCA					
T4	10.833 (2.288-51.299)	.003			
High grade	4.156 (1.361-12.693)	.012			

Abbreviations: AC CA, acinar cell carcinoma; Ad Cy CA, adenoid cystic carcinoma; ANOS, adenocarcinoma not otherwise specified; BCA, basal cell adenocarcinoma; CA EPA, carcinoma ex pleomorphic adenoma; CI, confidence interval; EMC, epithelial-myoepithelial carcinoma; MEC, mucoepidermoid carcinoma; OR, odds ratio; SDC, salivary ductal carcinoma.

Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients.
Otolaryngol Head Neck Surg 154:121-30, 2016.

Predictors of neck metastasis

Histology risk groups:

- LOW: Mucoepidermoid low grade; Acinic cell; Ca ex-PA; Epithelial-myoepithelial CA; Basal cell adenoCa
- INTERMEDIATE: Mucoepidermoid intermediate grade; Adenoid cystic
- HIGH: Mucoepidermoid high grade; Salivary duct; AdenoCa NOS; SCCa

Variable (Index)	Expβ (95% CI)	*P*	β(SE)
Major nerve invasion (1)	3.841 (1.679-8.787)	.001	1.346 (0.422)
Histologic type		<.01	
Low risk (1)			
Middle risk (2)	4.276 (1.002-18.224)	.050	1.453 (0.740)
High risk (3)	34.599 (9.115-131.335)	<.01	3.544 (0.681)
Lymphatic/vascular invasion (1)	10.282 (2.514-42.051)	.001	2.330 (0.719)
Extracapsular invasion (1)	2.744 (1.068-7.047)	.036	1.009 (0.481)
Constant	0.014	<.01	−4.253 (0.690)

Exp(β) = odds ratio; CI = confidence interval; SE = standard error.

Low
- Low histology risk + 0 or 1 pathology features
- Middle histology risk + 0 pathology features

Middle
- Low histology risk + 2 pathology features
- Middle histology risk + 1 pathology features

High
- Low histology risk + 3 pathology features
- Middle histology risk + 2 pathology features
- High histology risk + 1 pathology features

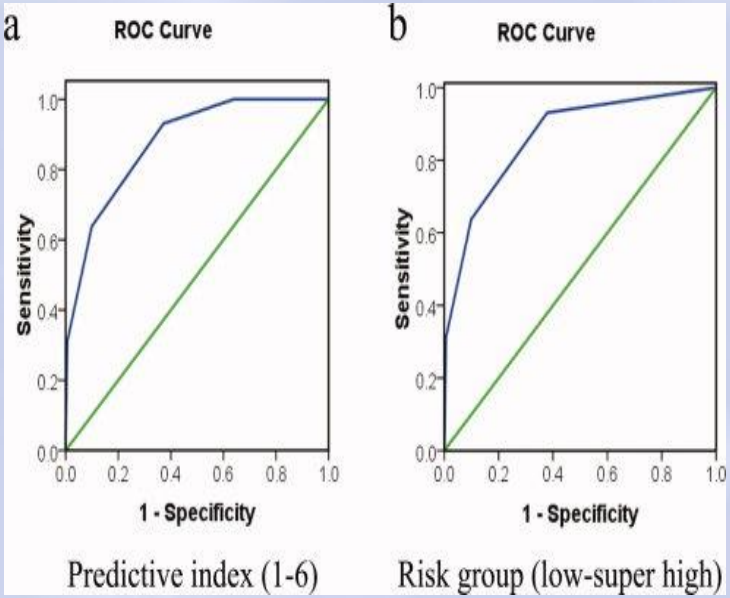
Super high
- Middle histology risk + 3 pathology features
- High histology risk + > 2 pathology features

Chinese retrospective study - 1998-2011 - 219 patients – ND in N0 unclear

Wang YL, Li DS, Gan HL, Lu ZW, Li H, Zhu GP, et al. Predictive index for lymph node management of major salivary gland cancer. *Laryngoscope* 122:1497-506,2012.

Predictors of neck metastasis

Risk Group	Total Index	pN+/Total Cases (%)	OR (95% CI)	*P*	LN Metastasis Level (%)		
					1 Level	Level II	>Level II
Low (ref)	1, 2	4/105 (3.8)			50	50	
Middle	3	17/61 (27.9)	9.76 (3.10-30.67)	<0.01	41.2	23.5	35.3
High	4	19/34 (55.9)	31.98 (9.57-106.93)	<0.01	26.3	21.1	52.6
Super high	5, 6	18/19 (94.7)	454.50 (48.00-4303.34)	<0.01	22.2	27.8	50.0



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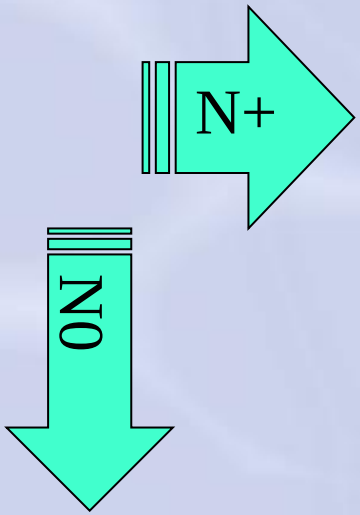
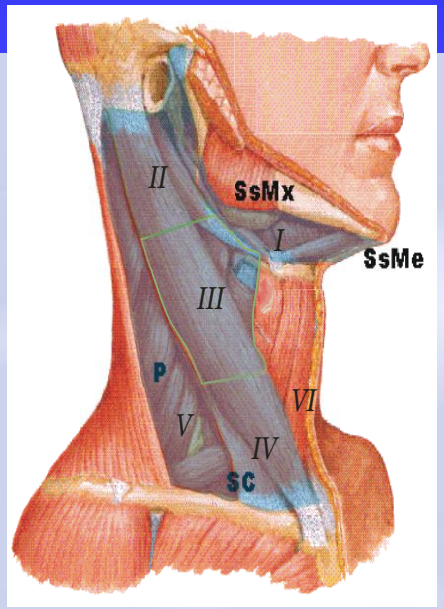
Neck metastasis - summary





+ T stage

Table 7. Recommendations for Elective Treatment of the Neck (cN0).

Elective Treatment Recommended	Elective Treatment Not Recommended
High-grade carcinoma ex pleomorphic adenoma	Low-grade carcinoma ex pleomorphic adenoma
High-grade mucoepidermoid carcinoma	Low-grade mucoepidermoid carcinoma
High-grade acinar cell carcinoma	Low-grade acinar cell carcinoma
High-grade adenocarcinoma not otherwise specified	Low-grade adenocarcinoma not otherwise specified
High-grade adenoid cystic carcinoma	Low-grade adenoid cystic carcinoma
High-grade salivary ductal carcinoma	Low-grade salivary ductal carcinoma
	All epithelial myoepithelial carcinomas
	All basal cell adenocarcinomas

Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of Nodal Metastasis in Parotid Malignancies: A National Cancer Data Base Study of 22,653 Patients. *Otolaryngol Head Neck Surg* 154:121-30, 2016.

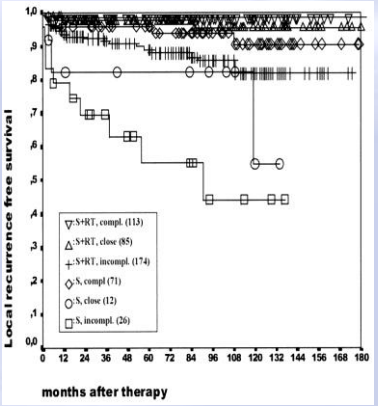
Primary radiotherapy:

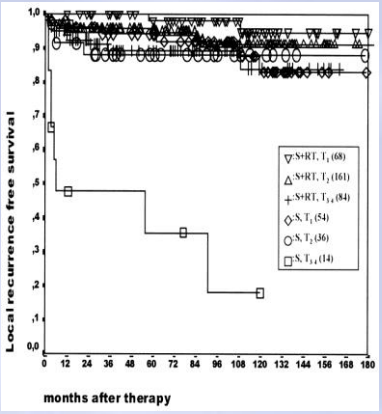
- palliation (distant metastasis, inoperable, high comorbidities)

Adjuvant radiotherapy:

- close (<5mm) or positive margins
- T3-T4
- perineural invasion
- bone invasion
- recurrence
- *high grade tumors*

Consider proton therapy





Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys* 61:103-11, 2005.

Overall prognostic index

Table 35.6 Prognostic indices PS1 and PS2[28]

PS1 = 0.024 A + 0.62 P + 0.44 T + 0.45 N + 0.63 S + 0.91 F	
Variable	*Number to enter in the formula*
A = age at diagnosis	Number in years
P = pain on presentation	1 = no pain, 2 = pain or numbness
T = clinical T classification*	T1 (< 2 cm) = 0, T2 (2–4 cm) = 1, T3 (4–6 cm) = 2, T4 (> 6 cm) = 3
N = clinical N classification	N0 = 0, N1 = 1, N2a = 2, N2b = 3, N2c = 4, N3 = 5)
S = skin invasion	1 = no invasion, 2 = invasion
F = facial nerve dysfunction	1 = intact function, 2 = paresis–paralysis

PS2 = 0.018 A + 0.39 T + 0.34 N + 0.70 S + 0.56 F + 0.78 PG + 0.65 PM	
Variable	*Number to enter in the formula*
A = age at diagnosis	Number in years
T = clinical T classification	T1 (< 2 cm) = 0, T2 (2–4 cm) = 1, T3 (4–6 cm) = 2, T4 (> 6 cm) = 3
N = clinical N classification	N0 = 0, N1 = 1, N2a = 2, N2b = 3, N2c = 4, N3 = 5
S = skin invasion	1 = no invasion, 2 = invasion
F = facial nerve dysfunction	1 = intact function, 2 = paresis–paralysis
PG = perineural growth in the resection specimen	1 = no, 2 = yes
PM = positive surgical margins	1 = no, 2 = yes

Vander Poorten VL, Balm AJ,, et al. The development of a prognostic score for patients with parotid carcinoma. *Cancer* ;85:2057-67, 1999.
Vander Poorten VLM, Hart A, Vauterin Tet al. Prognostic index for patients with parotid carcinoma. *Cancer* 115:540-50, 2009.

Overall prognostic index

PS1 Level		PS1 Source Population*		PS1 National Validation†		PS1 International Validation‡	
		% (SE)	No.	% (SE)	No.	% (SE)	No.
1	<3.75	92 (5)	29	92 (7)	40	94 (5)	44
2	3.85-4.74	83 (7)	30	70 (9)	56	86 (5)	74
3	4.75-5.80	48 (11)	31	59 (11)	60	58 (7)	61
4	>5.80	23 (9)	28	42 (32)	27	42 (7)	56

PS1 indicates the pretreatment prognostic index; SE, standard error.

* Original sample from the Netherlands' Cancer Institute from which PS1 and PS2 were derived.

† National validation sample from the Dutch Cooperative Group on Head and Neck Cancer.

‡ International validation sample.

Vander Poorten VL, Balm AJ,, et al. The development of a prognostic score for patients with parotid carcinoma. *Cancer* ;85:2057-67, 1999.
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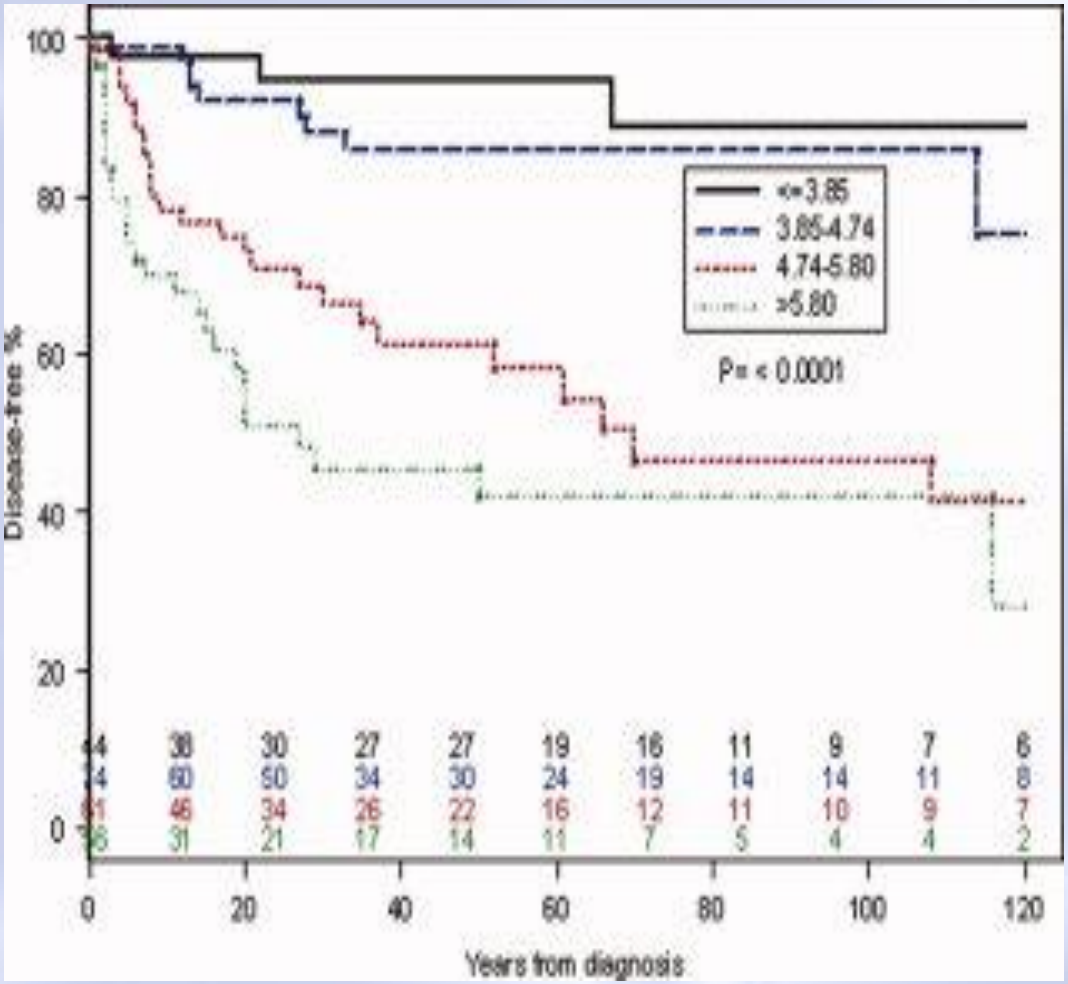
Overall prognostic index



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Vander Poorten VLM, Hart A, Vauterin Tet al. Prognostic index for patients with parotid carcinoma. *Cancer* 115:540-50, 2009.

Overall prognostic index

PS2 Level		PS2 Source Population*		PS2 National Validation†		PS2 International Validation‡	
		% (SE)	No.	% (SE)	No.	% (SE)	No.
1	<3.99	95 (5)	26	90 (10)	21	93 (4)	58
2	3.99-4.80	83 (8)	25	87 (7)	56	84 (5)	64
3	4.81-5.67	56 (12)	26	70 (10)	50	61 (8)	44
4	>5.67	42 (5)	26	40 (16)	44	40 (7)	64

PS2 indicates the post-treatment prognostic index; SE, standard error.

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‡ International validation sample.

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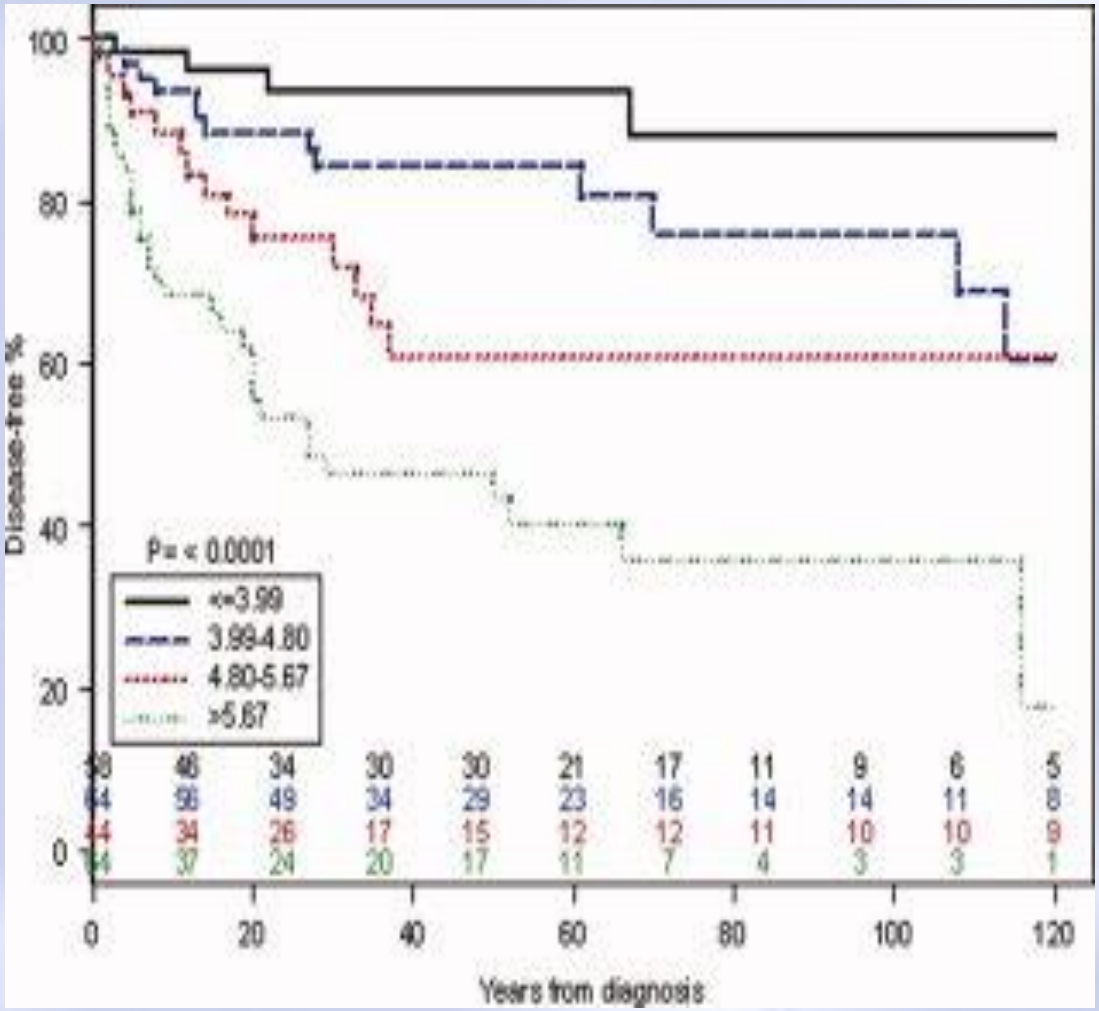
Overall prognostic index



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Parotid cancer: conclusions

An asymptomatic isolated parotid mass may be cancer

Workup: FNA; consider switching to core biopsy

If malignant: MRI

Histology, grade, and T stage are the key !!!

Calculate PS1

Treatment: superficial or total parotidectomy

If facial function is intact keep the nerve intact

N+: anterolateral or modified radical ND

N0 + high grade + T3-4: elective neck dissection

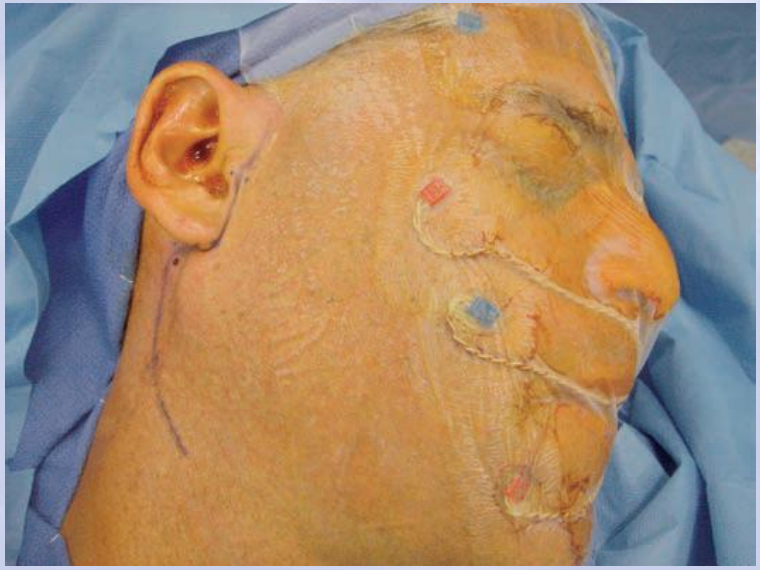
Calculate PS2

Radiation improves local control

Mandates of parotid surgery

1. Prevention of recurrence, which requires a complete tumor removal, ideally with a cuff of normal parotid tissue, and without tumor seeding by spillage
2. Facial nerve protection and preservation unless the nerve is directly involved by a malignant neoplasm
3. Prevention of occurrence of Frey syndrome
4. Prevention of other complications, such as salivary gland fistula, hematoma, wound infection, skin anesthesia
5. Optimal cosmetic results (incision; depression)

Parotidectomy - Positioning



General anesthesia:

- oral intubation
- tube to the controlateral side
- curare derivatives ↘ 20’

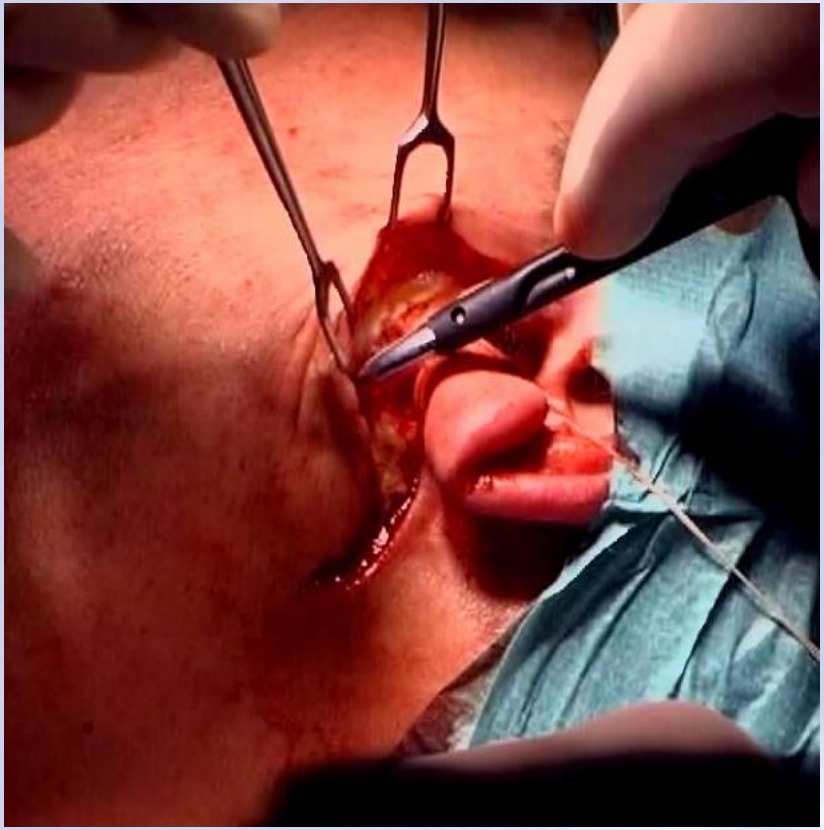
Patient positioning:

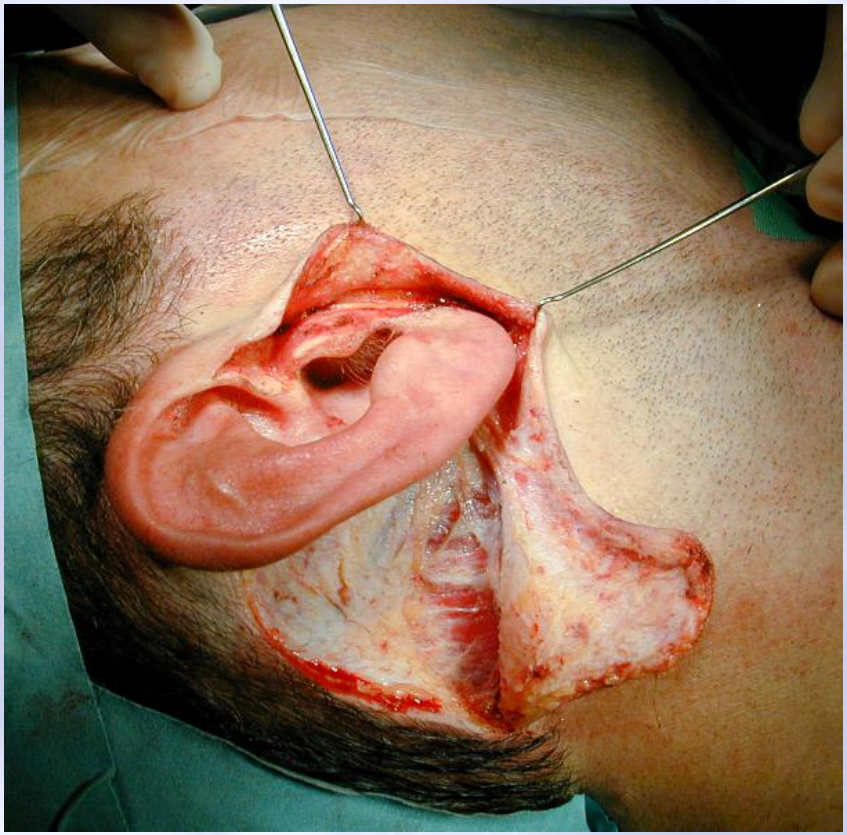
- torso & head at 20° (decrease of venous congestion)
- head gently extended
- head gently rotated to the other side

Infiltration : adrenalin 1:20 000 without lidocaine

Draping: entire facial half visible

Parotidectomy - Incision



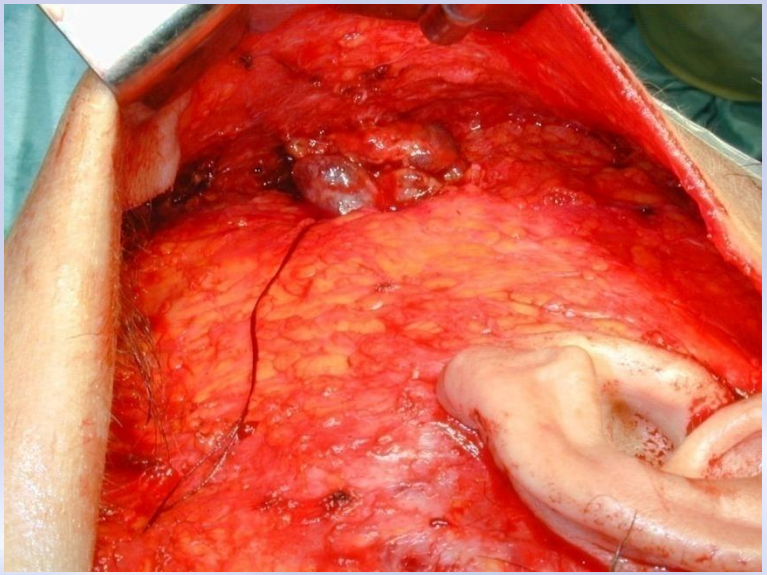


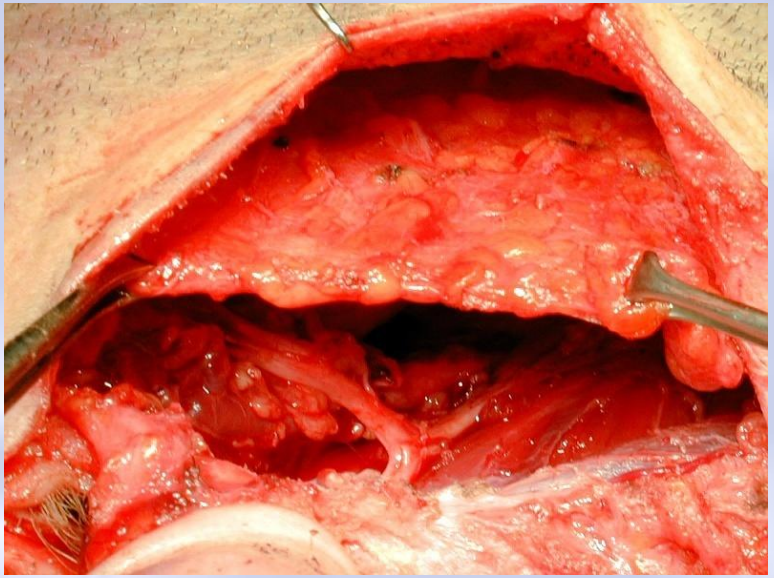
Parotidectomy - SMAS

Incision: lazy S or facelift

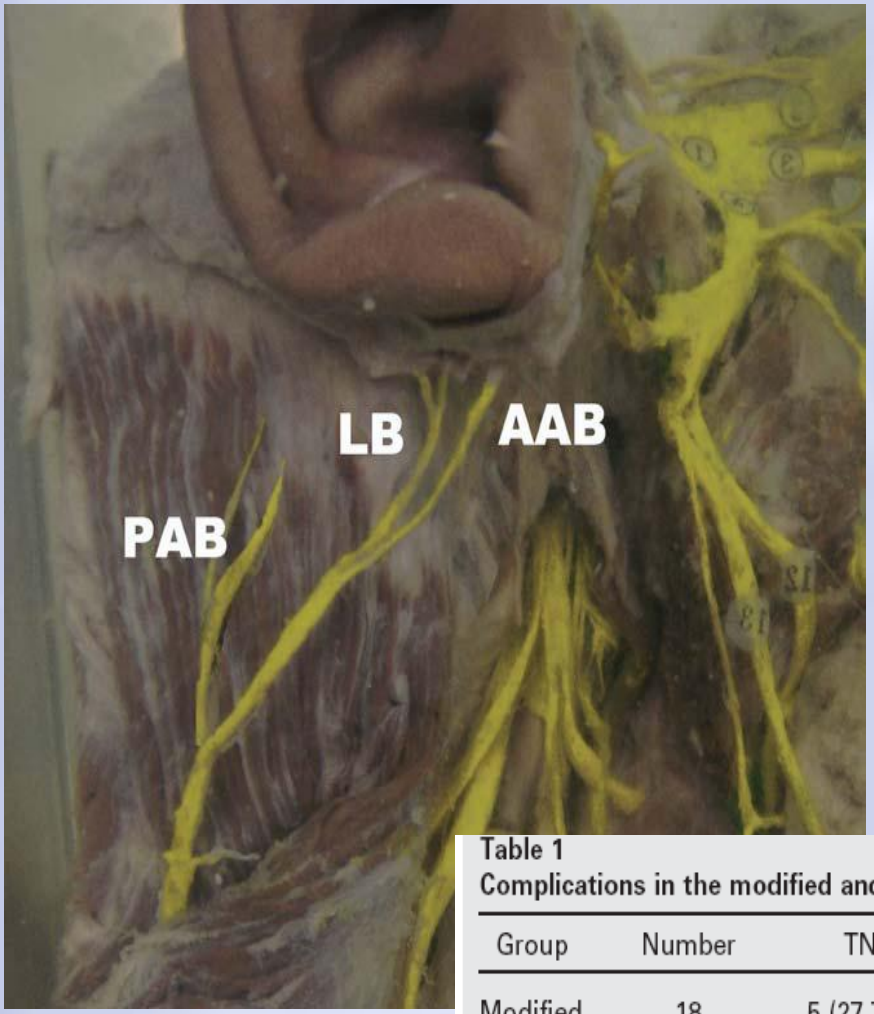
- identical anterior or preauricular limb
- facelift:
  - good for superficial lobe and inferiorly situated tumors
  - difficult for anterior and superior (preauricular) tumors

Anterior subcutaneous flap dissection





Parotidectomy - Greater auricular nerve



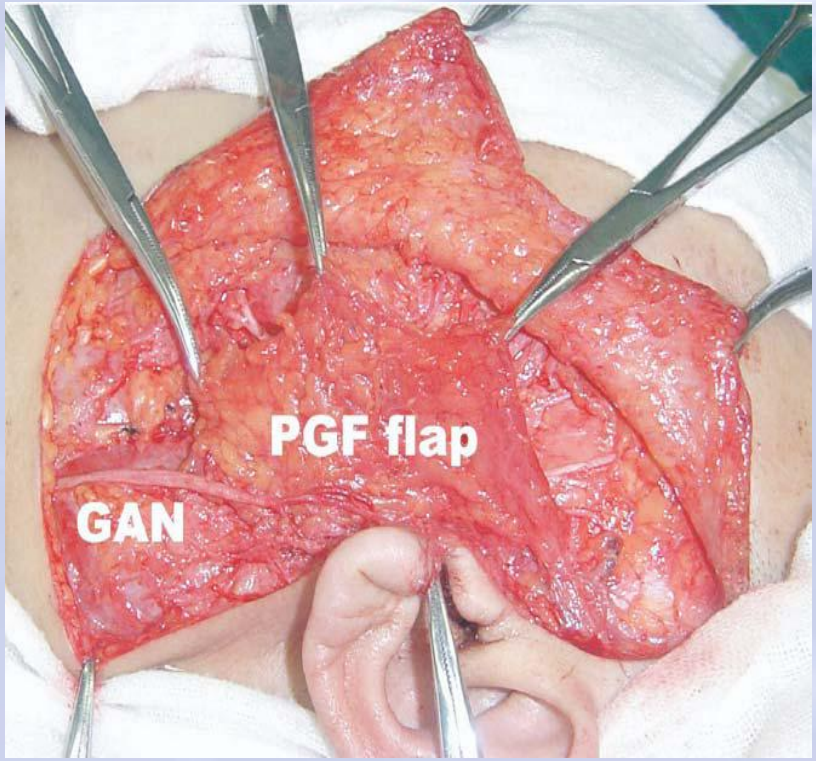


Table 1
Complications in the modified and control groups

Group	Number	TN	PN	FS	TND	PNP	SF	TR
Modified	18	5 (27.7%)*	0*	3 (16.7%)*	11 (61.1%)	0	0	0
Control	30	30 (100%)	4 (13.3%)	20 (66.7%)	17 (56.7%)	0	1 (3.3%)	0

*$P < 0.01$, *TN*, transient numbness; *PN*, permanent numbness; *FS*, Frey's syndrome; *TND*, transient facial nerve disable; *PNP*, permanent facial nerve disable; *S*, salivary fistula; *TR*, tumor recurrence.

Zumeng Y et al. Modified superficial parotidectomy: preserving both the great auricular nerve and the parotid gland fascia. *Otolaryngol Head Neck Surg* 135:458-62, 2006.

Parotidectomy - Facial nerve identification

Useful landmarks for the facial nerve trunk include:

1. the "cartilaginous pointer" - trunk is said to be 1 cm deep and 1 cm inferior to the pointer

TABLE I.
Facial Nerve Measurements* during Parotidectomy.

Topography	Mean	95% Confidence Interval	Minimum	Maximum
Tragal pointer to main trunk facial nerve (n = 78)	6.37	5.84–6.89	2	14

Cannon CR, Replogle WH, Schenk MP. Facial nerve in parotidectomy: a topographical analysis. Laryngoscope 114:2034-7, 2004.

Parotidectomy - Facial nerve identification

Useful landmarks for the facial nerve trunk include:

2. the posterior belly of the digastric muscle and its mastoid insertion, which is slightly lateral to the stylomastoid foramen
3. the tympanomastoid suture, which can be appreciated by palpation. The trunk is said to be 2 mm from the "inferomedial end of the suture“

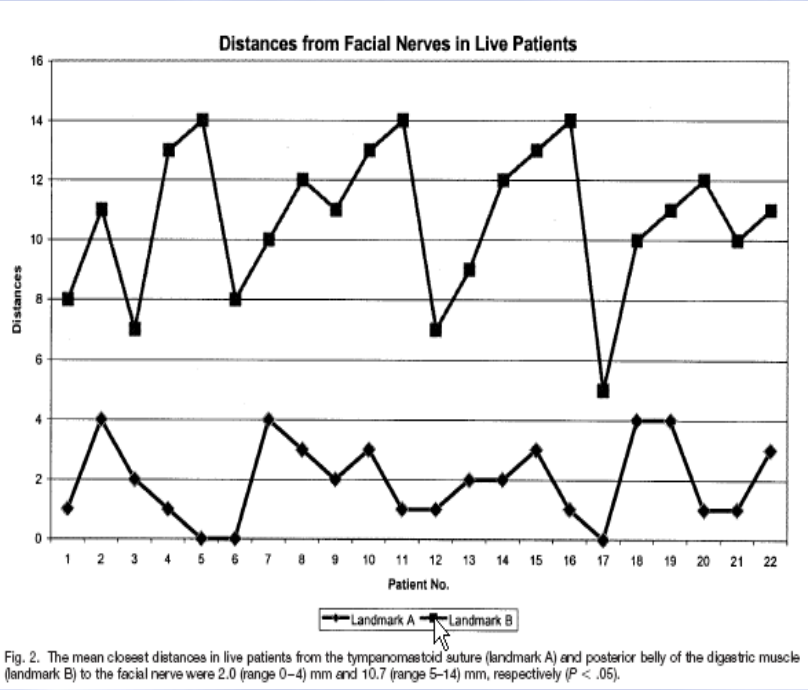
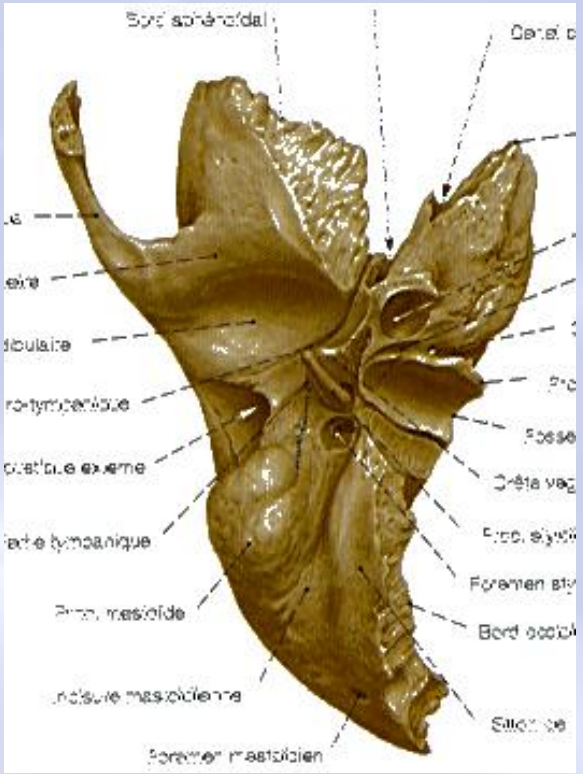


Fig. 2. The mean closest distances in live patients from the tympanomastoid suture (landmark A) and posterior belly of the digastric muscle (landmark B) to the facial nerve were 2.0 (range 0–4) mm and 10.7 (range 5–14) mm, respectively ($P < .05$).

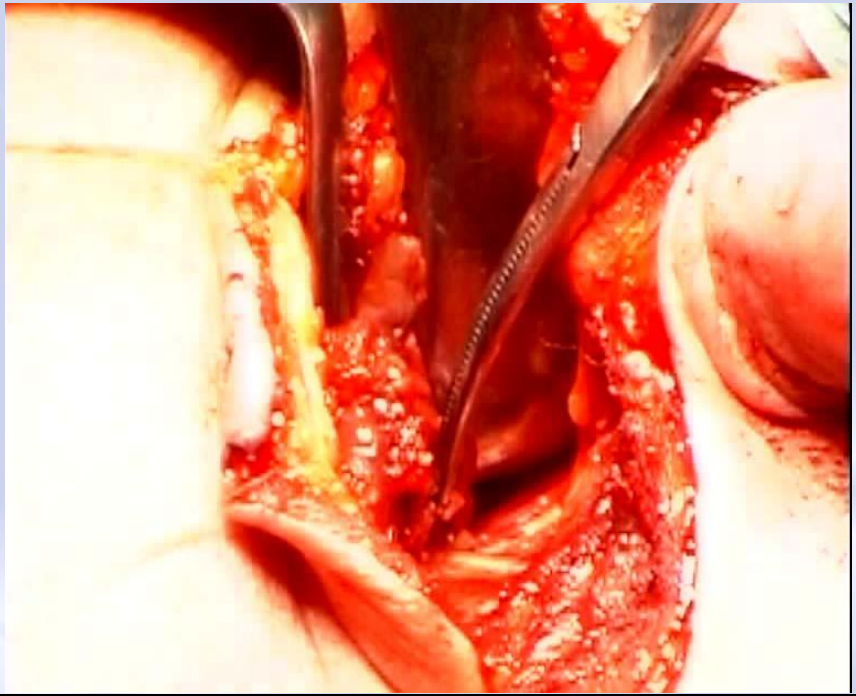


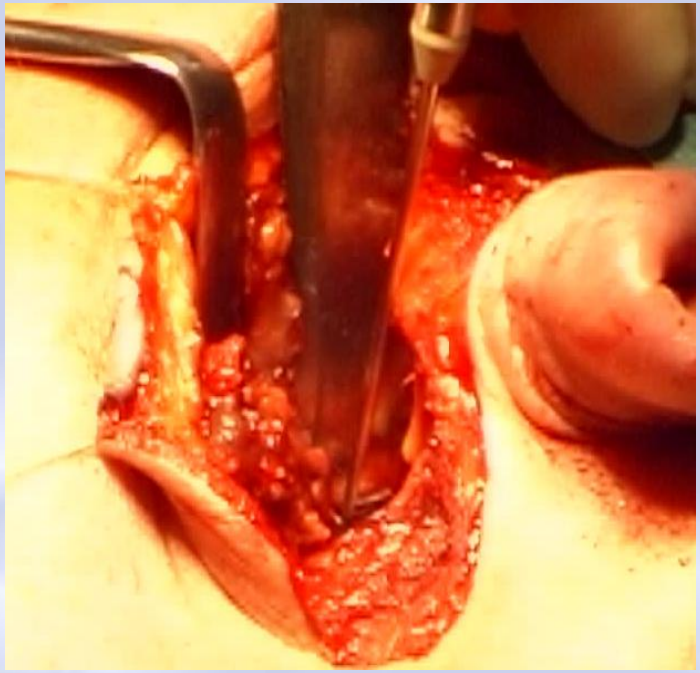
Witt RL, Weinstein GS, Rejto LK . Tympanomastoid suture and digastric muscle in cadaver and live parotidectomy. *Laryngoscope* 115:574-7, 2005.

Parotidectomy - Facial nerve identification

Useful landmarks for the facial nerve trunk include:

4. the stylomastoid artery running with its vein a few millimeters lateral to the facial nerve
5. the styloid process which is located deep to the facial nerve. It can be palpated, but its visualization before identification of the nerve usually means that the nerve has been injured





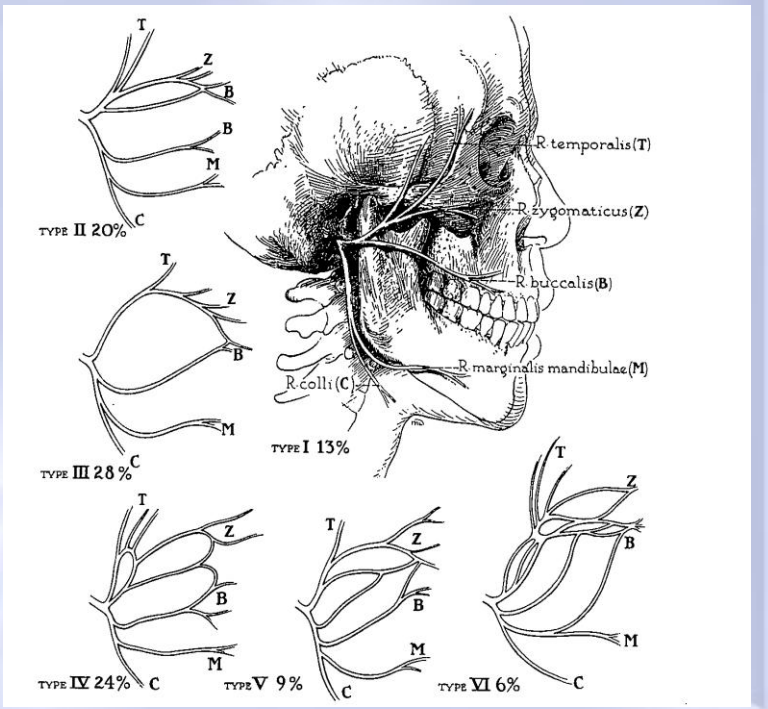
Parotidectomy - Facial nerve branches

Branches located at the extremities of the nerve distribution receive fewer anastomosis with other branches

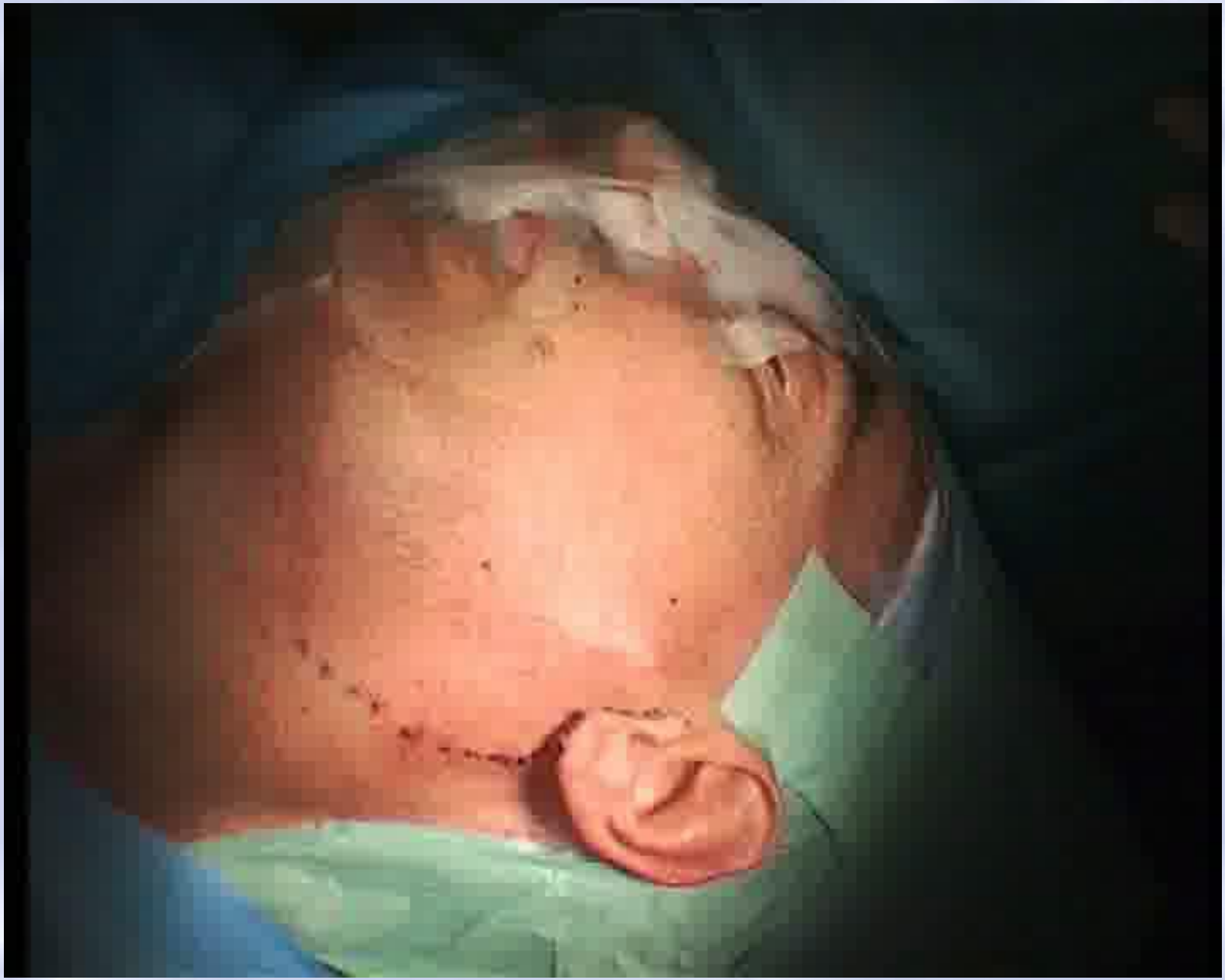
The majority of anastomosis occur between the buccal and zygomatic divisions, forming the so-called parastenon plexus

The number of anastomosis decreases in caudal branches, with the marginal mandibular branch receiving anastomosis in only 6.3%

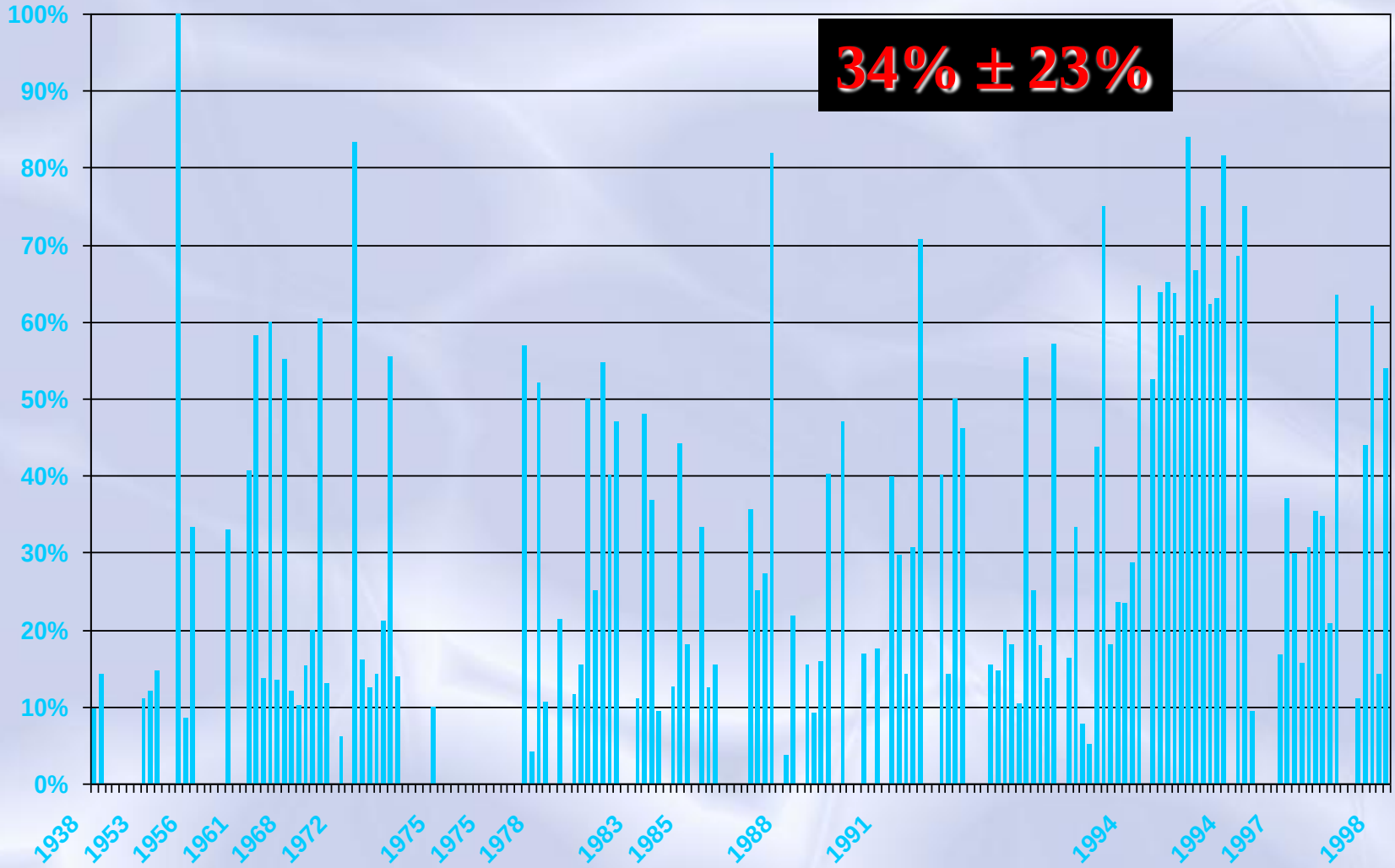
There is no anastomosis between the cervical and other branches



Davis RA, Anson BJ, Budinger JM, Kurth RE. Surgical anatomy of the facial nerve and parotid gland based upon a study of 350 cervicofacial halves. *Surg Gynecol Obst* **102**:385-412,1956.

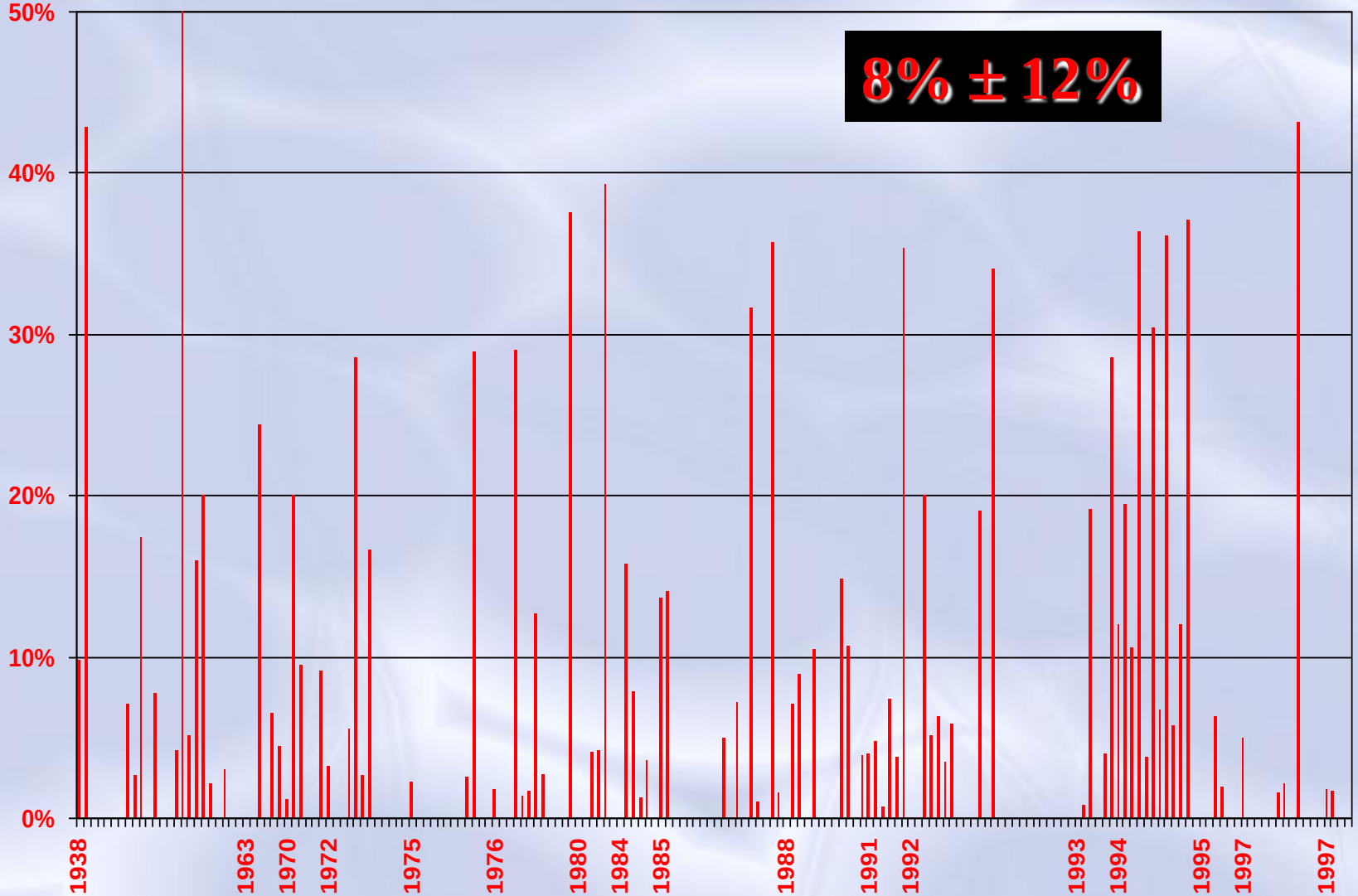


Facial paralysis - immediate or transitory



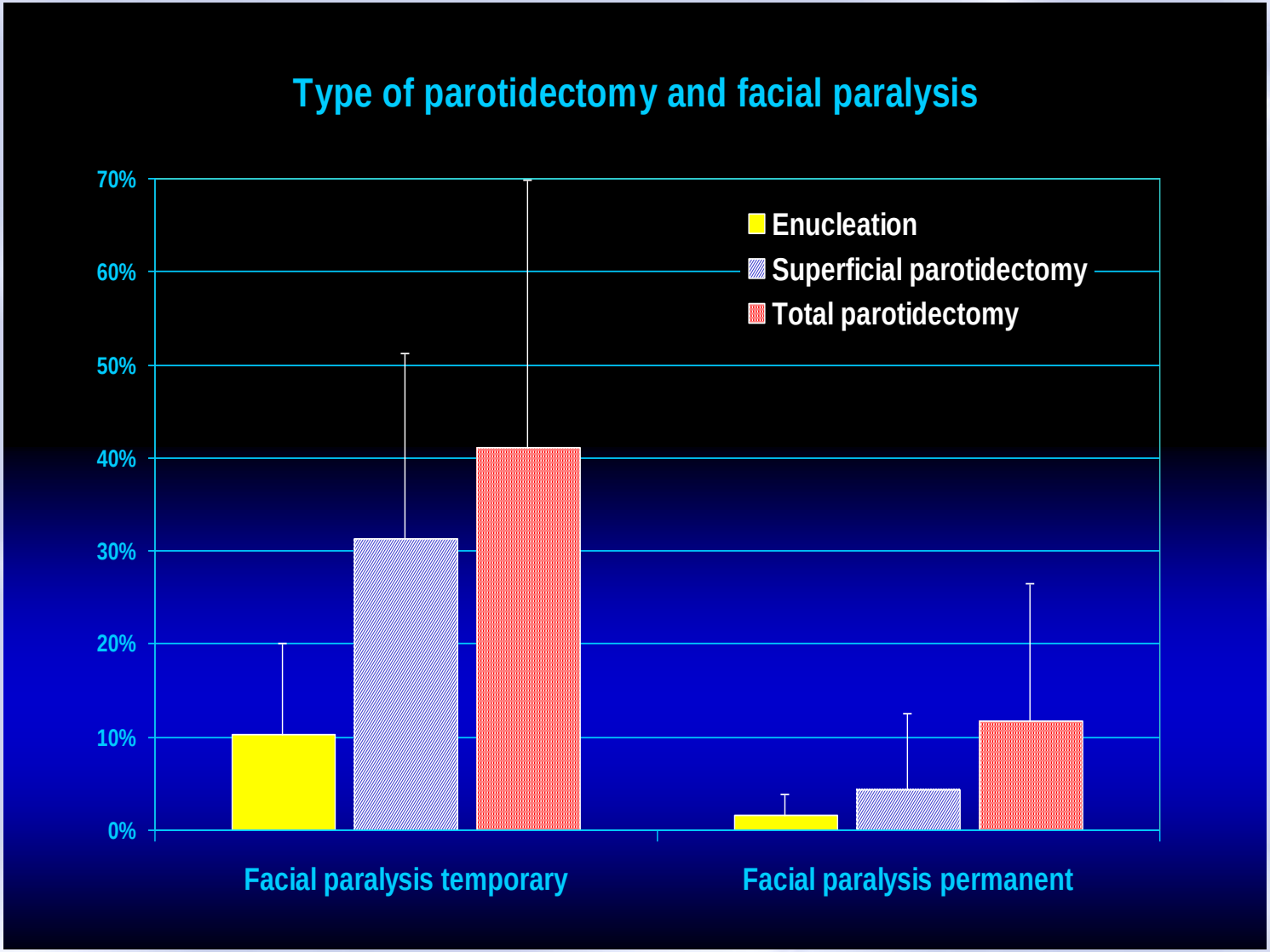
Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

Facial paralysis - definitive



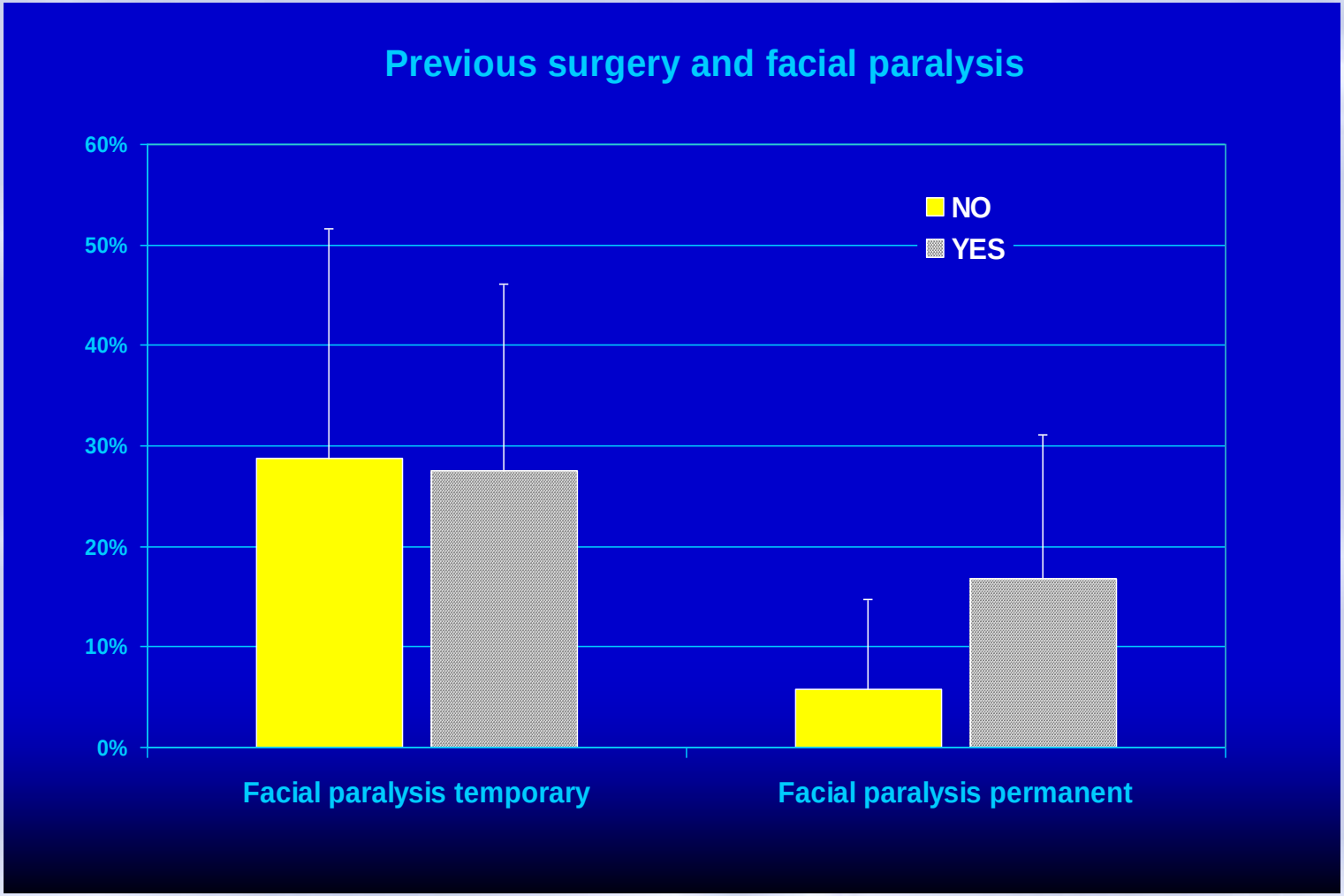
Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

Facial paralysis increases with the extent of surgery



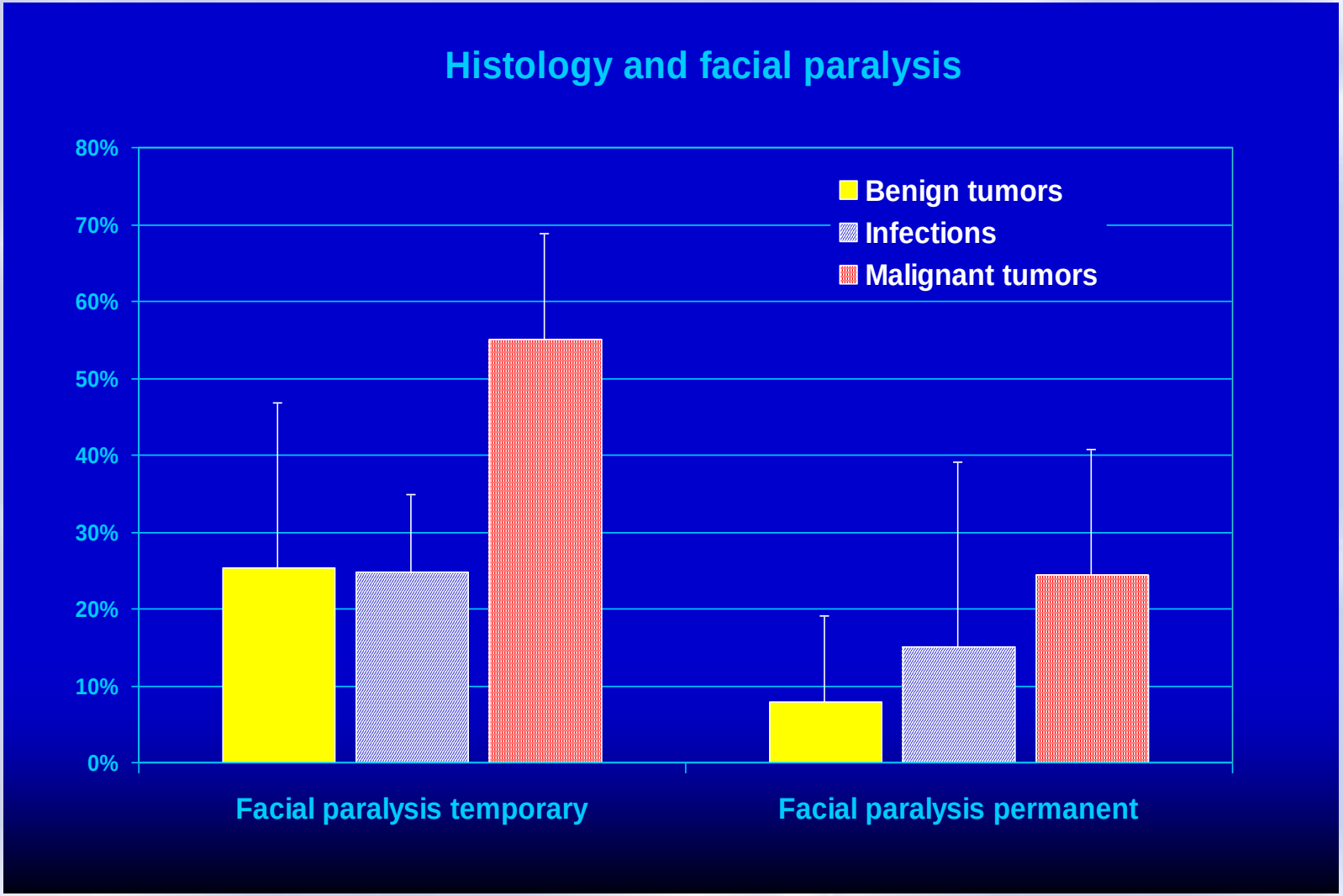
Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

More permanent facial paralysis during re-operations



Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

Facial paralysis is increased when surgery for infection or cancer



Dulguerov, P: Parotidectomy complications. New techniques for their objective evaluation, prevention and treatment. PD Thesis, 1999.
http://archive-ouverte.unige.ch/unige:22052

Variable	Values	VMGi average	VMG standard deviation	Statistical test	p
Age		89.11%	18.26%	Pearson correlation	.199
Sex	M	89.49%	17.06%	Student t-test	.841
	F	88.60%	20.04%		
Type of surgery	Superficial	93.67%	9.3%	Student t-test	.007
	Total	81.85%	25.62%		
Branches sectioned	No	91.90%	13.92%	Student t-test	.001
	Yes	67.50%	31.57%		
Histology	Benign	94.49%	7.52%	One way ANOVA	< 0.001
	Cancer	77.29%	28.57%		
	Infection	66.33	30.14%		
Diameter of the lesion		89.11%	18.26%	Pearson correlation	.04
Duration of the procedure		89.11%	18.26%	Pearson correlation	<0.001

Dulguerov P, Marchal F, Lehmann W. Postparotidectomy facial nerve paralysis:
possible etiologic factors and results with routine facial nerve monitoring. Laryngoscope 109:754-62,1999.

Parotidectomy - Facial nerve - Conclusions

Intraoperative monitoring of facial nerve is useful

Transitory facial paresis 27% (14%) and definitive 4% (2%).

No important paresis (HB > 2) in benign tumor.

Definitive paralysis only if section of facial nerve branches.

Factors associated with increased frequency of transitory facial paresis:

- total parotidectomy
- section of facial nerve branches
- histopathology infectious or cancerous
- size of lesion > 3 cm
- long duration of procedure

Dulguerov P, Marchal F Lehmann W (1999): Postparotidectomy facial nerve paralysis: possible etiologic factors and results with routine facial nerve monitoring. *Laryngoscope 109: 754-62.*

Parotidectomy – Frey syndrome

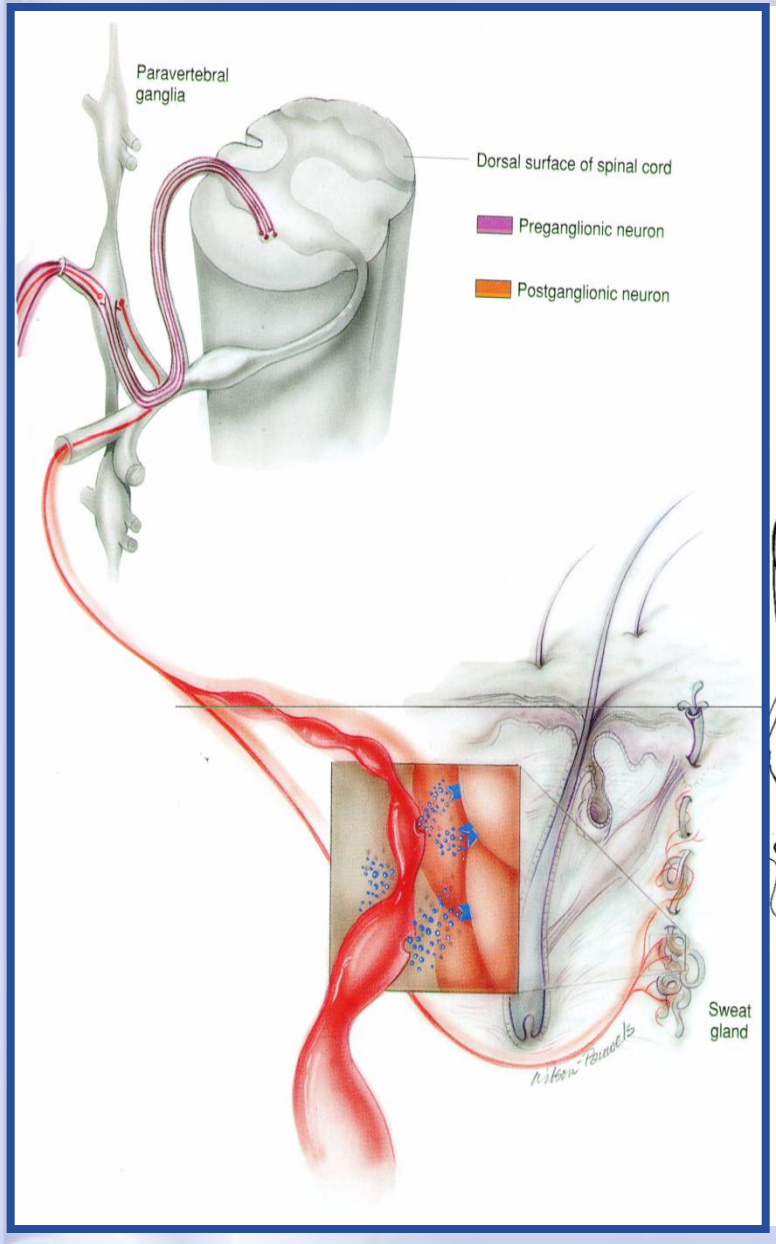
Facial sweating during eating

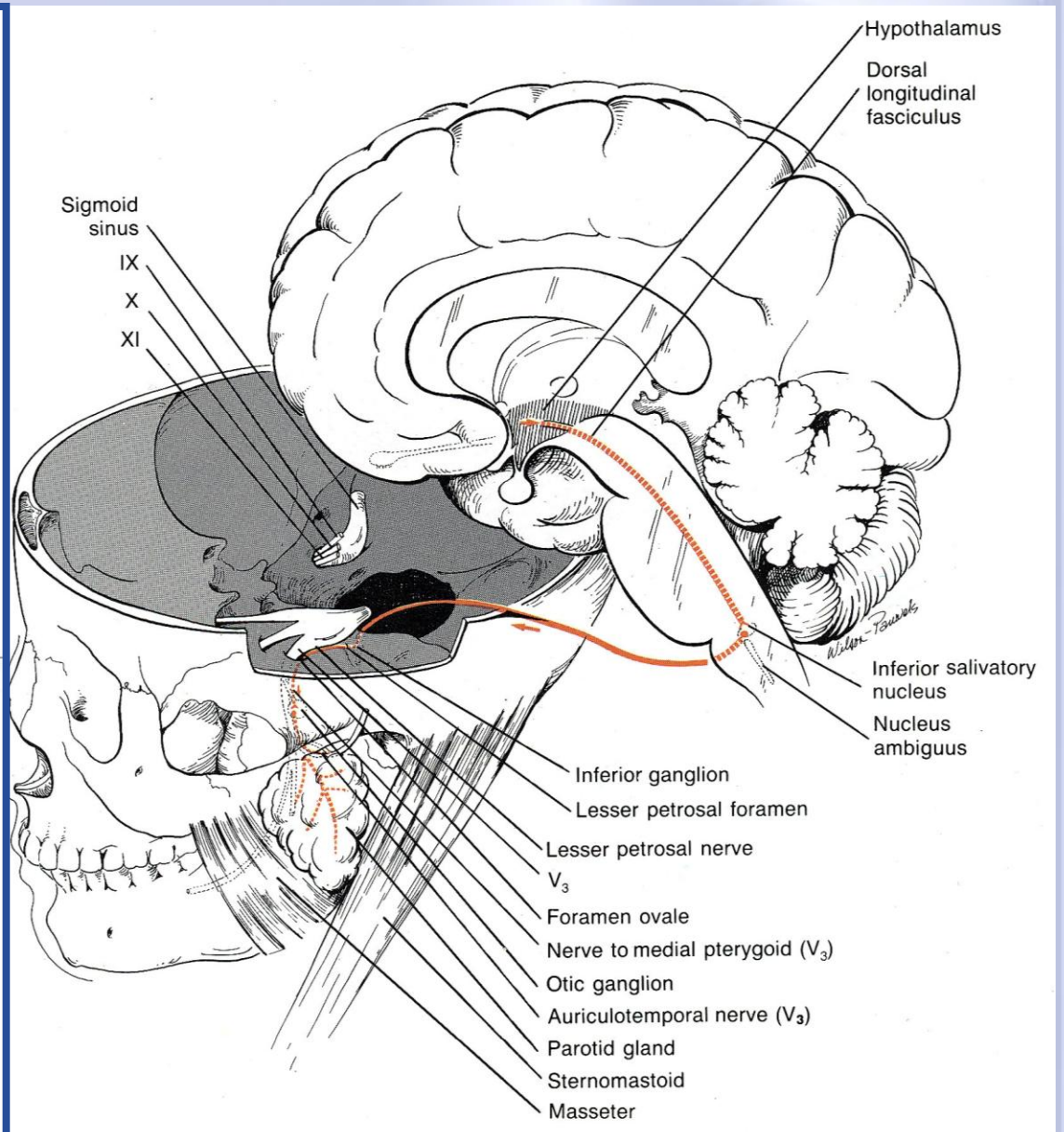
Facial flushing during eating

No relation with mastication

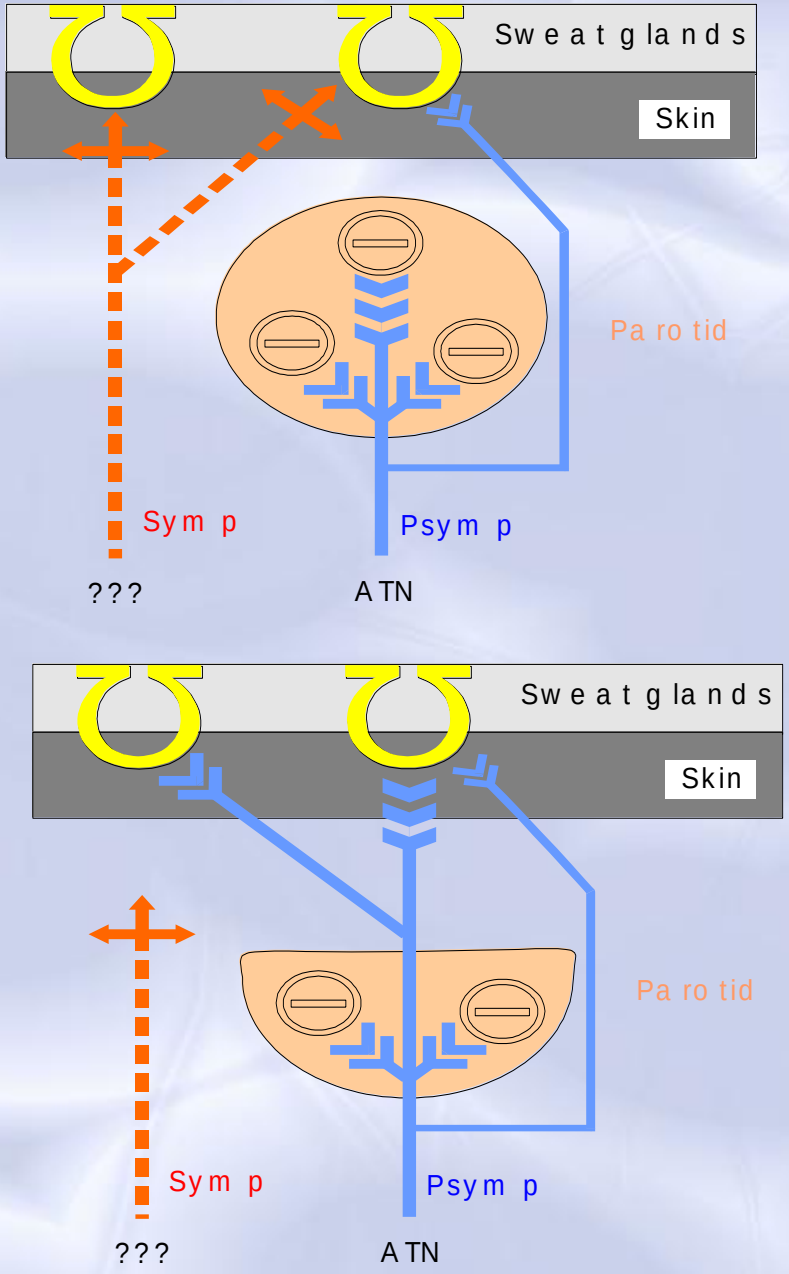
No spontaneous resolution

Dulguerov, Marchal, Gysin: Frey syndrome before Frey. *Laryngoscope* 109:1471,1999.


Paravertebral ganglia
Dorsal surface of spinal cord
Preganglionic neuron
Postganglionic neuron
Sweat gland


Hypothalamus
Dorsal longitudinal fasciculus
Sigmoid sinus
IX
X
XI
Inferior salivatory nucleus
Nucleus ambiguus
Inferior ganglion
Lesser petrosal foramen
Lesser petrosal nerve
V3
Foramen ovale
Nerve to medial pterygoid (V3)
Otic ganglion
Auriculotemporal nerve (V3)
Parotid gland
Sternomastoid
Masseter

Aberrant regeneration theory



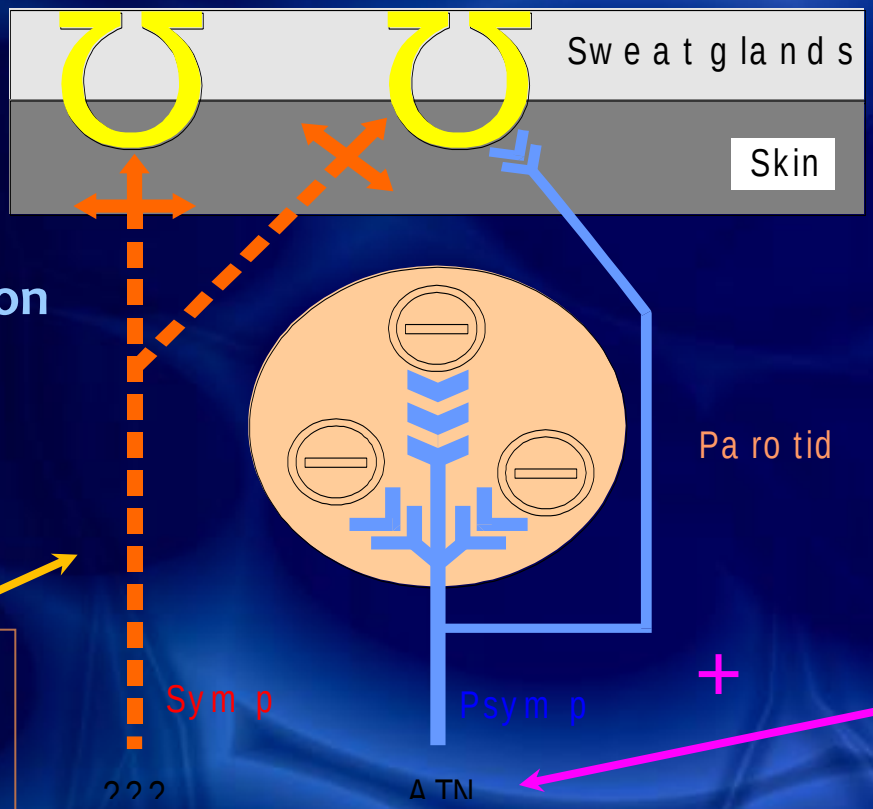
Dulguerov: Treatment of Frey syndrome. *In* Myers: Salivary glands, Springer-Verlag, 2007.

Latency of symptoms and progressive increase of the involved area

Wilson – Clin Sci, 1936
List & Peet – Arch Neurol Psych, 1938
Haxton – Brain, 1948
Laage-Hellman – Acta Otolayngol, 1958
Linder – Laryngoscope, 1997

Atropine; Botox

Freedberg – J Clin Invest, 1948
Glaister – Brit Med J, 1958
Drobik – Acta Otolaryngol, 1995



Local hypersensitivity to cholinergic drugs

Wilson – Clin Sci, 1936
Freedberg – J Clin Invest, 1948
Glaister – Brit Med J, 1958

Local absence of sympathetic function

List & Peet – Arch Neurol Psych, 1938
Freedberg – J Clin Invest, 1948
Haxton – Brain, 1948
Glaister – Brit Med J, 1958

Anesthesia

Freedberg – J Clin Invest, 1948
Glaister – Brit Med J, 1958
Drummond – J Auton Nerv Syst, 1995

Stimulation

Ross – Laryngoscope, 1970

Anesthesia

Freedberg – J Clin Invest, 1948
Glaister – Brit Med J, 1958

Prevention by permanent barrier

Dulguerov – Arch Otolaryngol HNS, 1999

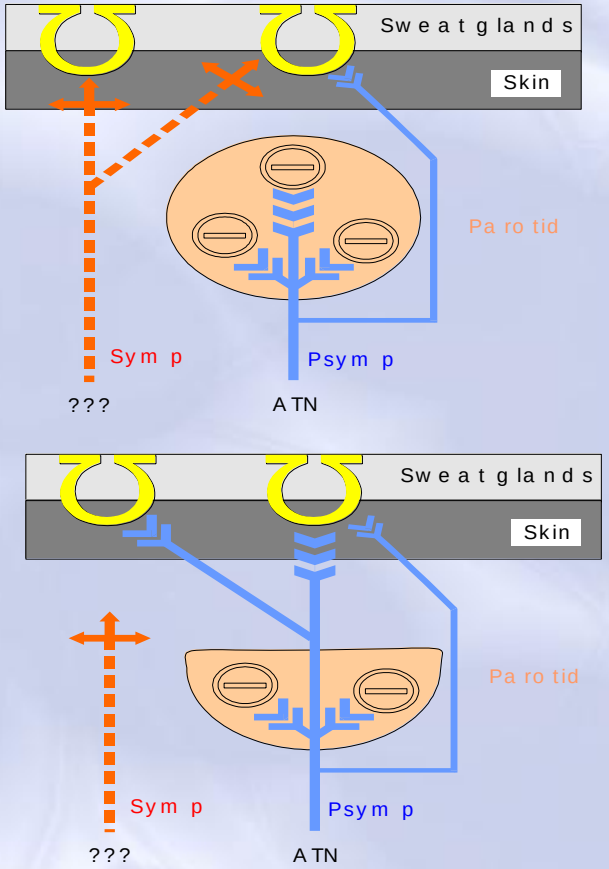
The etiology of Frey syndrome is the sympathetic denervation of sweat glands

Trauma to the parotid area

- parotidectomy
- mandibular surgery
- neck dissection
- drainage of abscess
- blunt (mandibular fractures) and penetrating trauma

Surgery or lesions of the cervical sympathetic chain

THE KEY ELEMENT IS THE DENERVATION OF THE SWEAT GLANDS, THUS A LESION OF THE SYMPATHETIC FIBERS



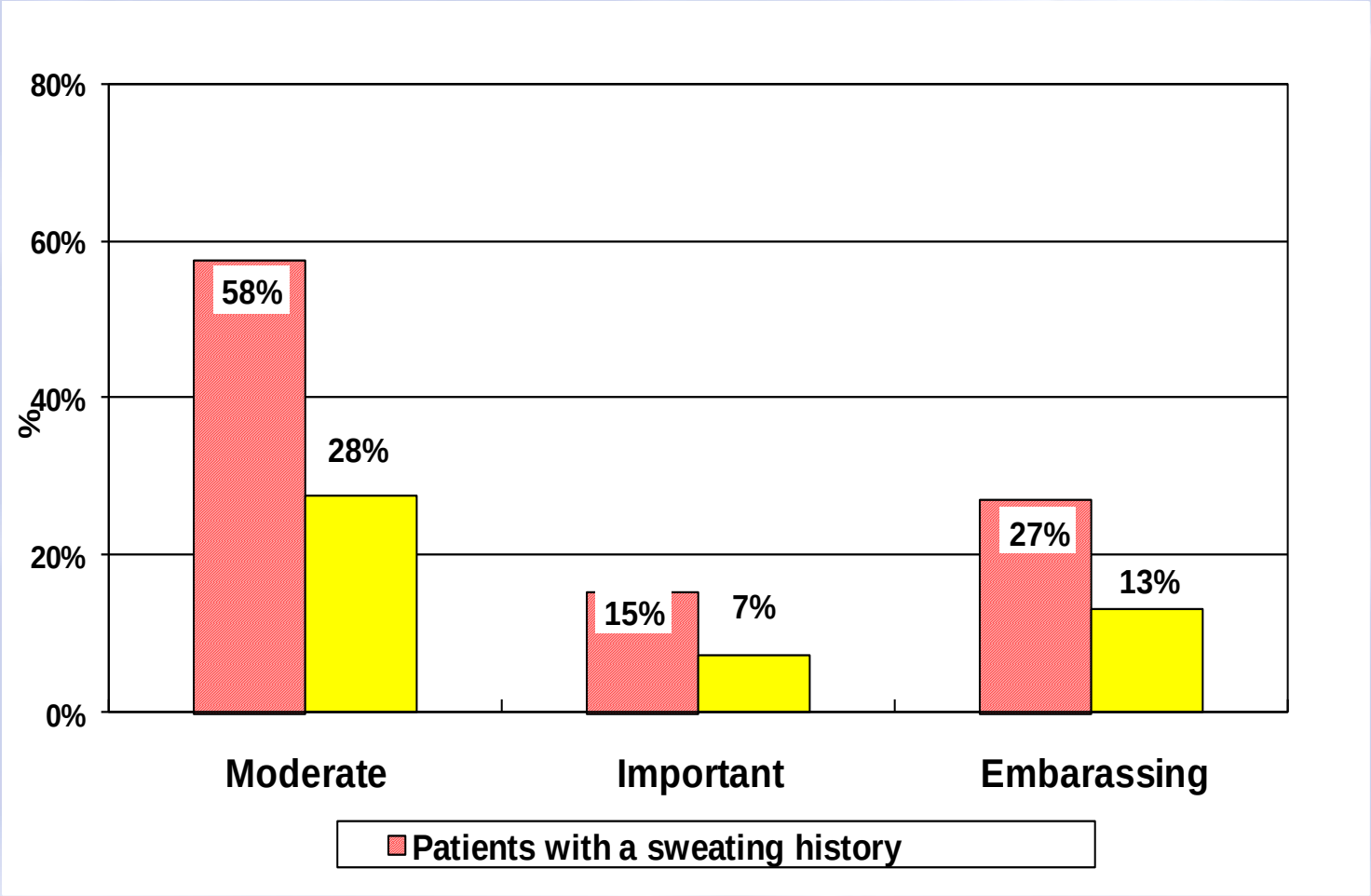
Frey syndrome is a frequent complication of parotidectomy

Author	Year	Number of patients	Incidence of clinical Frey's syndrome (%)	Incidence of objective Frey's syndrome (%)
Laage-Hellman [74]	1958	123	62	98
Kornblut et al. [69]	1974	35	43	97
Gordon and Fiddian [53]	1976	50	34	100
Farrell and Kalnins [39][a]	1991	21	14	43
Yu and Hamilton [146]	1992	35	6	14
Allison and Rappaport [2]	1993	35	83	87
Linder et al. [88]	1997	26	43	96
Nosan et al. [104]	1991	23	44	70
Dulguerov et al. [35]	1999	24	53	76
Laskawi et al. [84]	1998	81	63	100
Cavalot [16]	2000	86	47	86

45% **90%**

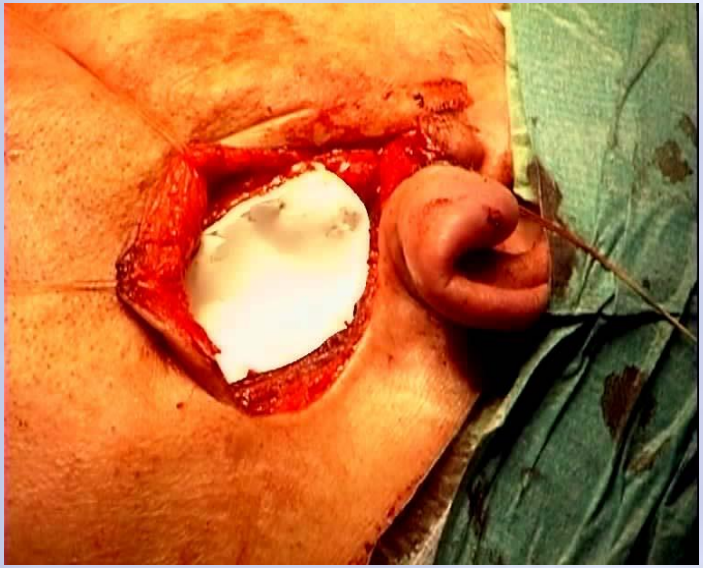
Dulguerov: Treatment of Frey syndrome. *In* Myers: Salivary glands, Springer-Verlag, 2007.

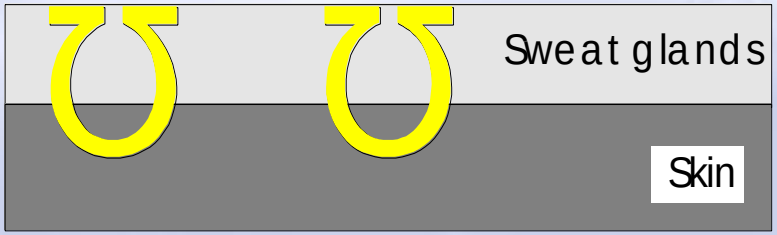
Severity of sweating is important in about 40%

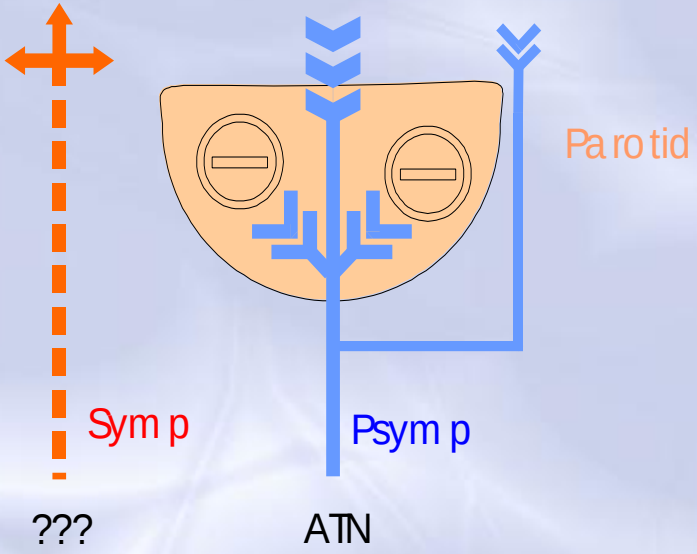


Laage-Hellman JE. Gustatory sweating and flushing after conservative parotidectomy. *Acta Otolaryngol* 48:234-52, 1957

Prevention of Frey syndrome

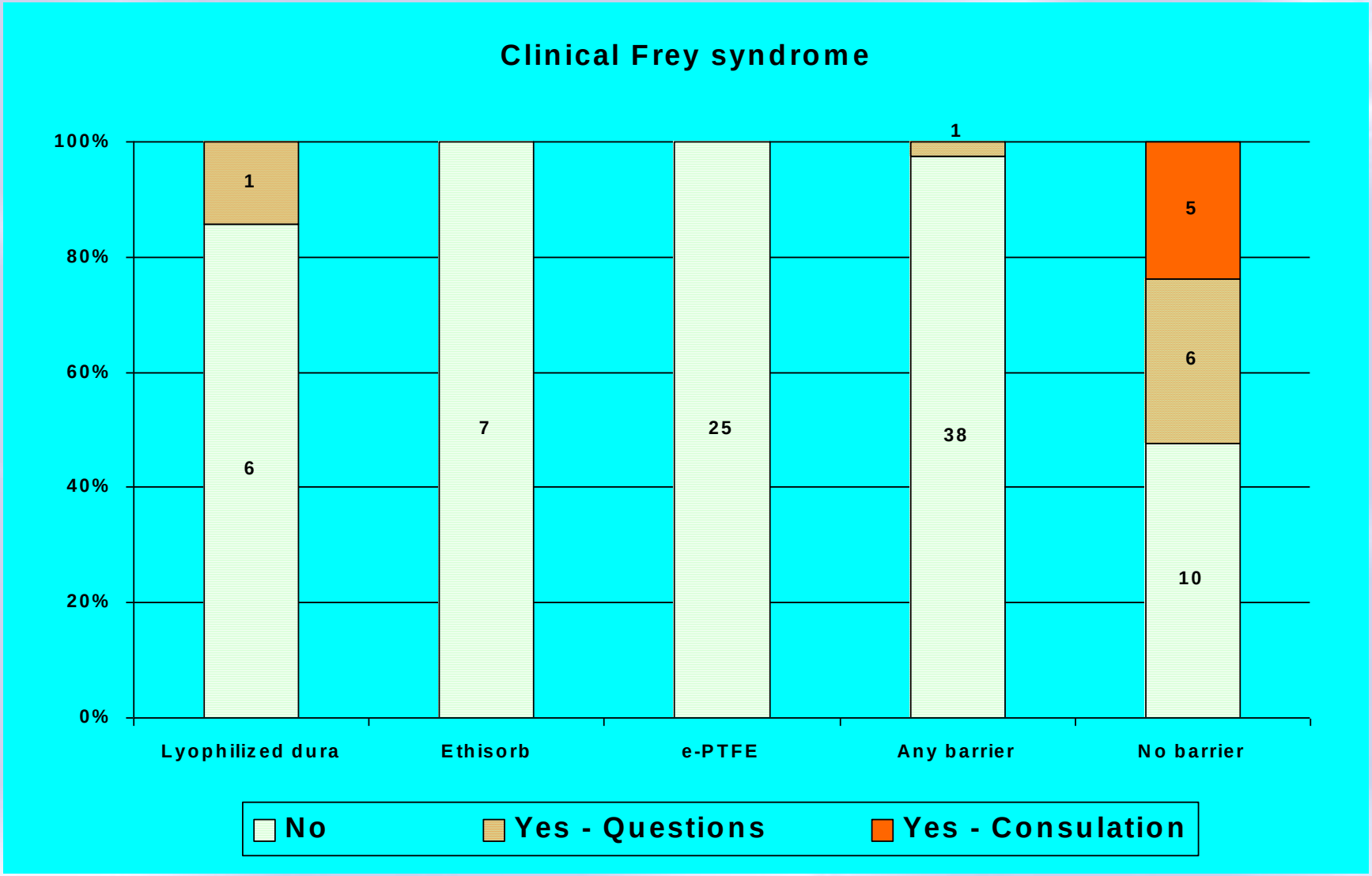






Dulguerov et al: Prevention of Frey syndrome during parotidectomy. *Arch Otolaryngol HNS* 125:833,1999.

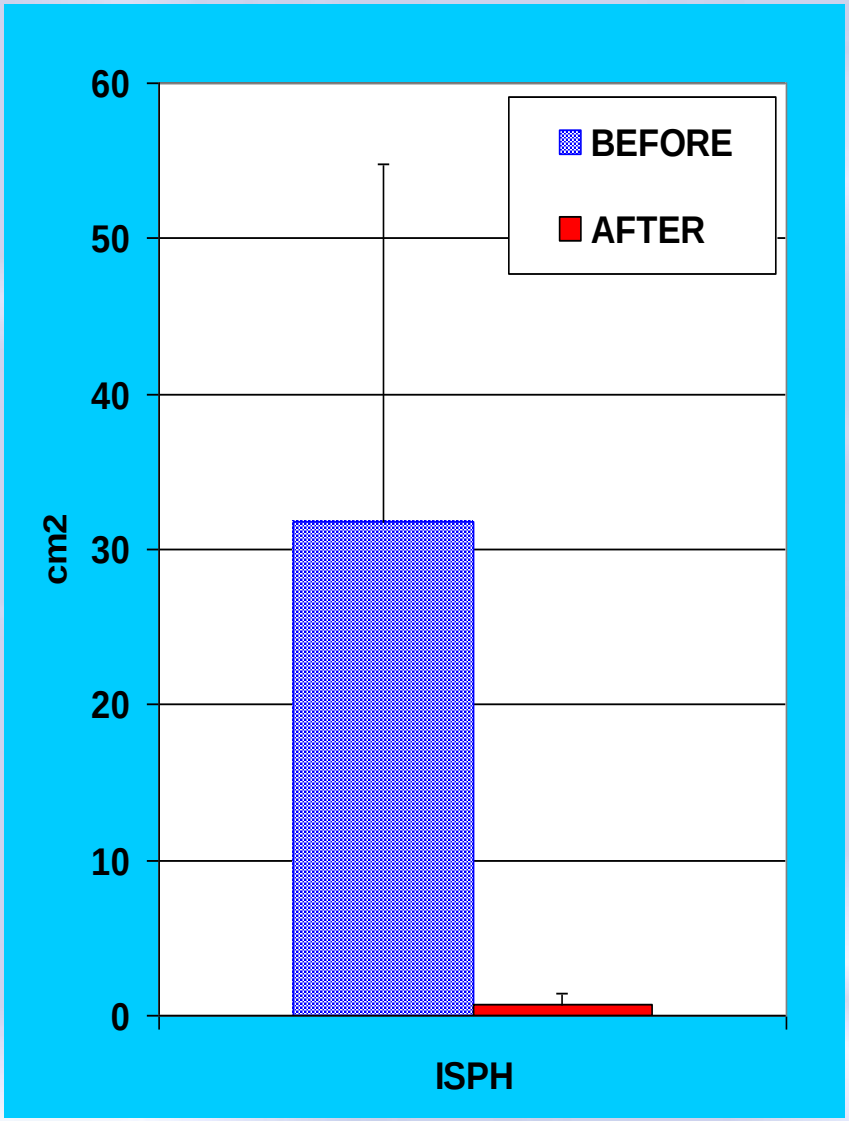
Frey syndrome is preventable

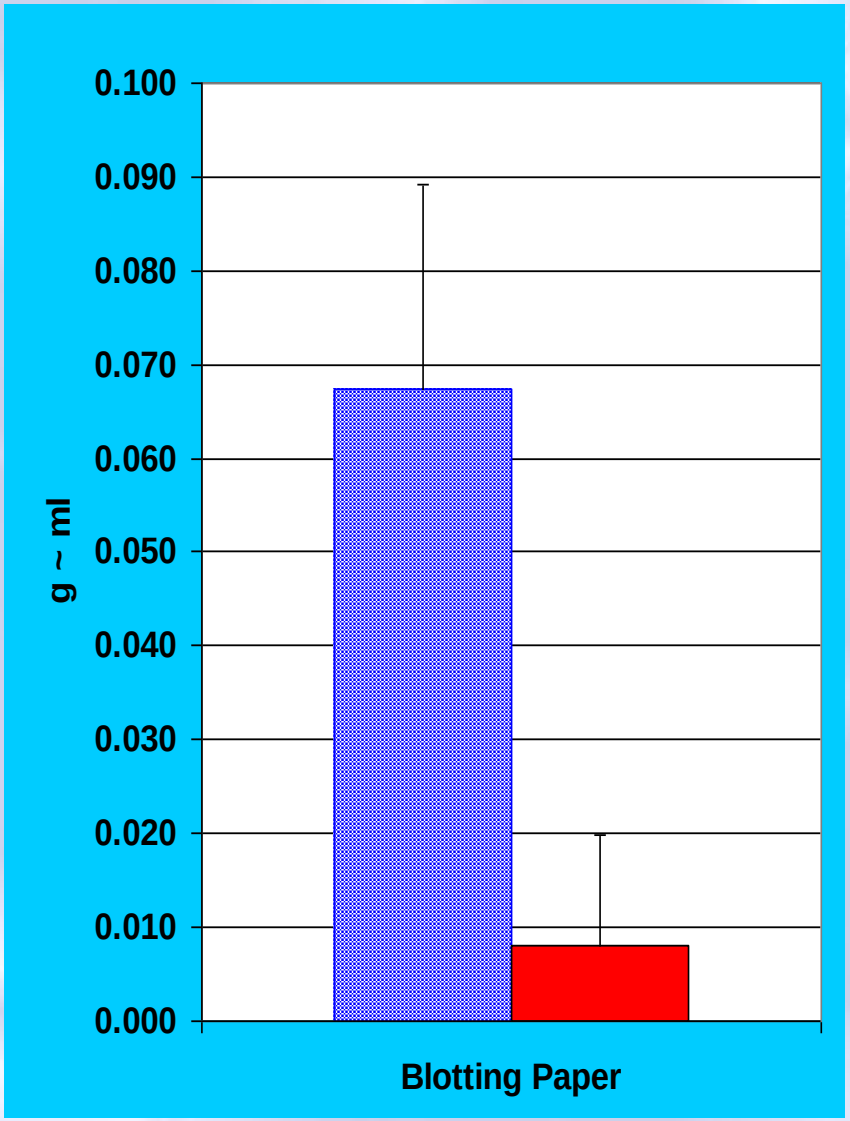


Dulguerov et al: Prevention of Frey syndrome during parotidectomy. *Arch Otolaryngol HNS* 125:833,1999.

Author	Year	Number of patients	Prevention technique	Evaluation	Minimal follow-up	Incidence with prevention	Incidence without prevention	p (χ^2)
Kidd [79]	1955		Nerve section	History	?	20%	24%	0.7
Singleton [146]	1980	164	Thick flap	History	8 weeks	3%	12.5%	0.02
Kornblut et al. [81] [82]			SCM	History	1-6 years	43%	23%	0.07
				Minor	1-6 years	97%	94%	0.5
Casler [21]	1991	16 /	SCM	History	2 years	12.5%	47%	< 0.01
Kim [80]	1999	9 / 10	SCM	History	1 year	22%	50%	
Sood [151]	1999	11 / 11	SCM	Minor	1 year	18%	82%	<0.01
Gooden [59]	2001	13 / 13	SCM	Minor	1 year	31%	23%	
Kerawala [78]	2002	21 / 15	SCM	Minor	1 year	90%	73%	0.21
Filho [49]	2004	24 / 19	SCM	Minor	1 year	0%	37%	< 0.01
Casler [21]	1991	16 /	SMAS	History	2 years	0%	47%	< 0.01
Yu & Hamilton [170]	1992	20	SMAS	Minor	2.5 years*	15%	---	---
Allison & Rappaport [3]	1993	91/35	SMAS	History	1 year	1%	83%	<0.01
		79/30		Minor	1 year	2%	87%	<0.01
Belli [11]	1996	45 / 35	SMAS	History	2 years	40%	57%	0.13
Ahmed [2]	1999	24 / 23	Temporal fascia	Minor	1 year	17%	70%	<0.01
Bonanno	2000	160	SMAS	Minor	1 year	0%	---	---
Taylor [156]	2000	15 / 13	SMAS	Minor	0.8 years	73%	54%	0.14
Dulguerov [43]	1999	/ 24	GoreTex / Lyophilized dura	ISPH	1 year	10%	76%	
Govindaraj [62]	2001	15 / 15	Alloderm	Minor	0.5 years	0%	40%	<0.01
Sinha [147]	2003	10 / 10	Alloderm	Minor	1 year	20%	80%	<0.05

Frey syndrome is treatable by Botox intradermal injections





Dulguerov et al: Frey syndrome treatment with botulium toxin. *Otolaryngol HNS* 122:821,2000.

Parotidectomy – Frey syndrome - Conclusions

The incidence of Frey syndrome after parotidectomy is 40% for the clinical and 90% for the objective evaluation.

A subcutaneous barrier placed as prevention decreases this incidence to 2% for the clinical and 10% for the objective evaluation.

Botulinum toxin type A is an efficient, well tolerated, uncomplicated treatment of Frey syndrome