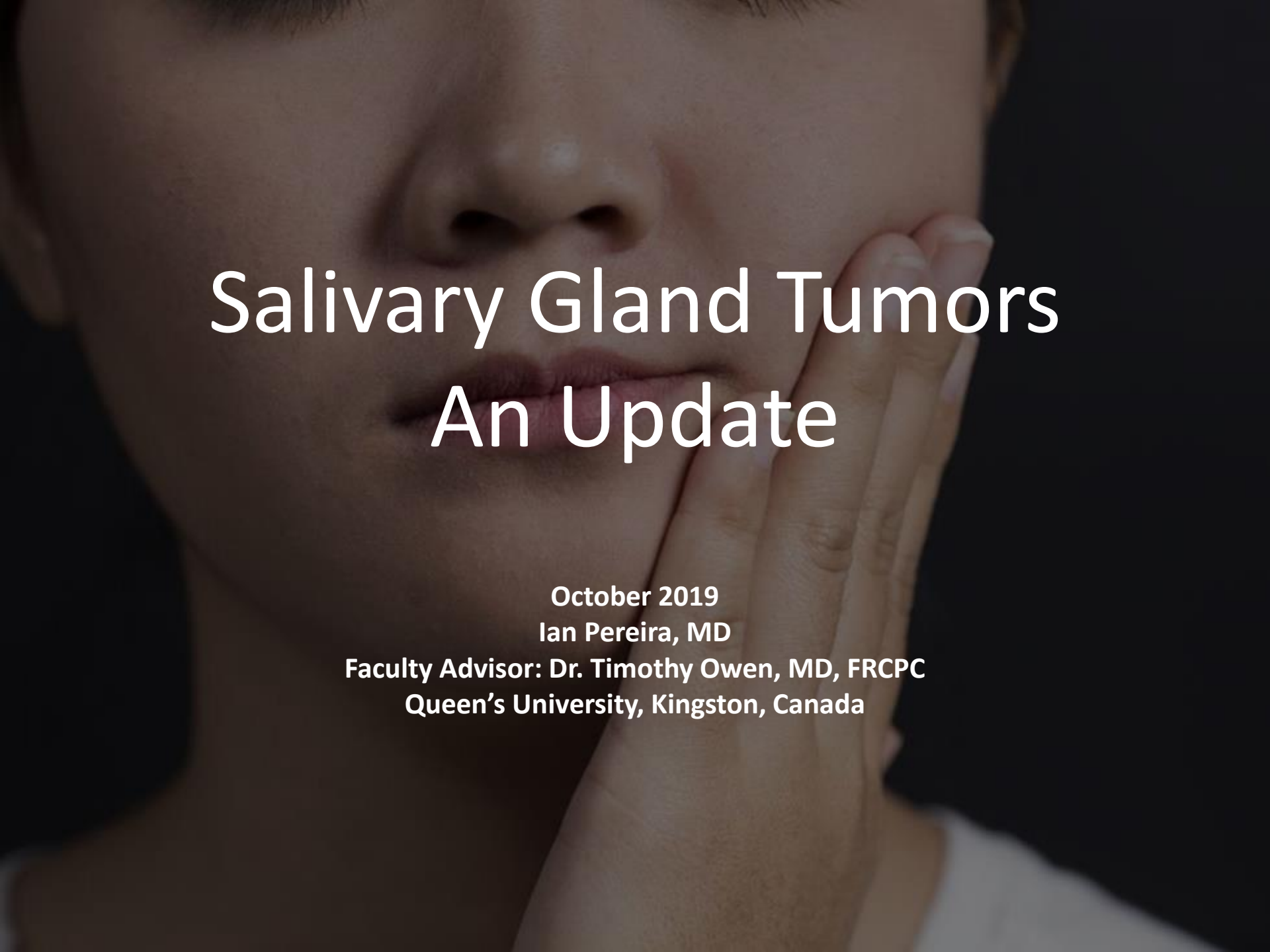

Salivary Gland Tumors
An Update

October 2019
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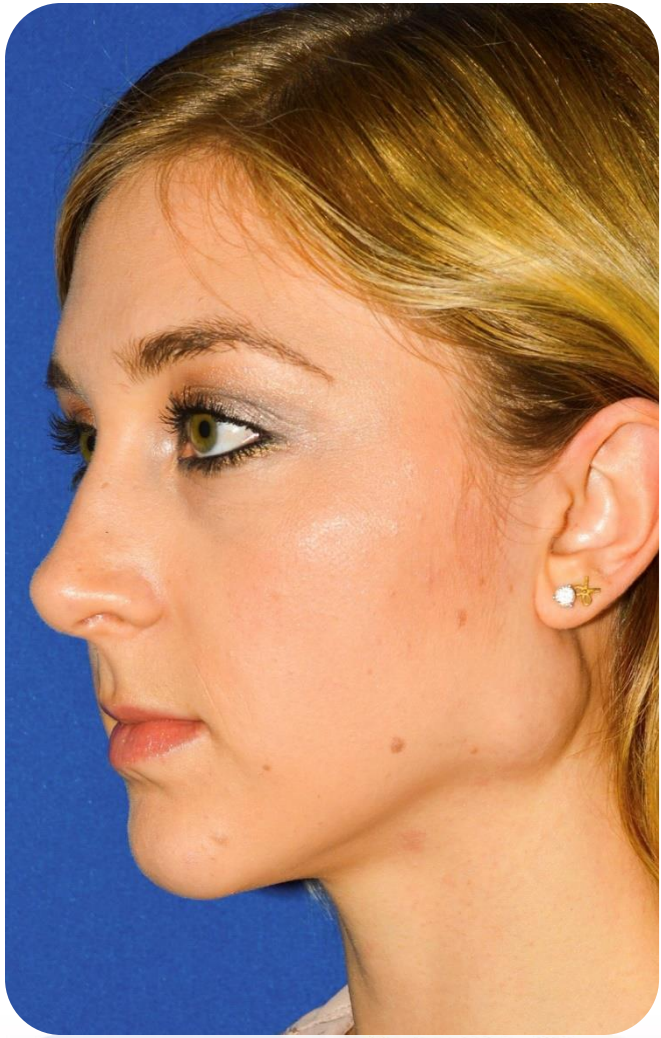
Objectives

Build on previous ARROCases for salivary gland tumors (SGTs)[1] including benign & malignant disease:

1. Recognize the presentation of pleomorphic adenoma (PA) and carcinoma ex PA (CaXPA)
2. Develop a framework for managing benign & malignant SGTs
3. Understand the epidemiology, classification, & prognosis
4. Review relevant clinical trials

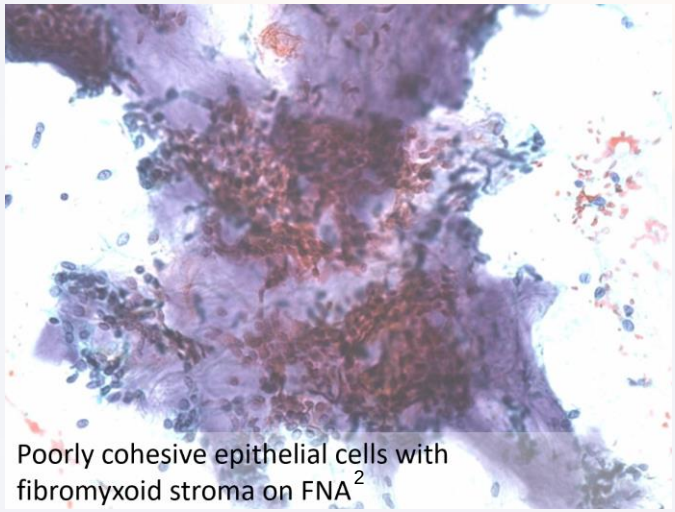
A lump in the neck

- 40-year-old aesthetician with a slowly growing mass in her neck over 3-4 months
- No pain, trismus, facial weakness, numbness, dysphagia, or odynophagia
- Physical exam with focus on the head & neck (H&N):
  - A 3cm, firm, nontender, mobile mass at the angle of the mandible
  - No other palpable masses or adenopathy
  - Cranial nerve exam is normal
  - Oral mucosa & skin are intact

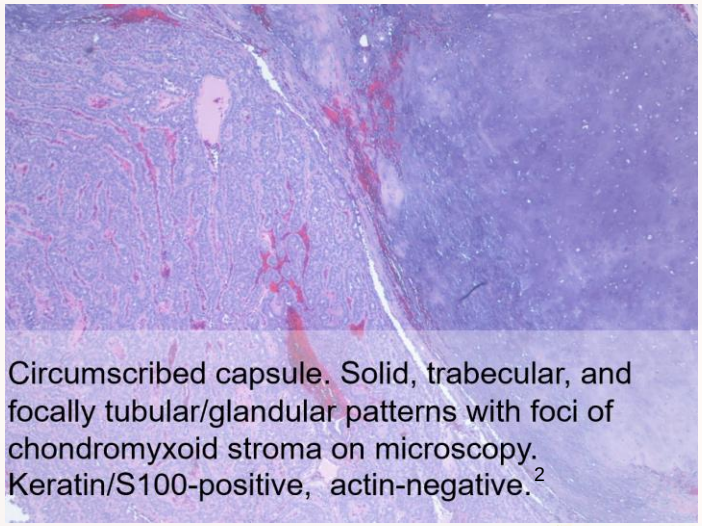


Referred to ENT

- Ultrasound shows a single hypoechoic mass in the parotid with posterior acoustic enhancement
- Fine Needle Aspiration & Biopsy (FNAB) consistent with pleomorphic adenoma (PA)
- Superficial parotidectomy reveals a tumor in the superficial lobe of the parotid
- Pathology shows PA **with a ruptured capsule**
- Transient CN VII paralysis with recovery 4 months later
- Discharged to her GP after 5 years of uneventful follow-up



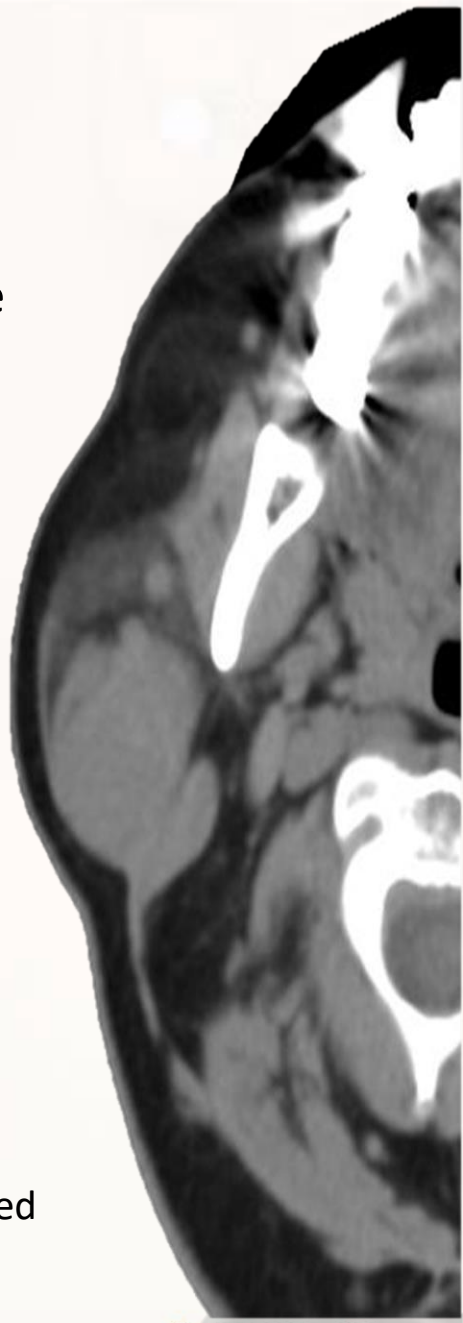
Poorly cohesive epithelial cells with fibromyxoid stroma on FNA[2]



Circumscribed capsule. Solid, trabecular, and focally tubular/glandular patterns with foci of chondromyxoid stroma on microscopy. Keratin/S100-positive, actin-negative.[2]

5 Years Later…

- She returns with a 2-year history of a mass in same location at the angle of the mandible
- CT shows an enhancing mass adjacent to the residual deep lobe with necrosis
- FNAB shows **recurrent pleomorphic adenoma**
- Discussed at multidisciplinary cancer conference (MCC)
  - Resectability borderline, but **definitive radiation felt to be inferior to surgery**
- Revision parotidectomy shows **one mass & two nodules** in the **deep parotid remnant**
- Final pathology is **again PA with a close margin**
- Postop MRI shows no residual tumor
- Discussed again at MCC
  - Not a candidate for re-resection and consensus for adjuvant radiation treatment based on **high-risk features for local recurrence**
    - 5000cGy in 20 daily fractions for microscopic residual disease to the tumor bed and surgical scar with a bolus

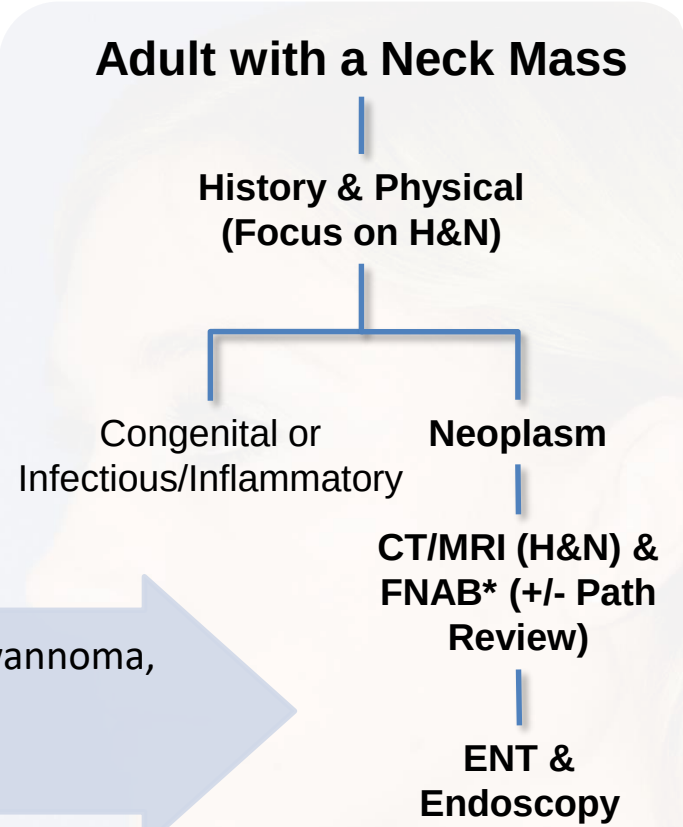


Approach to a lump in the neck

Congenital
- Usually seen in children

Infectious/ Inflammatory
- Infectious: viral, bacterial, parasitic
- Noninfx: stone, sarcoid, Castleman, Kawasaki

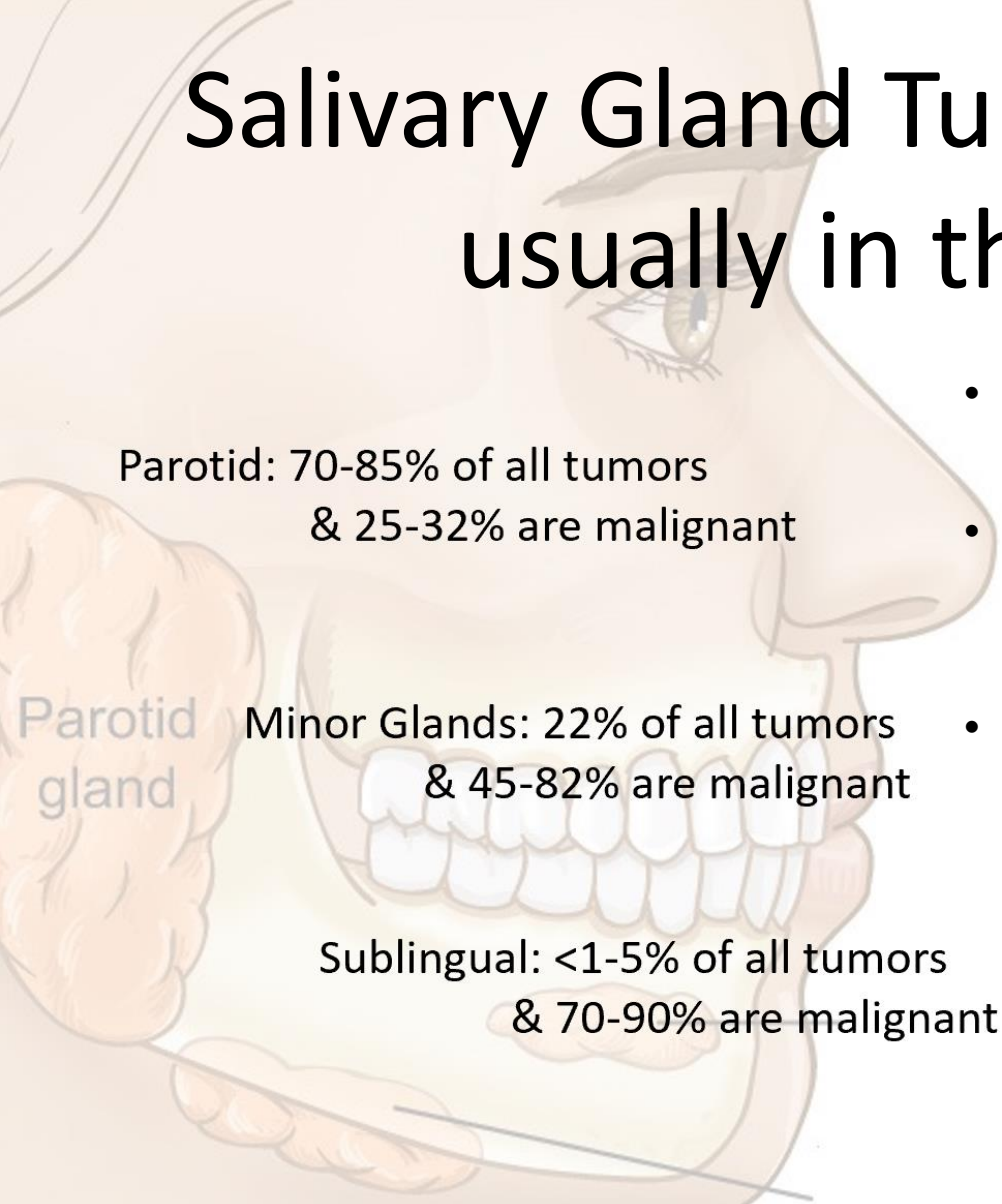
Neoplastic (benign or malignant)
- Primary (Salivary, thyroid, paraganglioma, schwannoma, lymphoma, lipoma/cyst)
- Mets (aerodigestive or skin)



*role of FNAB in workup is controversial, but often recommended because it can change management in 35% of cases [3,4]

*for a non-neoplastic parotid mass: **SP1TS** **S**alivary duct stone, **P**arotitis, **1**st brachial cleft cyst, fatty parotid **T**ail, **S**arcoidosis*
@RadOncMnemonics[5]

Salivary Gland Tumors (SGTs) are usually in the parotid



Parotid: 70-85% of all tumors
& 25-32% are malignant

Minor Glands: 22% of all tumors
& 45-82% are malignant

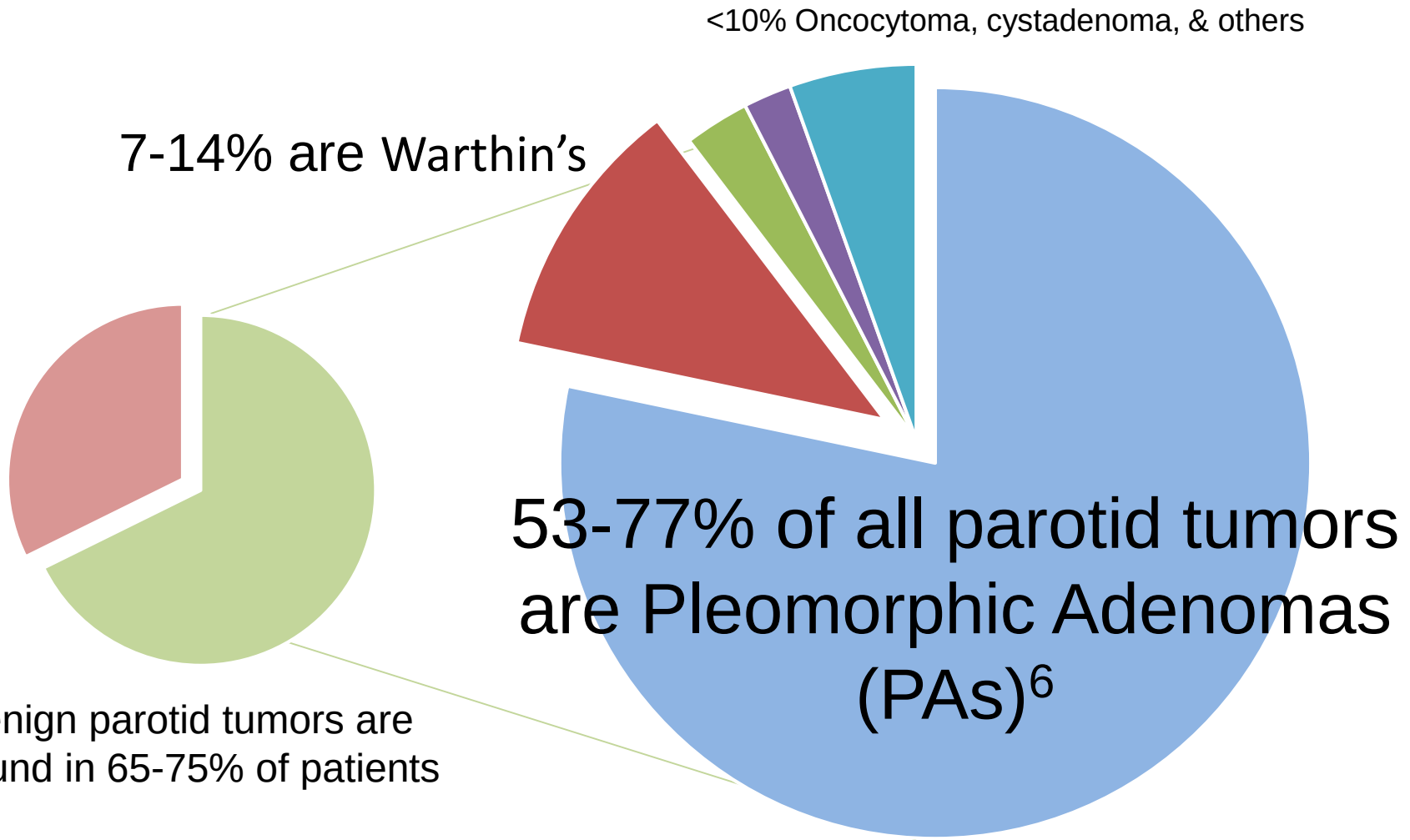
Sublingual: <1-5% of all tumors
& 70-90% are malignant

Submandibular Glands: 8% of all tumors
& 37-45% are malignant[6]

- Uncommon (5.5 per 100,000)
- Benign tumors more common in young females (median age 46)
- Malignant tumors more common in older men (median age 54)

Rule of thumb: as the size of the gland decreases the incidence of malignancy increases (25/50/75% for Parotid/ Submandibular/Sublingual or minor)

Most SGTs are Pleomorphic Adenomas



PA is one histology of many for SGTs

Histologic classification for salivary gland tumors in the WHO 4th Edition has 22 carcinomas, 11 benign tumors, 4 non-neoplastic epithelial lesions, 3 benign soft-tissue entities, and MALT Lymphoma, making it one of the most extensive classifications for tumors[7]

Malignant tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Polymorphous adenocarcinoma
- Clear cell carcinoma
- Basal cell carcinoma
- Intraductal carcinoma
- Adenocarcinoma, NOS
- Salivary duct carcinoma
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Secretory carcinoma
- Sebaceous adenocarcinoma
- Carcinosarcoma
- Poorly differentiated carcinoma
  - Undifferentiated carcinoma
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Lymphoepithelial carcinoma
- Squamous cell carcinoma
- Oncocytic carcinoma
- Uncertain malignant potential
  - Sialoblastoma

Benign tumors

- Pleomorphic adenoma
- Myoepithelioma
- Basal cell adenoma
- Warthin tumor
- Oncocytoma
- Lymphadenoma
- Cystadenoma
- Sialadenoma
- Ductal papillomas
- Sebaceous adenoma
- Canalicular adenoma and other ductal adenomas

Non-neoplastic epithelial lesions

- Sclerosing polycystic adenosis
- Nodular oncocytic hyperplasia
- Lymphoepithelial sialadenitis
- Intercalated duct hyperplasia

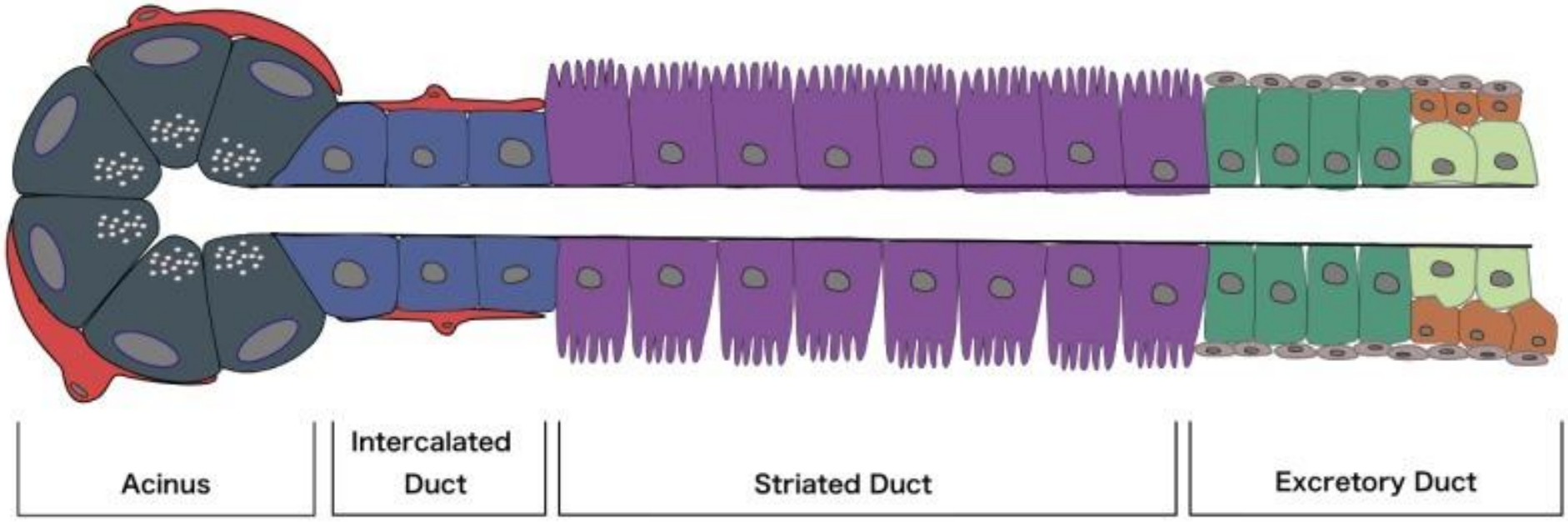
Benign soft tissue lesions

- Hemangioma
- Lipoma/sialolipoma
- Nodular fasciitis

Hematolymphoid tumors

- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

SGT histologies having different anatomical origins

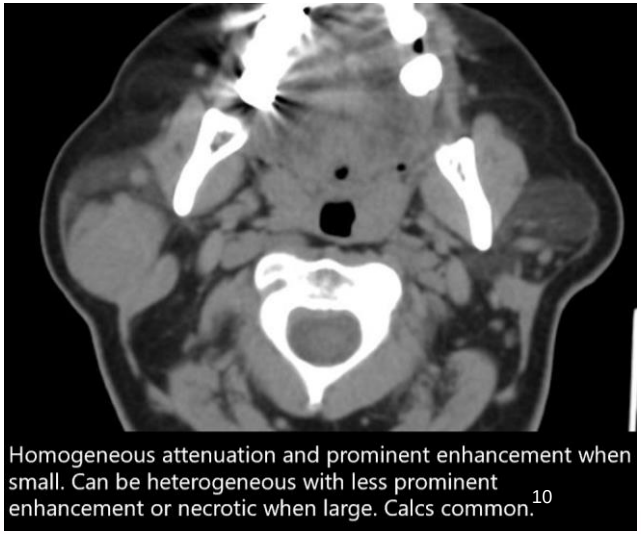


Acinus	Intercalated Duct	Striated Duct	Excretory Duct
Acinic cell ca	Basaloid adenoca Myoepithelial ca Adenoid cystic ca **Pleomorphic adenoma** Epithelial-myoepithelial ca	Warthin's Oncocytic ca	Mucoepidermoid ca Salivary duct ca Adenocarcinoma

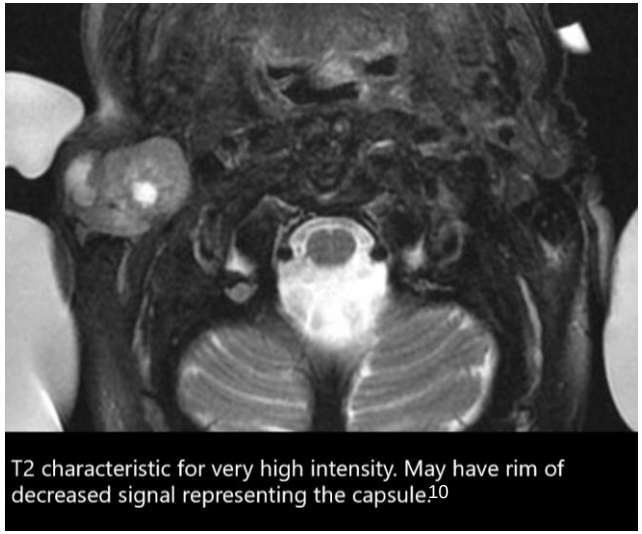
Source: StatPearls[8]

PA often presents as painless swelling

- Painless swelling in 87%
- Advanced disease will have more site-specific symptoms (e.g facial nerve palsy, trismus, pain, or dysphagia for the parotid)
- FNA has 50-85% sensitivity & 75-99% specificity[9]



Homogeneous attenuation and prominent enhancement when small. Can be heterogeneous with less prominent enhancement or necrotic when large. Calcs common.[10]



T2 characteristic for very high intensity. May have rim of decreased signal representing the capsule.[10]

PA has an unclear etiology

Relationships to consider asking on history for any suspected SGT

Viral: EBV, HHV-8, HPV[11-13]

Genetic: KIT, MYB-NFIB, PLAG1, ECT1-MAML2, MAD1L1, HMGIC, HER2/neu, RAS, c-fos, Sox, BCL2, TrkC/NTRK3[16]

Occupational: Hairdresser, mining (asbestos), plumber, automobile manufacturing[14]

Ionizing Radiation[15]

The most evidence (for salivary carcinomas) is previous ionizing radiation at a young age or at least 20 years prior

Management of PAs

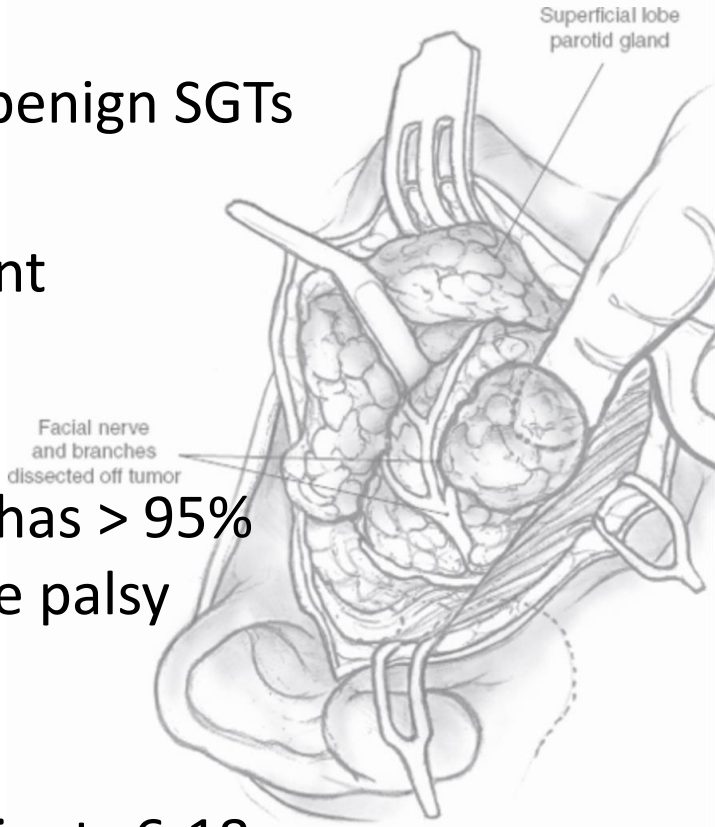
Management of pleomorphic adenomas is similar to most benign SGTs, with the exception of more evidence for radiation treatment in special situations for PAs.

Local Disease	Primary surgical treatment is dependent on location (parotid superficial or deep lobe, submandibular gland, or other gland). **Adjuvant RT is sometimes considered for high-risk features for local recurrence.** **Definitive RT is second-line** for unresectable disease Observation alone for some benign histologies (e.g. Warthin's) may be appropriate.
Neck	Usually no neck dissection or elective nodal irradiation is indicated.
Recurrent Disease	Surgery is first-line **and consideration for adjuvant RT including other high-risk features.** If unresectable, **consider definitive RT**.
Follow-up	In a multidisciplinary clinic with radiation oncologists & H&N surgeons -At least weekly on treatment -2-6 weeks post-treatment for the first follow-up -Years 1-2 at least q3 months (CT/MRI at 10-12 weeks post-treatment) -Year 3 at least q4 months -Years 4-5 at least q6 months -Then annually Fiber-optic nasopharyngoscopy, speech language pathology for pharyngeal/laryngeal function, dental, audiometry, or ophthalmology assessments as clinically indicated

Sources: PMH 2019[21], Thielker 2018[39]

PAs are often treated with surgery alone

- Treatment for PA is similar to that of most benign SGTs with primary treatment being surgery[17]
- If left untreated, PAs have a risk of malignant transformation
  - 2% at 5 years & 10% at 15 years[18]
- Parotid surgery with preservation of CNVII has > 95% chance of cure at 10 years,[18]but facial nerve palsy seen in 5-15% of patients[18]
- Frey syndrome (sweating & flushing in the preauricular area) seen in up to 62% of patients 6-18 months postop[18]
- Salivary fistulas and keloids are less common (<5%)[18]



Parotid PA surgery is limited, but not too limited

Improved local control

Technique	Extent of Surgery	Comments
Enucleation	Shelling out of capsular contents	Not appropriate for most SGTs due to high risk of recurrence (20-45%).
Extracapsular dissection	Removal of tumor with capsule	Technically difficult. Not appropriate for malignant disease.
Partial superficial parotidectomy	SGT + 1-2cm margin.	Margins may not be achievable.
Superficial parotidectomy	Superficial lobe	Requires extensive nerve dissection. Less than 5% risk of recurrence.
Total parotidectomy.	Entire parotid gland.	Considered with deep lobe involvement. Required for most malignant lesions. Higher risk of permanent CN VII injury.

Less CNVII damage

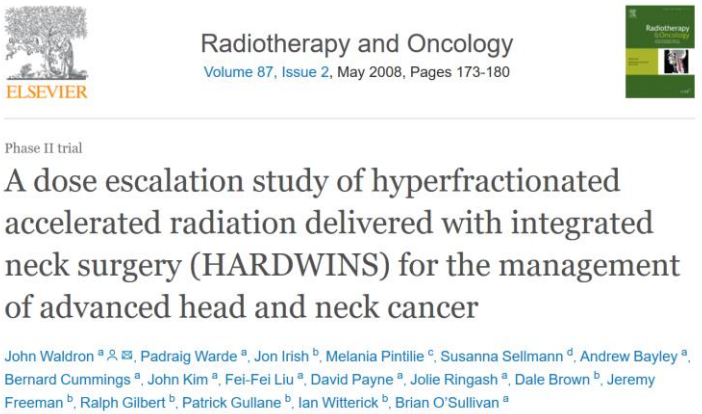
Historically, enucleation alone was used for pleomorphic adenomas to minimize side effects. This was later found to have high local recurrence rates of 20-45% compared to <5% for superficial parotidectomy and enucleation was abandoned.

Definitive Radiation Treatment for PAs

Unresectable gross benign disease may be considered for radiation treatment alone based on limited retrospective data

Off Trial: Definitive RT (70Gy in 35 daily fractions) has only ~40% cure rate at 2-5 years so consider intensification[19,20]

- DAHANCA (70Gy with 6 fractions/wk over 6 wks) or
- HARDWINS (60-66Gy with 10 fractions/wk over 4 wks)



Adjuvant RT for Pleomorphic Adenomas

No mature results from trials. Single-institution series suggest improvements in local control ~10-20% at 10-15 years, especially for high-risk features (e.g. inadequate surgery such as enucleation, positive margins, and multifocal or recurrent disease)[21]

Select studies of the treatment for recurrent pleomorphic adenoma

Study (reference)	*n*	Modality	LC (%)	TTF (y)	FU (y)
Carew *et al.* (27)	31	S/SR	94	6.1	7.3*
Phillips and Olsen (12)	126	S	68	9.9	14.5†
Yugueros *et al.* (23)	39	S/SR	79	7.5	10.0†
Douglas *et al.* (25)	16	SR	85	2.4	6.9*
Glas *et al.* (1)	52	S	85	NA	9.0*
Renehan *et al.* (26)	114	S/SR	85	6.1	14.0*
Fee *et al.* (21)	26	S	65	2.1	NA
Gleave *et al.* (8)	42	SR	95	NA	NA
Niparko *et al.* (22)	48	S	53	6.0	16.1†
Dawson (16)	28	SR	79	NA	8.5†
Leonetti *et al.* (24)	42	S	83	5.4	7.2†
Zbaren *et al.* (13)	33	S	73	8.8	8.3†
Chen *et al.* (UCSF)	34	SR	94	3.3	17.4*

n = number of patients; S = surgery alone; SR = surgery + postop RT; LC = local control; TTF = time to failure; FU = follow-up
✶ median
† mean

Adjuvant RT indications for PAs

High-Risk Features for Local Recurrence of Pleomorphic Adenoma

	Hazard ratio	95% CI	P^*
Univariate analyses			
Age, yr			0.471
<42	1		
≥42	0.624	0.173–2.247	
Sex			0.354
Female	1		
Male	1.864	0.500–6.952	
Duration of symptoms, yr	0.916	0.768–1.092	0.328
Size, cm			
<2	1		
2–4	2.912	0.362–23.402	0.315
≥4	1.790	0.111–28.733	0.681
Pathological subtype			
Cellular type	Infinite	0.993	
Classic type	1		
Myxoid type	2.291	0.635–8.264	0.205
Incomplete capsule			0.457
Absent	1		
Present	1.672	0.432–6.473	
Pseudopodia			0.512
Absent	1		
Present	1.534	0.427–5.519	
Satellite nodule			0.003
Absent	1		
Present	6.782	1.897–24.248	
Resection margin *			0.005
Negative	1		
Positive	6.016	1.732–20.898	
Rupture			<0.001
Absent	1		
Present	20.456	4.454–93.947	
Multivariate analyses			
Satellite nodule			0.010
Absent	1		
Present	5.431	1.486–19.848	
Rupture			0.001
Absent	1		
Present	14.057	3.060–64.571	

*when inadequate margins cannot be managed surgically

Also mentioned in the literature as indications are recurrences, especially multiple recurrences, and multifocal disease[20,22,23]

Postop radiation is not always used for tumor spill or close margins (up to ~90% cure with no further treatment).[17,23]
Consider discussion at a multidisciplinary cancer conference (MCC) for all cases of radiation for pleomorphic adenoma.[23]

Adjuvant RT Schedules for PA

- Microscopic residual disease or other high-risk features:
  - 50Gy in 20 - 25 daily fractions to the tumor bed *
    - Consider elective treatment to the remaining parotid
    - Consider elective treatment to the parapharyngeal space and infratemporal fossa for deep lobe involvement or post-total parotidectomy
- Gross residual disease:
  - 60Gy in 30 daily fractions*
- Usually no elective neck (nodal) irradiation for PA
- Consider including the scar and areas of potential dermal spread, especially for tumor spillage
- **Setup:** Supine, thermoplast mask, neck and knee rest, +/- bolus to the scar and potential areas of dermal spread

*Based on the PMH Guidelines although literature has also described doses up to ~70Gy[20,24]

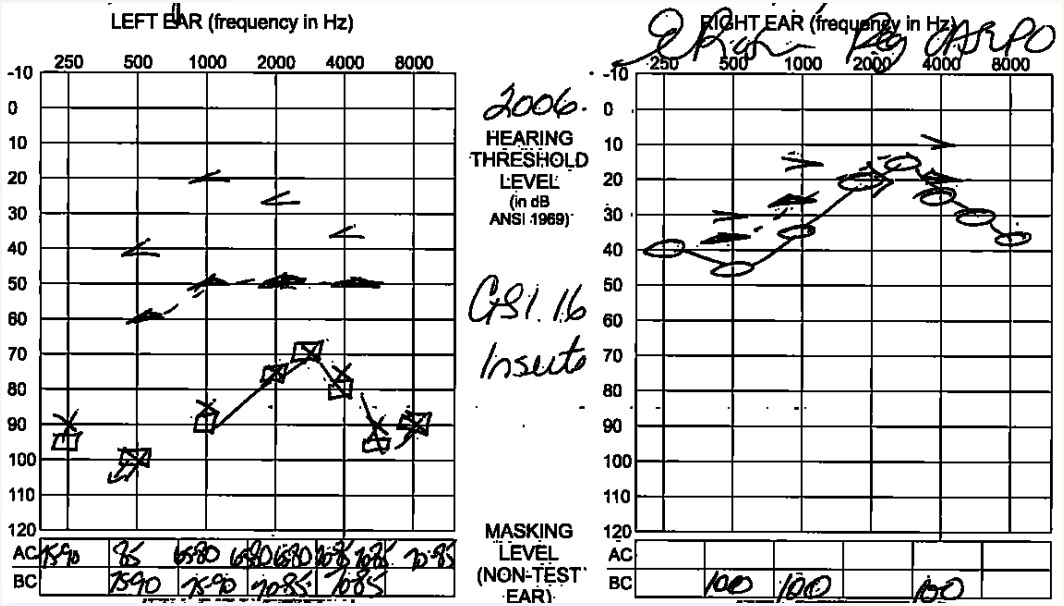
Potential Toxicities

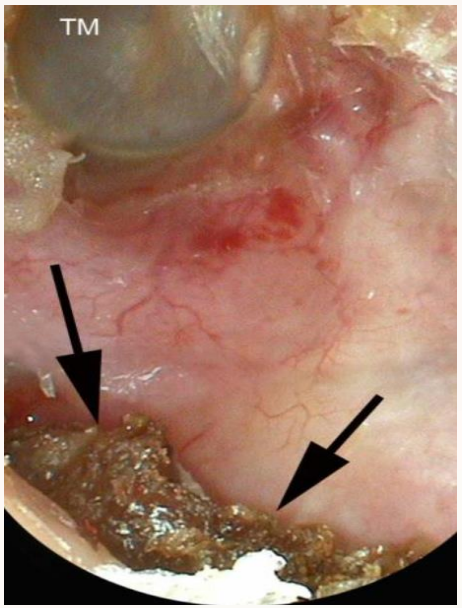
Dermatitis, xerostomia, mucositis, dysgeusia, odynophagia/dysphagia that may require a G-tube, alopecia, **osteonecrosis, otitis**, **hearing loss**, **cholesteatoma,** trismus, fibrosis

7 years later…

Back to the case

- Referred back to ENT for left-sided **hearing loss & a bad smell**
  - Audiometry shows left **sensorineural hearing loss (SNHL)** - hearing aid
  - Examination shows significant wax that is removed to **show skin loss & exposed bone** – debrided every few months including removal of a cyst
  - Settles with Garamycin drops

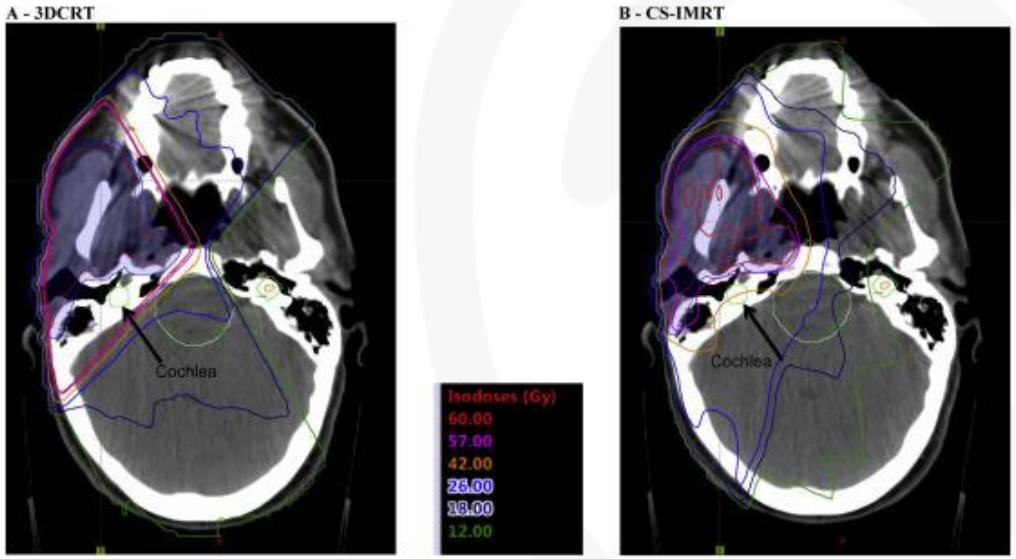




Hearing loss after radiation

- Radiation to the inner ear has been shown to cause sensorineural hearing loss (SNHL) with damage to the stria vascularis, spiral ligament, basilar membrane or cells within the Organ of Corti
- SNHL is described in 30-60% of patients after postoperative 3D Conformal Radiation Treatment (3DCRT) for parotid cancers treated to 60-65Gy in 30 daily fractions
- Ipsilateral cochlea is usually close to the PTV and receives a dose >50Gy with 3DCRT
- IMRT is able reduce the dose to the cochlea to <40-45Gy
- **Can IMRT prevent SNHL with cochlear-sparing (CS-IMRT)?**

CS-IMRT lowered dose to the cochlea



3DCRT

Cochlear Sparing IMRT (CS-IMRT)

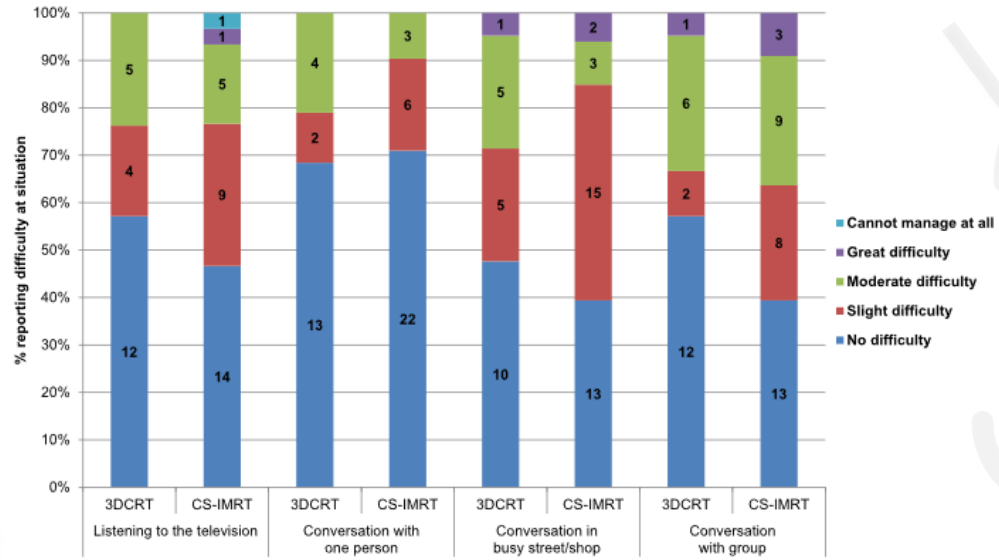
COSTAR [25]
Phase III RCT
110 pts w/parotid cancer
(pT1-4, N0-3, M0)

	3DCRT (N = 54)	CS-IMRT (N = 56)
Radiotherapy dose (Gy)		
Median dose to the primary tumour and involved nodes	65.0 (64.9–65.0; 51)	65.0 (65.0–65.0; 54)
Mean dose to contralateral cochlea	6.1 (2.9–8.8; 51)	8.3 (6.6–9.3; 54)
Mean dose to ipsilateral cochlea[b,c]	56.2 (44.6–61.0; 51)	35.7 (30.0–39.0; 54)

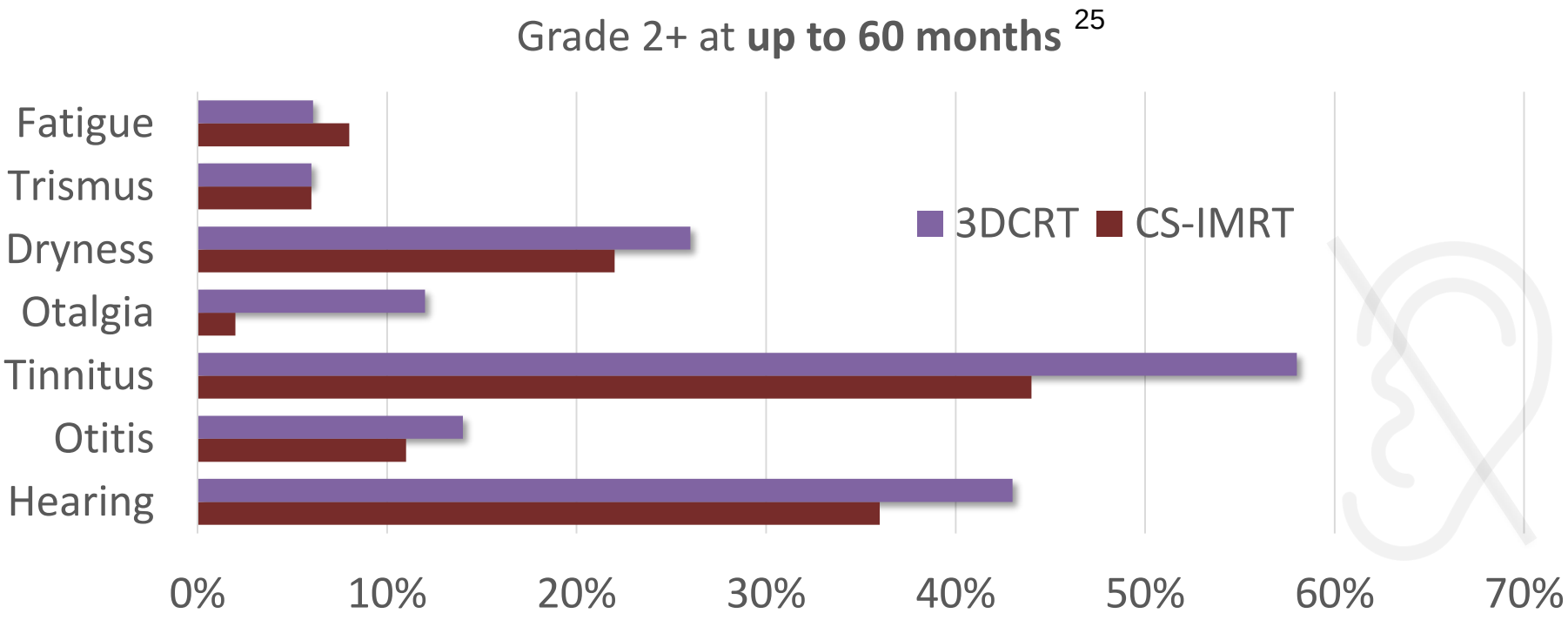
But provided no clinically significant differences in hearing

Audiometry and vestibular function at 12 months after radiotherapy (primary end-point).[25]

Audiometry	N with paired data	Threshold level (dB) at 4000 Hz Median (IQR)			N with ≥10 dB loss	%	p-value for 3DCRT versus CS-IMRT[b]
		Pre-radiotherapy	12 months after radiotherapy	Change[a]			
Bone conduction—Ipsilateral ear[c]							
3DCRT	36	30 (10–42.5)	40 (15–50)	5 (-5–15)	14	38.9	0.81
CS-IMRT	31	20 (10–45)	35 (15–55)	5 (0–10)	11	35.5	
Air conduction—Ipsilateral ear							
3DCRT	42	35 (15–55)	50 (20–70)	10 (0–20)	23	54.8	0.53
CS-IMRT	44	25 (10–45)	40 (15–62.5)	5 (0–22.5)	21	47.7	



COSTAR did help quantify toxicities

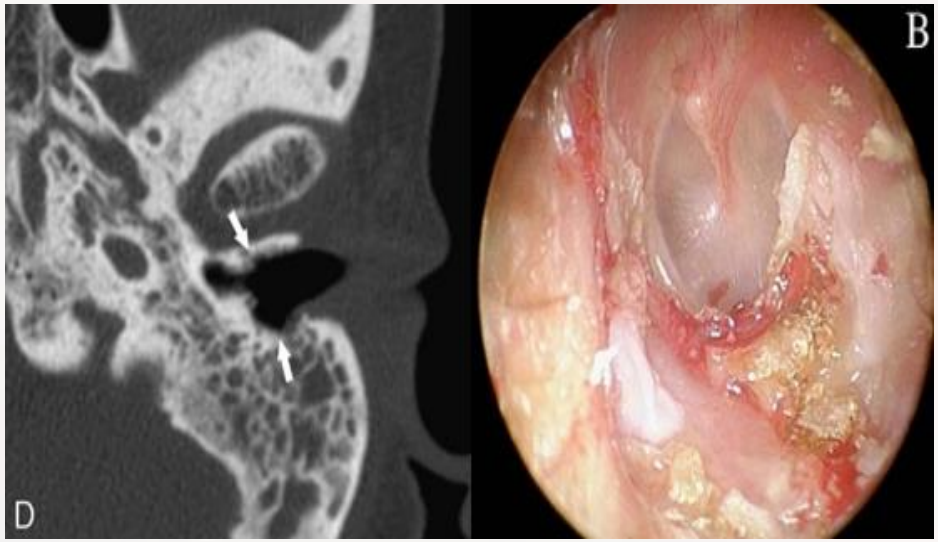


But not osteoradionecrosis…yet

- Osteoradionecrosis (ORN) may be defined as exposed irradiated bone that fails to heal in 3 months without evidence of tumour
- May be caused by radiation arteritis leading to a hypocellular, hypovascular & hypoxic environment
- The temporal bone is at particular risk due to its superficial position (like the mandible) and the external ear canal is more susceptible due to thin overlying skin and poor vasculature
- Osteoradionecrosis of the temporal bone is seen in 10-15% of patients receiving postoperative RT for parotid tumors with **a mean time from treatment of 7-11 years**[26]

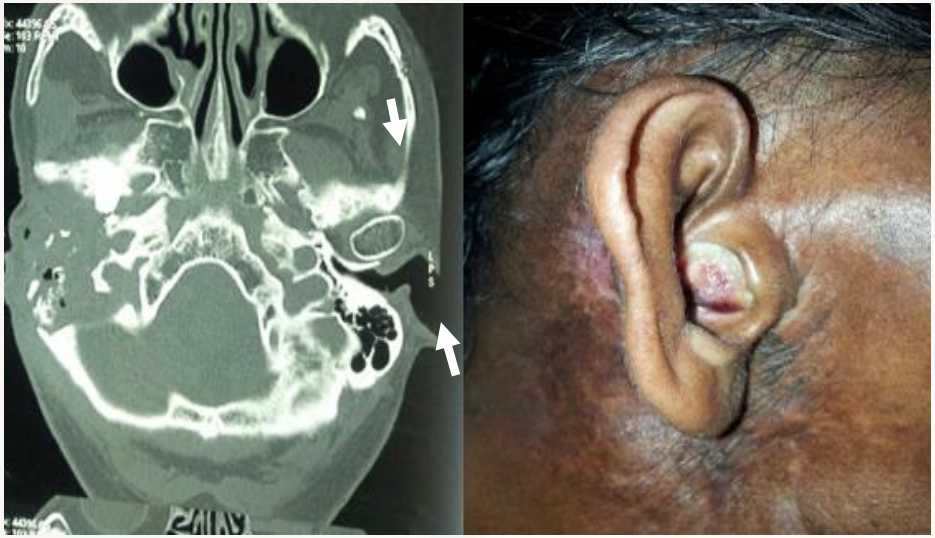
Simple Classification for Temporal Bone ORN

Localized



Presents with exposed dead bone in the external auditory canal (EAC), otalgia, & otorrhea

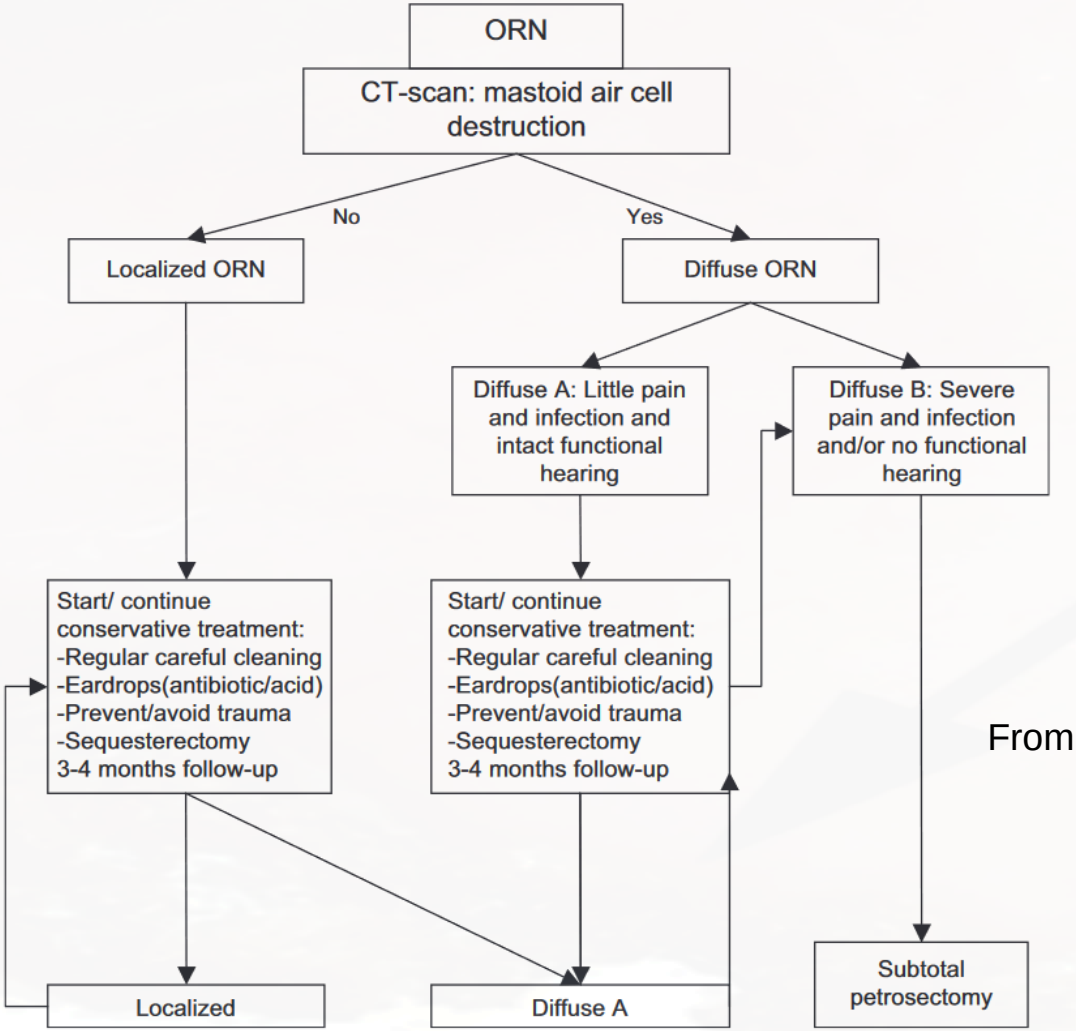
Diffuse



Presents with extensive involvement of the temporal bone, extreme boring pain, +++otorrhea, foul odor, and complications such as mastoid necrosis, fistula, exposed dura, meningitis, brain abscess, & **facial nerve palsy**

Classification described by Ramsden et al.[27] Others include those by Marx, Epstein, Schwartz, & Notani based on a combination of physical & imaging findings

Managing Temporal Bone ORN



From Kammeijer et al.[26]

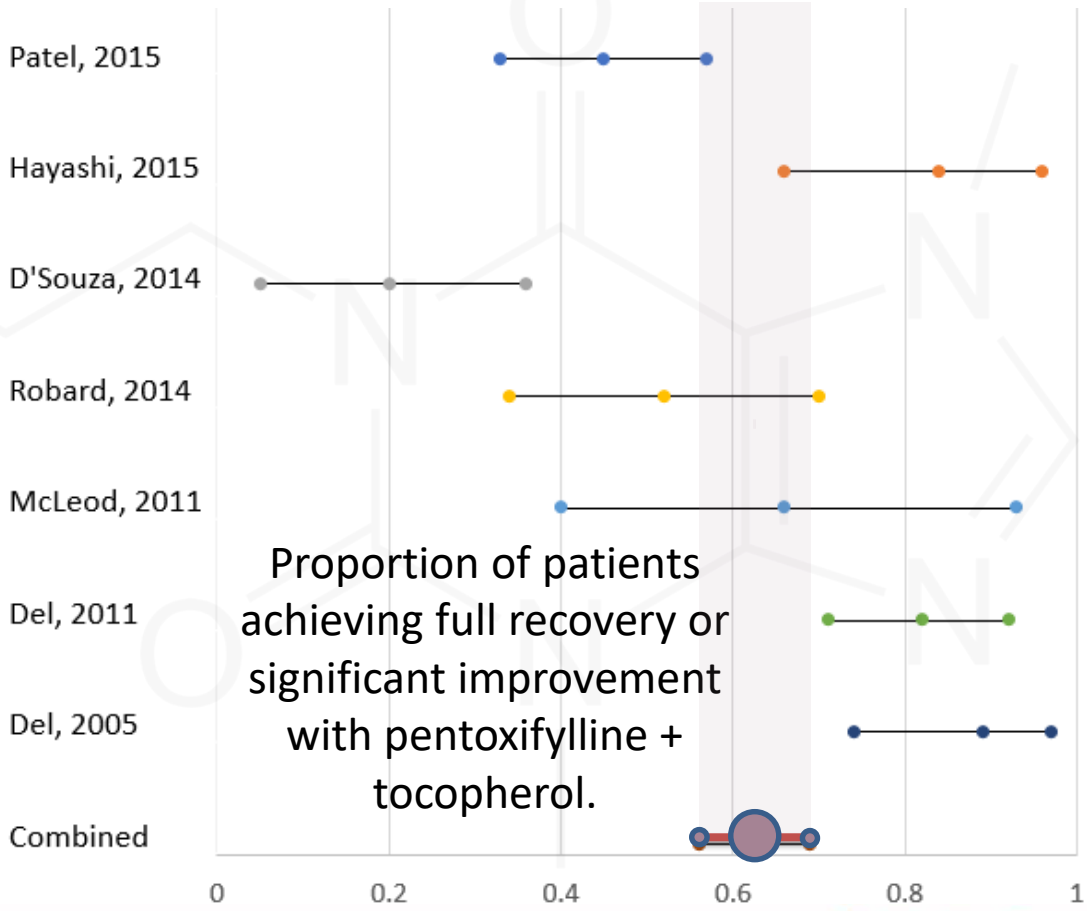
HBOT for ORN?

- Hyperbaric Oxygen Therapy (HBOT): Limited evidence for benefit in ORN
  - 1 RCT & 3 Cohorts
    - Highest level of evidence is from ORN96, a prospective, multi-centre, double-blind RCT terminated early due to worse outcomes in the HBOT arm (19% resolution of ORN with HBOT versus 32% with placebo)[29]
  - Some guidelines such as Dana-Farber (2017) recommend against its use

Pentoxifylline for ORN?

Pentoxifylline: Weak evidence for benefit in 7 retrospective studies[30]

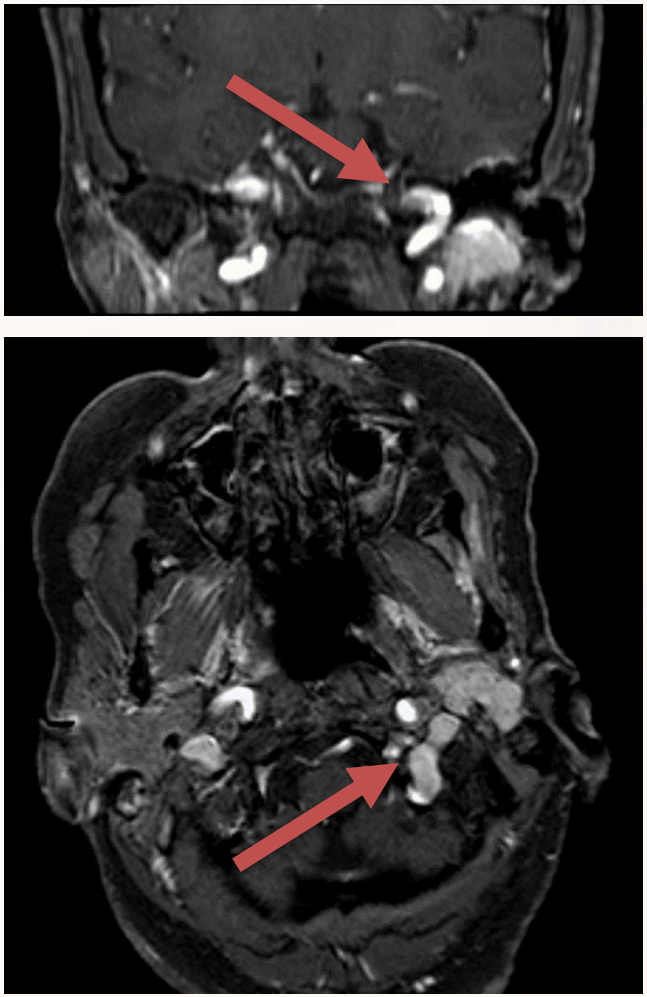
Pentoxyfilline has anti-TNF and vasodilatory effects while decreasing blood viscosity and clotting. Dosing is 200-400mg po tid. It is often given together with Tocopherol (Vitamin E) 1000IU po daily, an antioxidant.



2 years later…

Back to the case

- New left-sided facial spasms
- MRI shows 2 x 2cm mass high in the residual parotid at the skull base surrounding the styloid process
  - Low intensity on T1
  - High intensity on T2
  - Homogeneous enhancement post-Gad
- ENT performs a revision parotidectomy/ debulking
  - A rind was left on the superior carotid and facial nerve to preserve function
  - Final pathology still suggests recurrent PA



6 months later…

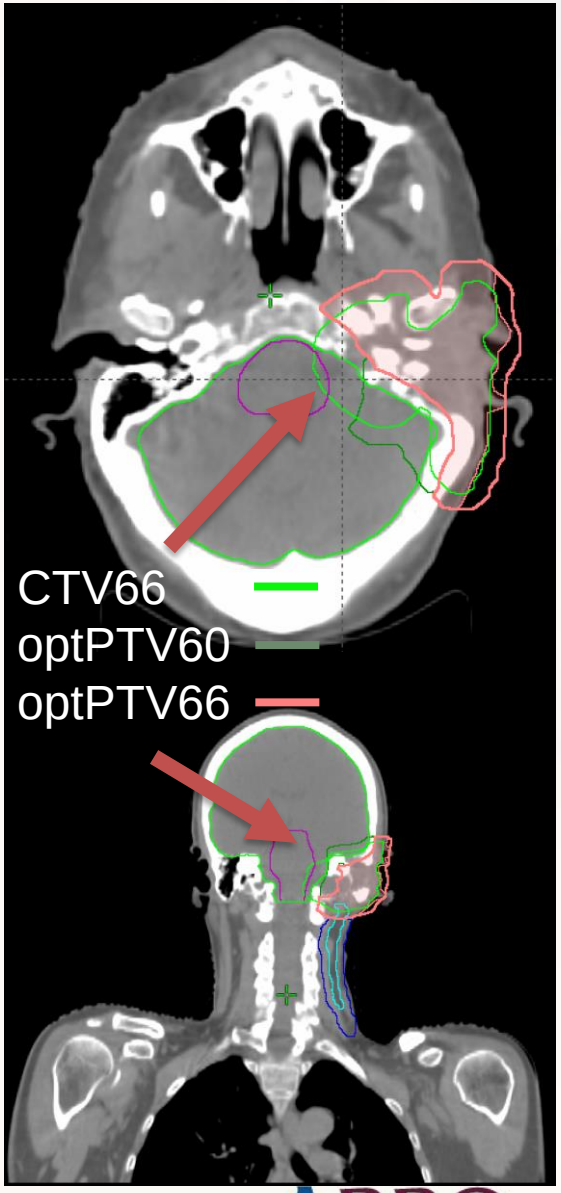
- The mass grew back
- MRI shows a 4cm mass in the parotid bed encasing the carotid artery and **invading the left temporal bone**
  - T1 & T2 heterogenous
  - Also two new satellite nodules
- Another debulking suggests increased cellularity and that **carcinoma could not be ruled out**

Case continued

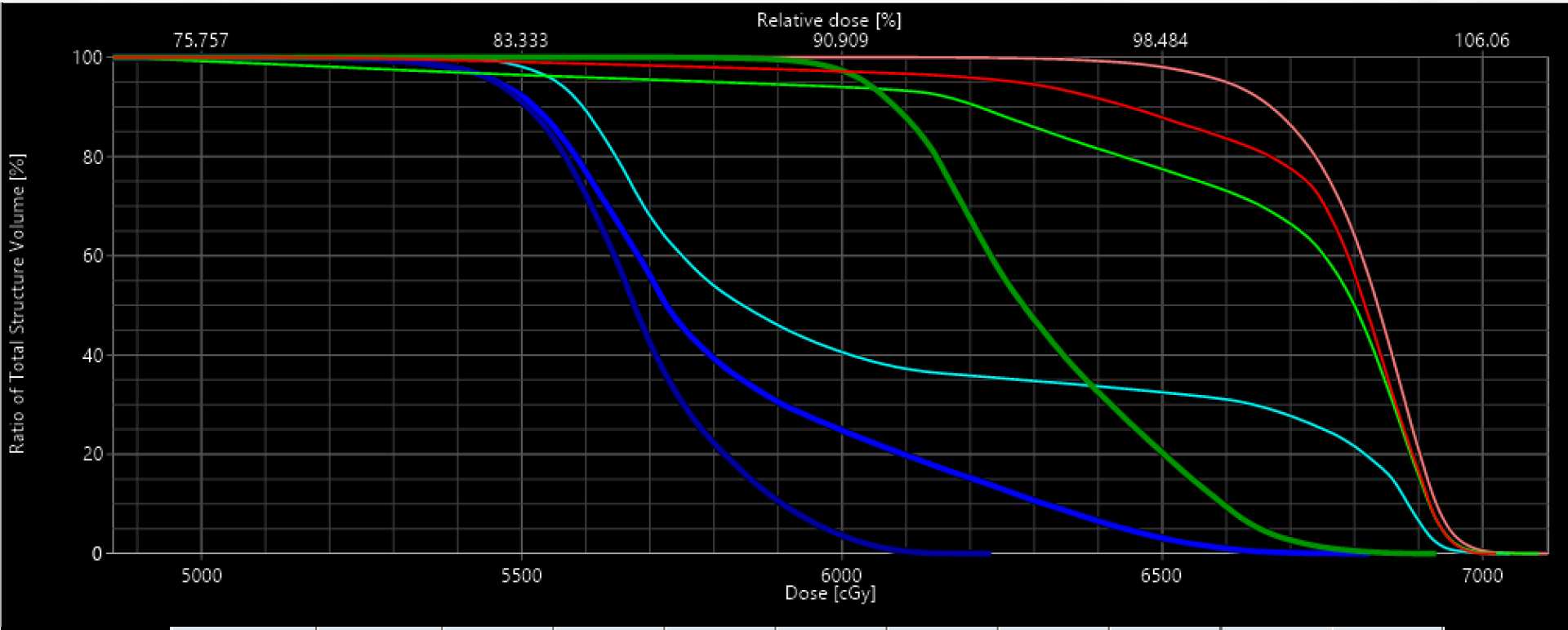
- Based on MRI findings, pathology, & rapid growth she is diagnosed with **Carcinoma Ex Pleomorphic Adenoma (CaXPA)**
- Staging shows no brain, nodal, lung, or bone metastases **(Stage IVB cT4b cN0 M0)**
- MCC suggests no room for further surgery and no role for chemotherapy, but **to consider re-irradiation**

Re-irradiation Treatment Plan

- Diagnostic MRI fused with planning CT
- Gross Disease to 66Gy in 1.1Gy/# BID
  - GTV: Gross mass & the 2 satellite nodules
  - CTV66: GTV + 5mm expansion cropped to anatomical structures not at risk + postoperative bed
  - PTV66: CTV + 3mm expansion
  - **After comparison with the previous plan and estimation of cumulative doses, optPTV is cropped to the brain & brainstem PRV (critical OARs)**
  - **An intermediate dose (optPTV60) is determined to have safe overlap with brain, but still needs to be cropped to the brainstem for safety**
- Elective nodes to 54Gy in 0.9Gy/# BID
  - CTV54: Left levels II-IV
  - PTV54: CTV + 3mm expansion
- Setup: 1.5cm bolus to cover gross disease, supine, arms at side, with thermoplast head & shoulder mask

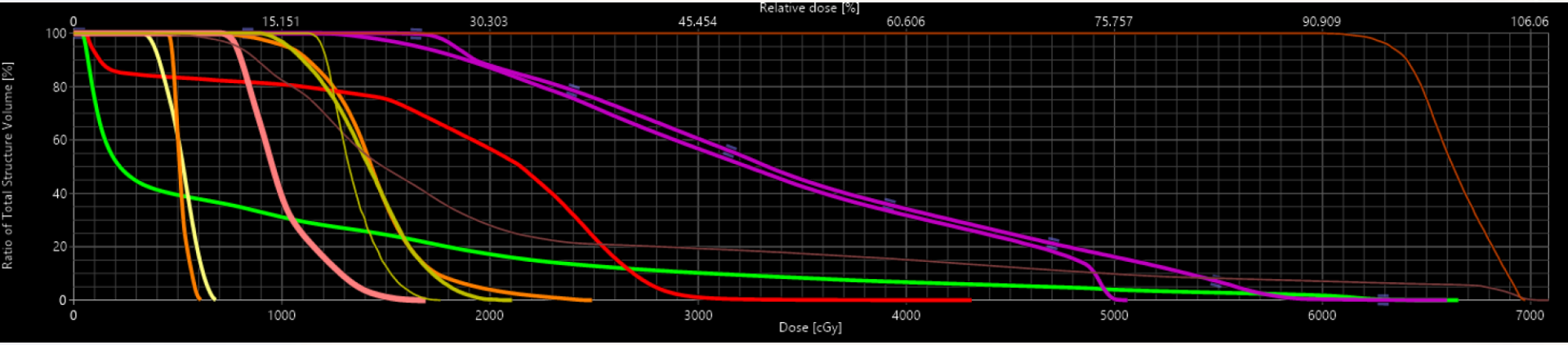


DVHs for the Targets



Show DVH	Structure	Approval...	Plan	Course	Volume [...	Dose Cov...	Sampling...	Min Dose...	Max Dose...	Mean Do...
☑	optPTV66	Approved	PARL	C1	121.8	100.0	100.1	5580.9	7102.9	6813.5
☑	optLPTV54b	Approved	PARL	C1	55.4	100.0	100.0	4958.4	6234.6	5690.2
☑	optLPTV54a	Approved	PARL	C1	20.5	100.0	100.2	4953.5	6824.9	5823.4
☑	PTV60	Approved	PARL	C1	37.7	100.0	100.0	5549.1	6929.4	6314.9
☑	LCTV54	Approved	PARL	C1	35.7	100.0	100.1	5226.4	7044.1	6107.8
☑	GTV	Approved	PARL	C1	45.5	100.0	100.0	5042.3	7021.6	6738.0
☑	CTV66	Approved	PARL	C1	100.3	100.0	100.1	4867.9	7089.1	6645.7

DVHs for the Organs at Risk (OARs)



Show DVH	Structure	Approval ...	Plan	Course	Volume [cm³]	Dose Cover.[...	Sampling C...	Min Dose [c...	Max Dose [c...	Mean Dose [...
☑	BRAIN	Approved	PARL	C1	1165.1	100.0	100.0	38.6	6659.3	1006.2
☑	BRSTEM	Approved	PARL	C1	27.9	100.0	99.9	1161.8	5065.6	3327.2
☑	RPAROTID	Approved	PARL	C1	25.7	100.0	100.0	683.9	2493.4	1441.5
☑	Spinal Canal	Approved	PARL	C1	36.0	100.0	99.9	57.2	4315.4	1831.7
☑	LARYNX	Approved	PARL	C1	24.0	100.0	100.1	1446.0	6605.9	3515.6
☑	LLENS	Approved	PARL	C1	0.2	100.0	100.5	327.7	687.7	519.6
☑	RLENS	Approved	PARL	C1	0.1	100.0	99.6	451.0	611.5	514.3
☑	RSUBMAND	Approved	PARL	C1	4.5	100.0	100.1	889.7	2110.1	1416.5
☑	CHIASM	Approved	PARL	C1	1.4	100.0	100.0	704.1	1696.8	999.3
☑	MANDIBLE	Approved	PARL	C1	51.7	100.0	100.1	364.6	7086.5	2144.9
☑	LCOCHLEA	Approved	PARL	C1	1.4	100.0	100.2	5983.8	6975.1	6632.9
☑	RCOCHLEA	Approved	PARL	C1	1.9	100.0	99.9	1124.7	1764.0	1347.3

Select Dose Constraints

Brain	Dmax < 60Gy	Symptomatic Necrosis	<3%
Brain	Dmax < 72Gy	Symptomatic Necrosis	<5%
Brainstem	Dmax < 54Gy	Neuropathy/Necrosis	<5%
Rt Parotid	Mean Dose <= 26Gy	Salivary flow < 25%	<20%
Lens	Mean Dose <= 7Gy	Cataracts at 5 years	<25%
Rt Submandibular	Mean Dose <= 39Gy	Xerostomia	N/A
Chiasm	Dmax < 50Gy	Optic Neuropathy	<3%
Spinal Canal	Dmax < 48Gy	Myelopathy	<0.2%
Mandible	V70Gy <= 0.1cc	Osteonecrosis	<10%
Lt Cochlea	Dmax < 40Gy	Sensorineural Hearing Loss	<30%
Rt Cochlea	Dmax < 40Gy	Sensorineural Hearing Loss	<30%
Larynx	Mean Dose <= 45 Gy	Edema	<20%
Larynx	V50Gy <= 67%	Aspiration	<30%

*All constraints are in 2Gy per fraction and adapted from RTOG 1008

Consent included these risks, with possible higher rates of complications where tolerances were not met and due to the previous treatment

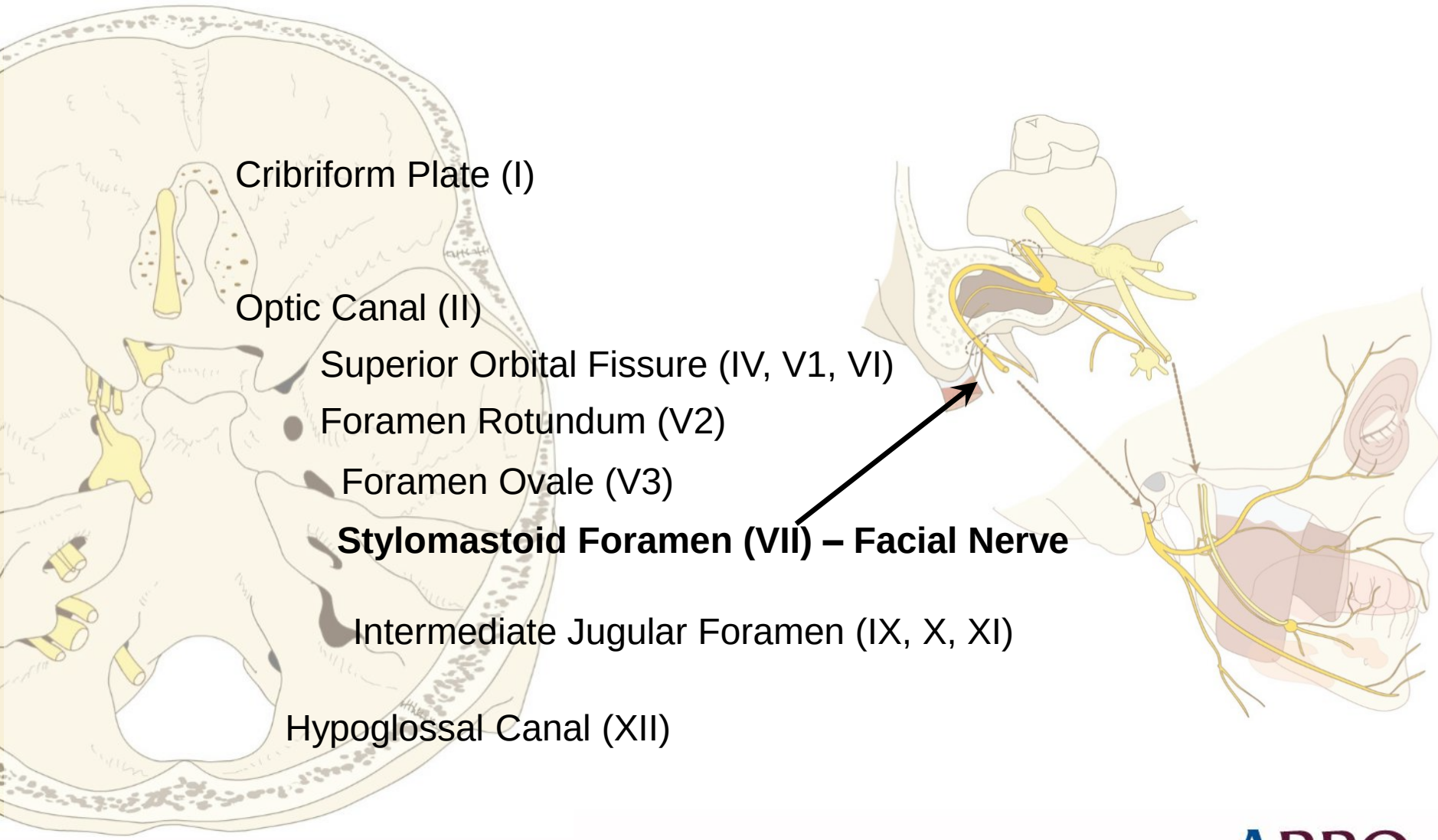
Peer Review and Audit

- The ipsilateral cochlea could not be preserved without compromising coverage to the GTV. Given significant baseline hearing loss, the GTV was not compromised here.
- Coverage for the CTV66, CTV60, and GTV was compromised adjacent to the brainstem to maintain cumulative dose tolerances to this critical OAR. After significant discussion, it was felt that the risks of treating this area including cumulative dose from previous treatment, even with hyperfractionation, outweighed the benefits and the plan was approved.

2 years later…

- She has persistent left-sided hearing loss, mild dysphagia, and mild facial weakness, but is otherwise well

Compressed VII at the base of skull?



Cribriform Plate (I)

Optic Canal (II)

Superior Orbital Fissure (IV, V1, VI)

Foramen Rotundum (V2)

Foramen Ovale (V3)

Stylomastoid Foramen (VII) – Facial Nerve

Intermediate Jugular Foramen (IX, X, XI)

Hypoglossal Canal (XII)

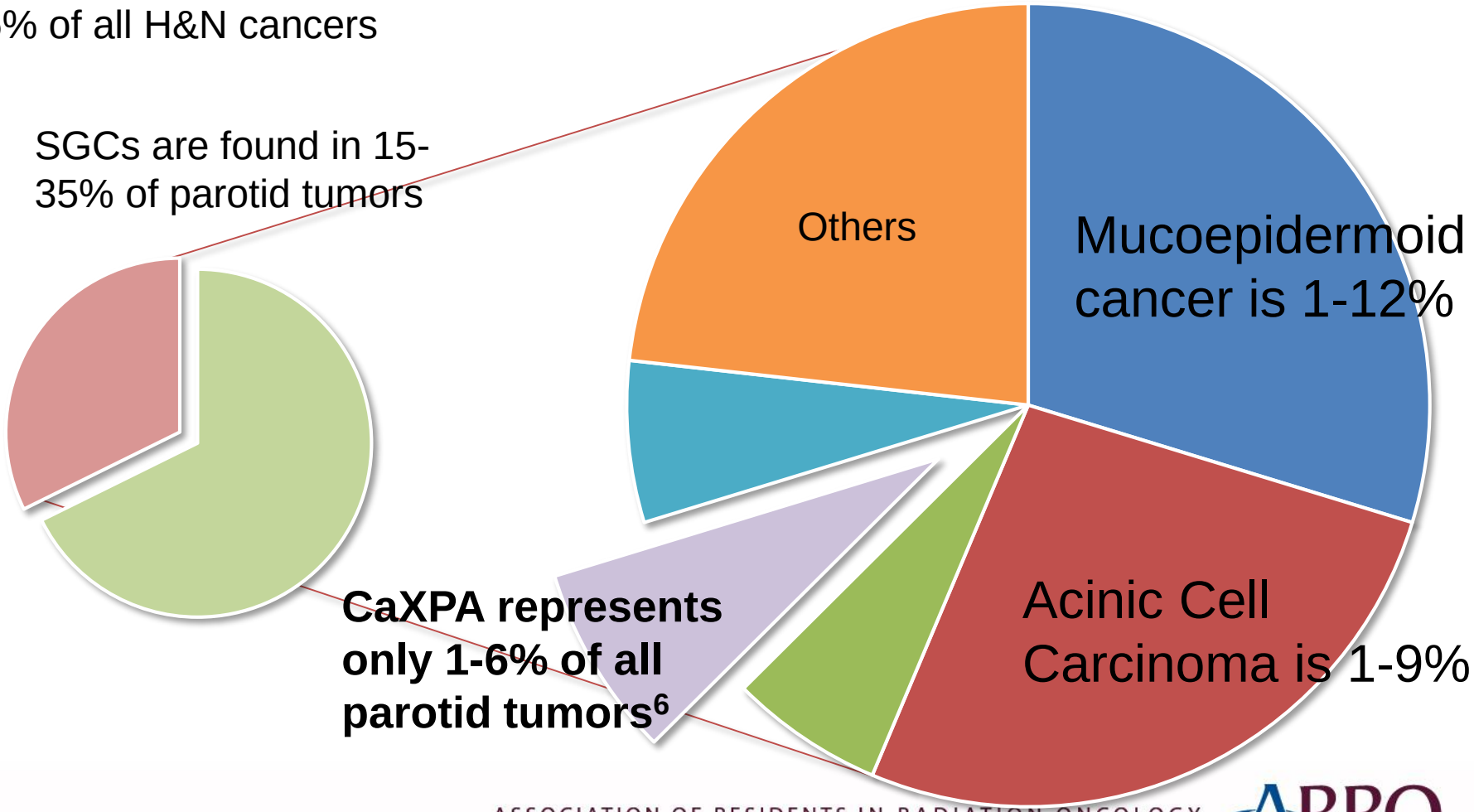
Carcinoma Ex-Pleomorphic Adenoma (CaXPA)

- See CaXPA ARROCase by A Albert et al for more details[1]
- In brief:
  - 4% of SGTs and 12% of salivary gland cancers (SGCs)
  - Develops in association with a pleomorphic adenoma with increasing risk of CaXPA with increasing time of in-situ PA
    - But 80% of patients do not have a prior history of PA
    - Other risk factors include **age, previous ionizing radiation, and larger or recurrent benign disease**
  - Median age is 55
  - Presents **as a sudden increase in growth**, pain, **facial paralysis, tingling, or trismus** (22% local recurrence of another salivary tumor, 56% have nodal metastases, and 44% have distant mets to lung, bone, GI, CNS, or kidneys)
  - Mixed findings on MRI (usually heterogeneous on T1, low on T2,)
    - Apparent Diffusion Coefficient is usually low (compared to high for PAs)
  - Poor survival (25-65% at 5-10 years and 0-38% at 20 years)

CaXPA is a minority

Salivary Gland Cancers (SGCs) represent ~6% of all H&N cancers

SGCs are found in 15-35% of parotid tumors



CaXPA represents only 1-6% of all parotid tumors[6]

Workup & Staging

- Similar workup as for a neck mass
- MRI better for perineural spread & intracranial or parapharyngeal extension
- CT Chest
- Dental, nutrition, & SLP assessment
- Other investigations or multidisciplinary cancer conference as clinically indicated

cT or pT		N0	N1	N2a N2b N2c	N3a N3b
T1	<=2cm	I			
T2	2.1-4cm	II			
T3	>4cm +/- EPE(+)	III			
T4a	Invasion[1]	IVA			
T4b	Invasion[2]	IVB			
M1	Distant Mets	IVC			

N Stage (pN or cN)

N1 Single ipsilateral LN ≤ 3cm and ENE(–)

N2 a. Single ipsilateral LN 3-6cm and ENE(–)

b. Multiple ipsilateral LNs ≤ 6cm and ENE(-)

c. Bilateral or contralateral LNs ≤ 6cm and ENE(-)

N3 a. LN > 6cm and ENE(-)

b. LN > 3cm and ENE(+)

AJCC 8th Edition (2017). Nodal staging is the same as for other H&N cancers. Major changes include addition of N3a & b categories. EPE = extraparenchymal extension. ENE = extranodal extension. [1]T4 is moderately advanced disease invading the skin, mandible, or ear canal. [2]T4b is very advanced disease invading the skull base and/or pterygoid. For major salivary glands only. Tumors from minor salivary glands are staged according to SCCs.

Treatment for Salivary Gland Cancers

Local Disease	Extent of primary surgical treatment depends on location (parotid, submandibular gland, or other gland), T/N-status, and grade. **Adjuvant RT is based on high-risk features for local recurrence. Definitive RT is second-line for unresectable disease**
N0 Neck	Lack of consensus. Consider observation for benign or low-grade malignancies. Elective neck dissection (II-V, +/- I) for high-grade*, T3+, submandibular involvement, EPE(+), or LVI. **Elective neck RT for high-risk features of nodal spread.****
N+ Neck	Selective neck dissection (II-V, +/- I or based on involved nodal location) **and adjuvant RT**.
Recurrent Disease	Surgery is first line **and adjuvant RT if feasible.** If unresectable, **consider RT** +/- systemic treatment. If unresectable and RT not feasible, consider systemic treatment.
Metastatic Disease	Usually palliative RT or systemic treatment. Metastectomy may be considered for select patients depending on site (e.g. limited lung mets), when the primary is controlled, complete resection of mets is possible, and patient can tolerate surgery.
Follow-up	Similar schedule as for pleomorphic adenoma Long-term follow-up is strongly recommended, especially for certain tumor types like Adenoid Cystic Carcinoma that have a protracted course Includes chest imaging

*retrospective studies suggest high-risk pathology is more important than stage for nodal spread and usually warrants a neck dissection.[31]
**some guidelines suggest elective neck RT for high-risk features in undissected neck regions[21]

Adjuvant RT indications for SGCs

High-Risk Features

Local Recurrence

High-risk pathologies:

- Adenocarcinoma
- Salivary duct carcinoma
- High-grade mucoepidermoid ca
- Adenoid cystic ca
- CaXPA
- Other high-grade tumours

Positive margins

Perineural invasion or spread (microscopic or major nerve)

Deep parotid lobe cancer

Relative

T3+

Close margins (<1-5mm)

Bone involvement

Submandibular gland primary

Nodal Recurrence

High-risk pathologies

Locally Advanced (T3+ or N+)

Extracapsular extensions (ECE)

Relative

LVI

Facial nerve paralysis

RTOG 1008 allows omitting elective nodal radiation for early Adenoid Cystic Carcinomas (pT1-2 N0)

Sources: PMH Guidelines 2019, UICC 2015, RTOG 1008 2012, Hsieh et al, Terhaard et al 2004.[21,31-33]

Radiation Schedules for SGCs

Still no mature data from RCTs so guidelines are based on several retrospective studies that have consistently demonstrated benefit of adjuvant RT in select patients with high-risk features

Unresectable	Definitive RT may provide local control (~40% vs. 81% for surgery + RT at 10 years) & symptom palliation
	Fast Neutron Therapy is rarely used due to lack of availability
	May consider proton or carbon ions on clinical trials
	Target volumes are similar as in the adjuvant setting 70 Gy in 35 daily# to gross disease
Adjuvant*	For **high-risk features, adjuvant RT** may provide absolute benefit up to ~30-40% in LC & 40% in OS at 5-years[1]
	Boost to 66Gy in 33 daily# for close (≤ 1-5mm)/+margin or +pathologic extracapsular nodal extension (+ECE)
	60Gy in 30# for regions at high risk for microscopic disease (tumor bed or involved nodal regions)
	54-56Gy in 30-33# for elective nodal regions (indications include high-risk path or advanced ca (T3+, N+)) For involvement of a major nerve, consider coverage (54-56Gy) along course to skull base IMRT/VMAT is usually used to spare OARs
Reirradiation (Re-RT)**	Clinical trial if available (including proton or carbon ion)
	If no clinical trial consider re-RT* +/- systemic treatment

Sources: Mendenhall 2005, PMH Guidelines 2019, UICC 2015, RTOG 1008 2012[21, 31, 32]

*For detailed treatment volumes see Appendix 4

**For reirradiation treatment strategies see Appendix 5

Not so fast…photons are still used more than neutrons

- RTOG-MRC phase III compared fast neutrons to photons for unresectable SGTs[35]
  - Neutrons significantly improved local control (56% vs. 17% at 10-years) and less distant metastases, but no difference in OS
  - Severe late effects and limited centres around the world are why this technique is rarely used

- Protons and carbon ions are experimental and may reduce late toxicities[37]

What about Chemoradiation?

- RTOG 1008 is an ongoing randomized phase II comparing adjuvant chemoradiation (CRT) vs. RT alone for SGCs treated with surgery. Doses of 60-66Gy in standard (2Gy) fractionation +/- concurrent Cisplatin.[32]
  - Study complete date is October 2028
- GORTEC SANTAL is an ongoing phase III including SGCs and nasal tumors also comparing adjuvant CRT vs. RT alone. **Doses of 66-70Gy** in standard fractionation +/- concurrent Cisplatin.
- Retrospective studies comparing adjuvant CRT to RT in resected SGCs with high-risk features using multivariate and propensity-matched analyses showed mixed results:
  - One that only including adenoid cystic carcinoma suggested improved local control with CRT (97% vs. 67% at 8-years), even better on subgroup analysis with Stage III-IV disease, margin+, or PNI
  - Two suggested no difference in OS or PFS
  - Two suggested inferior OS

Re-Irradiation (Re-RT) for SGCs

- Many locoregionally recurrent H&N cancers after radiation cannot be salvaged by surgery
- Response rates for chemotherapy in this setting is limited (median survival 7.4 months)[14]
- Re-irradiation is potentially curative for some patients with unresectable disease, but…
  - theoretical risk of development of **radiation resistance** (in a cancer that is generally radioresistant) and dose is important
  - increased risk of **severe complications**

Severe Re-RT Toxicities

Acute	Mucositis	Grade 3-4 in 14%–26% of patients
Late	Dysphagia	
	Spinal cord myelopathy	Significant recovery after at least 6 months since the initial treatment, with continued recovery to 2-3 years May be <1% for cumulative dose < 60Gy accounting for recovery (e.g. 50% at one year)
	Carotid artery rupture	3% at a median of 7.7mos 76% are fatal Usually seen with accelerated or hypofractionated regimens
	Osteoradionecrosis	In < 7%
Death		In 5-20% From infection due to leucopenia, aspiration, and fatal hemorrhage from carotid rupture

Source: Kim et al, 2017[36]

Prognostic Factors for Re-RT

For better local control & overall survival	For less toxicities
Salvage surgery or debulking prior to re-RT	Lower cumulative dose to OARs
Site (Naso, larynx, & neck > others)	No concurrent chemotherapy
Histology/Low Grade	Older age
More time since prior RT	Mucosal involvement/ulceration
Higher delivered dose	Larger volumes
T Stage/Size	Re-RT schedules (1.1Gy BID > 1.5Gy BID)
Concurrent chemotherapy	Modality (PBT > 3DCRT)
No previous chemotherapy	
Younger Age	

Source: Kim et al, 2017[36]

Future Directions

- Answer the chemotherapy question:
  - RTOG 1008 results pending
  - GORTEC SANTAL is recruiting
- Bring targeted therapies to mainstream practice[38]
  - Phase I/II trials ongoing
  - For advanced/recurrent/metastatic SGCs NCCN suggests treatment for targetable mutations based on limited evidence such as:
    - Complete androgen blockade for androgen receptor+
    - Larotrectinib for NTRK gene fusion+
    - Trastuzumab for HER2+
- Improve understanding of predictive features for recurrence to improve patient selection for radiation
- Develop improved radiation strategies for unresectable disease or re-irradiation

Salivary Gland Tumor Summary

- Salivary Gland Tumors are rare, and as a result so is the evidence for their management
- Surgery is first-line for benign and malignant disease
- Adjuvant radiation is indicated for features suggesting high-risk for local or nodal recurrence
- Definitive radiation treatment is indicated for unresectable disease
- Re-irradiation is possible

APPENDIX

1: References

2: Photo References

3: Epidemiology of Salivary Gland Tumors by Site

4: Adjuvant RT Volumes for RTOG 1008

5: Reirradiation Treatment Strategies

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Appendix 3: Epidemiology of Salivary Gland Tumors by Site

TABLE 56-1 Sites of Occurrence of Primary Epithelial Salivary Gland Tumors

AUTHOR	NO. CASES	SITE OF OCCURRENCE			
		PAROTID	SUBMANDIBULAR	SUBLINGUAL	MINOR
Ellis et al.[5]	13,749	64%	10%	0.3%	23%
Spiro[4]	2,807	70%	8%	Included with minor	22%
Seifert et al.[3]	2,579	80%	10%	1.0%	9%
Eveson and Cawson[2]	2,410	73%	11%	0.3%	14%

TABLE 56-2 Frequency of Malignant Salivary Tumors at Different Sites

AUTHOR	NO. CASES	PERCENTAGE OF MALIGNANT CASES			
		PAROTID	SUBMANDIBULAR	SUBLINGUAL	MINOR
Ellis et al.[5]	13,749	32%	41%	70%	49%
Spiro[4]	2,807	25%	43%	Included with minor	82%
Seifert et al.[3]	2,579	20%	45%	90%	45%
Eveson and Cawson[2]	2,410	15%	37%	86%	46%

TABLE 56-3 Parotid Tumors

	ELLIS ET AL.[5]	EVESON AND CAWSON[2]	THACKRAY AND LUCAS[7]	ENEROTH[8]	FOOTE AND FRAZELL[9]
Total number of cases	8,222	1,756	651	2,158	764
Benign Tumors					
Pleomorphic adenoma	53.0%	63.3%	72.0%	76.8%	58.5%
Warthin tumor	7.7%	14.0%	9.0%	4.7%	6.5%
Oncocytoma	1.9%	0.9%	0.6%	1.0%	0.1%
Basal cell adenoma	1.4%	—	—	—	—
Other	3.7%	7.1%	1.8%	—	0.7%
Total	67.7%	85.3%	83.4%	82.5%	65.8%
Malignant Tumors					
Mucoepidermoid carcinoma	9.6%	1.5%	2.3%	4.1%	11.8%
Acinic cell carcinoma	8.6%	2.5%	1.2%	3.1%	2.7%
Adenoid cystic carcinoma	2.0%	2.0%	3.3%	2.3%	2.1%
Malignant mixed tumor	2.5%	3.2%	4.1%	1.5%	6.0%
Squamous cell carcinoma	2.1%	1.1%	1.0%	0.3%	3.4%
Other	7.5%	4.4%	4.7%	6.3%	8.1%
Total	32.3%	14.7%	16.6%	17.5%	34.2%

Source: Neville et al, 2009[6]

Appendix 4: Adjuvant RT Volumes - RTOG 1008

All SGCs

PTVx: 2.5-5mm margin on the corresponding CTVx

PTV3: Boost to 66Gy in 33# for close (≤ 1mm) or +margin, or +pathologic extracapsular nodal extension (+ECE)*

PTV2: 60Gy in 30# over 6wks for regions at high risk for microscopic disease**

PTV1: 54Gy in 30# for elective nodal regions considered at risk or coverage to the base of skull for gross involvement of a major nerve

Parotid Gland

CTV1: Primary

Preop volume of the involved parotid gland (GTV) and postop surgical bed***

Infratemporal fossa to the stylomastoid foramen

Surgical scar

+/- Deep lobe (post-superficial parotidectomy)

+/- Parapharyngeal space (for deep lobe tumors or post-total parotidectomy)

+/- Facial nerve canal through the petrous bone to the foramen ovale (if gross CN VII PNI or for Adenoid Cystic Carcinoma)

CTV1: Elective nodal regions

Usually ipsilateral II-IV****

+/- Ipsilateral Ib and retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

Submandibular & Sublingual Gland

CTV1: Primary

Preop volume (GTV) & postop surgical bed*** including entire submandibular space

Surgical scar

+/- Up to the hypoglossal canal (if gross XII involvement)

+/- Up to the foramen ovale (if gross lingual or inferior alveolar n. involved)

+/- Proximal mandible to the mandibular foramen (if gross inferior alveolar n. involved)

CTV1: Elective nodal regions

Usually ipsilateral Ib-IV****

+/- Contralateral I & II (if ipsilateral level I involved)

+/- Retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

Minor Salivary Gland

CTV1: Primary

Preop volume (GTV) and postop surgical bed***

+/- Along any named nerve to the skull base (if gross involvement)

Surgical scar

Preop volume (GTV) and postop surgical bed***

CTV1: Elective nodal regions

Usually ipsilateral Ib-IV****

+/- Contralateral neck (for primaries <1cm from the midline)

+/- Retrostyloid (if level II involvement)

+/- Ipsilateral V (if level II, III, or IV involvement)

*CTV3 includes the postop surgical bed +5mm margin & entire nodal level of any pathological ECE+ nodes

**CTV2 includes the postop surgical bed & site of involved named nerves +1cm margin & the entire nodal level of any N+

***Usually GTV + 1.5 - 2cm margin respecting anatomic boundaries not at risk for microscopic disease

****Elective nodal irradiation may be omitted for the N0 neck in early Adenoid Cystic Carcinoma (pT1-2)

Appendix 5: Re-RT Treatment Strategies

Unresectable	Re-RT indications are similar to other definitive RT SGC cases with consideration for time from last treatment (>6 month disease-free interval)
	Re-RT can provide local control, symptom palliation, and may be potentially curative
	>60-66Gy may be tumoricidal and dose thought to be important (~40% recur in high-dose region)
	No consensus for technique, volumes, or schedule – consider a clinical trial
	Hyperfractionation of 1.2-1.2Gy BID may be effective in sparing late-responding normal tissues
	Hypofractionation or ablative doses (~30Gy/5#) may overcome radioresistance
	PBT and Carbon ion are investigational
	PBT may decrease acute and late toxicities due to minimal entrance and exit[37]
	Carbon ion may be more biologically effective without increasing toxicity
	Volumes are based on a balance of risk and benefit and should consider cumulative doses
	IMRT CTVp: ~0.5-2cm from the GTV
	CTVn: no consensus due to unexpected lymph drainage in previously treated necks. May consider similar guidelines as for untreated necks
Adjuvant	Adjuvant re-RT indications are similar to other adjuvant RT SGC cases with consideration for time from treatment
	No consensus for technique, volumes, or schedule; consider as above
Chemotherapy	No consensus – consider a clinical trial
	Phase III (RTOG 1008) results are pending, GORTEC-SANTAL is recruiting, and retrospective results are mixed
	Phase II trials for targeted therapies are ongoing
	EORTC-1206-HNCG RCT for CT vs. ADT in AR+ SGCs

Sources: Kim 2017, Romesser 2016 [36,37]