Paraganglioma of the Skull Base

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Case Presentation

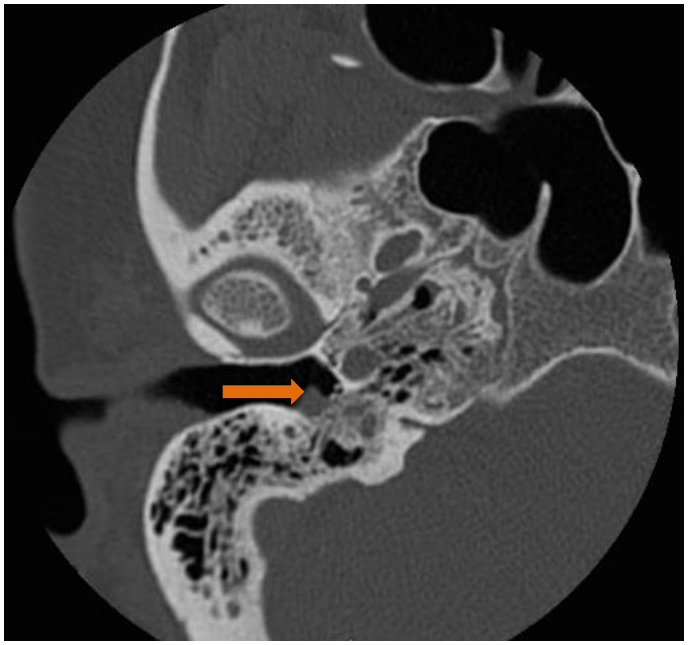
- 63-year-old female presents with right-sided progressive conductive hearing loss for several years
- Mild pulsatile tinnitus
- No other neurologic complaints
- Physical exam: Red-purple mass located behind right tympanic membrane, no cranial nerve (CN) deficits

Case Presentation

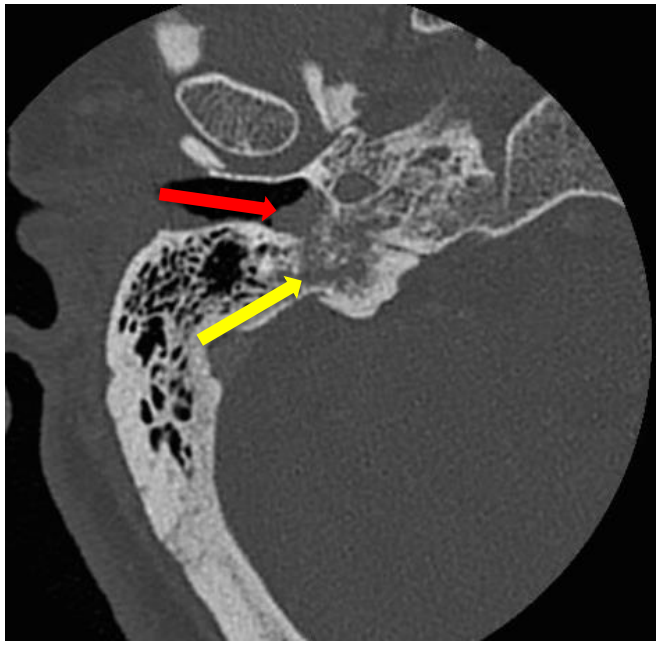
- CT temporal bone and MRI internal auditory canal: 4 mm soft tissue mass along the right cochlear promontory consistent with a glomus tympanicum
- Underwent right tympanoplasty with tumor resection, with pathology demonstrating paraganglioma
- Lost to follow-up until 4 years later, with progressive disequilibrium, right sensorineural hearing loss, and right pulsatile tinnitus

Case Presentation

- Repeat CT temporal bone (right; orange arrow denotes tumor) in comparison to initial pre-operative CT (left):
  - Evidence of recurrence in right middle ear cavity in the hypotympanum (red arrow) with new moth-eaten osseous destruction of the temporal bone (yellow arrow)



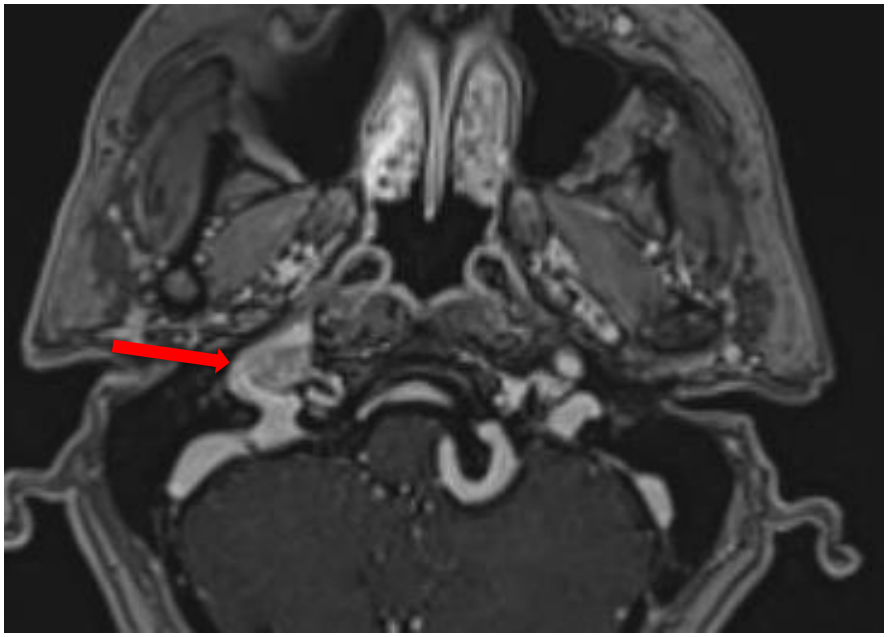
Pre-operative CT 2013



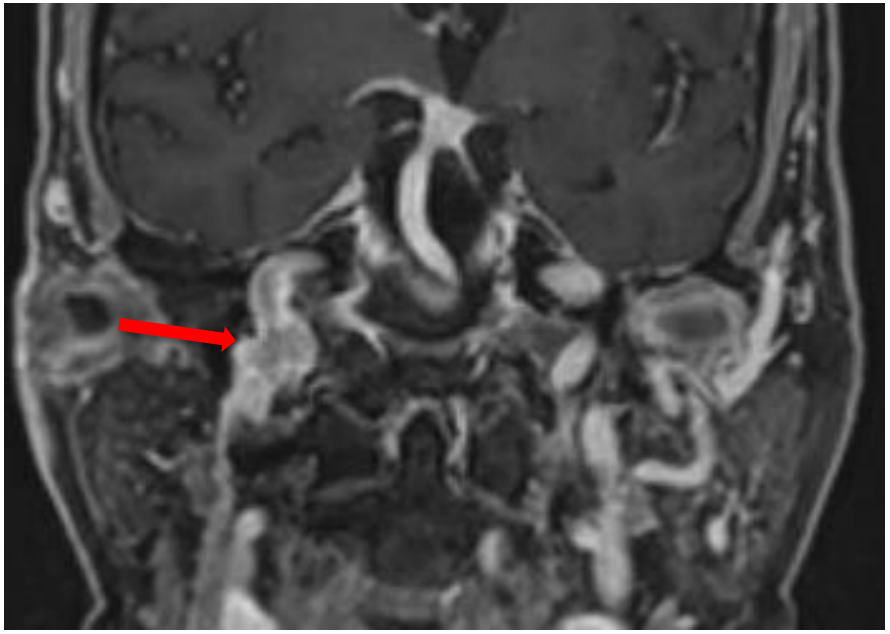
Repeat CT 2017

Case Presentation

- MRI brain with contrast:
  - Enhancing tumor (red arrow) along the medial margin of the right internal jugular vein, centered at the right jugular foramen with slight extension below the foramen.



T1+Contrast: Axial Plane



T1+Contrast: Coronal Plane

Background

- Affects approximately 1 case per 1.3 million patients per year
- Most common tumor of the middle ear
- Female predominance
- Most occur in patients aged 40-70
- Mostly benign, but <5% can metastasize

Terminology

- Jugulotympanic paraganglioma are also termed:
  - Glomus jugulare tumors
    - Arise from Jacobson nerve (branch of CN IX) or Arnold nerve (branch of CN X) within the jugular foramen
  - Glomus tympanicum tumors
    - Arise from the Jacobson nerve in the middle ear/cochlear promontory

Pathophysiology

- Neuroendocrine tumors arising from autonomic paraganglia (small organs of neuroendocrine cells derived from the embryonic neural crest)
- Most parasympathetic paragangliomas are non-secreting, distributed along vascular or neural structures of the skull base and neck
- Histologically, they are comprised of clusters of chief cells in a highly vascular stroma
- Can be locally invasive within the temporal bone/skull base and adjacent structures

Classification

- Fisch Classifications:
  - Type A: Limited to middle ear cleft/arise along tympanic plexus
  - Type B: Invasion into hypotympanum/limited to tympanomastoid area with no infralabyrinthine compartment involvement
  - Type C: Involves the infralabyrinthine compartment of the temporal bone, extending to the petrous apex
  - Type D: Intracranial extension

Classification

- Glasscock-Jackson:
  - Type 1: Involves jugular bulb, middle ear, mastoid process
  - Type 2: Extends under internal auditory canal
  - Type 3: Extends into petrous apex
  - Type 4: Extends beyond petrous apex into clivus or infratemporal fossa
    - Note: Types 2-4 may have intracranial extension

Clinical Presentation

- Gradual onset of symptoms
- Middle ear involvement: Conductive hearing loss, ear fullness, pulsatile tinnitus, otorrhea; otalgia is uncommon
- Involvement of inner ear: Vertigo, sensorineural hearing loss
- CN IX-XI involvement: Dysphonia, dysphagia, loss of gag reflex
- Intracranial involvement: Headache, nausea

Work-Up

- Thorough neurologic and otoscopic exam
- Audiogram
- CT temporal bone with contrast and with thin slicing
  - Delineates extent of osseous involvement
- MR brain with contrast
  - “Salt and pepper” appearance of intermixed high-intensity signals and signal voids: represents fast flowing blood
- MR angiogram may be helpful for further tumor delineation

Treatment options

- Observation
  - Asymptomatic, tumor size <2-3 cm
- Surgery
  - Early stage tumors: Tympanoplastic resection
  - More advanced tumors or those with jugular involvement: Resection using infratemporal approach
- Radiotherapy
  - Often used when resection would require extensive sacrifice of critical vascular or neural structures as well as for recurrent tumor after prior surgery
  - May utilize either fractionated external beam radiation therapy (EBRT) or stereotactic radiosurgery (SRS) approaches

Surgical Treatment

- Tympanoplastic surgery
  - Low risk of damage to cranial nerves
- Resection using infratemporal
  - More extensive
  - One systematic review of retrospective series reports high risk of post-operative cranial neuropathies

Radiotherapy: Principles

- Goal: Achieve durable radiographic and clinical stability
- However, tumors often to not regress in size
  - Locally symptomatic lesions should be considered for surgery when anatomically feasible

Systematic Review: RT vs Surgery

- Suarez et al: Systematic study examining efficacy and safety of surgery (n=715 in 41 studies), fractionated RT (n=461 in 20 studies), and SRS (n=254 in 14 studies) for jugular paragangliomas (JPGs)
- Mean duration of follow up: 65.6 months
- Surgery vs RT in JPGs:
  - Tumor control: 78.2% vs 91.5% (SS)
  - Major complications: 28.2% vs 11.4% (SS)
  - CN palsies after treatment (per patient): 0.9 vs 0.08 (SS)
- Conventional EBRT vs SRS in JPGs:
  - Tumor control: 89.1% vs 93.7% (NS)
  - Major complications: 10.4% vs 6.5% (NS)
  - CN palsies after treatment (per patient): 0.15 vs 0.002 (NS)
- Conclusions: EBRT and SRS offer similar chance of tumor control with lower risks of morbidity compared to surgery in patients with JPGs.

Retrospective Series: Fractionated RT

- Dupin et al: Retrospective series examining survival and toxicity outcomes for head and neck paraganglioma patients (n=66) receiving fractionated RT (mean dose 45 Gy in 25 fractions)
- Median follow up: 4.1 years
- Outcomes:
  - Local control: 100% at 5 years, 98.7% at 10 years
  - Cause-specific death: 2 patients within 6 months following RT
  - Acute toxicity: 9 patients hospitalized for weight loss, nausea, mucositis, or ophthalmic zoster
  - Late toxicity: 2 patients with vascular complications (middle cerebral artery and carotid stenosis) and 2 patients with RT-related meningiomas 15 and 18 years post-treatment
- Conclusion: Conventional fractionated EBRT is effective and safe, and achieves excellent local control.

Systematic Review: SRS

- Guss et al: Systematic review and meta-analysis of data on management of jugular paraganglioma tumors using SRS (n=335 patients in 19 studies) with either Gamma Knife-, CyberKnife-, or linear accelerator-based technologies.
  - Clinical control of 95% and tumor control of 96% at mean or median follow up time of > 36 months

Retrospective Series: SRS

- Sheehan et al reports a multicenter retrospective analysis examining outcomes after SRS in 132 patients undergoing 134 procedures.
- Median dose 15 Gy; median follow up 50.5 months
- Outcomes:
  - Overall tumor control: 93% at 5 years
  - Pulsatile tinnitus improved in 49% of patients
  - New or progressive CN deficits noted in 15% of patients
  - Improvement in preexisting CN deficits noted in 11% of patients
- Conclusions:
  - Gamma knife SRS was well tolerated, provides high rate of local control, and improves symptomatic tinnitus in approximately ½ of patients.
  - Overall neurologic status and CN function were preserved or improved in the majority of patients after SRS.

Radiotherapy: Treatment Planning

- Fractionated EBRT:
  - Dose: 45-50.4 Gy at 1.8-2 Gy/fraction to the PTV
- SRS:
  - Dose: 12-15 Gy in single fraction to ~50% isodose line
- Choice of approach depends on tumor size, normal tissue constraints, and tumor delineation.

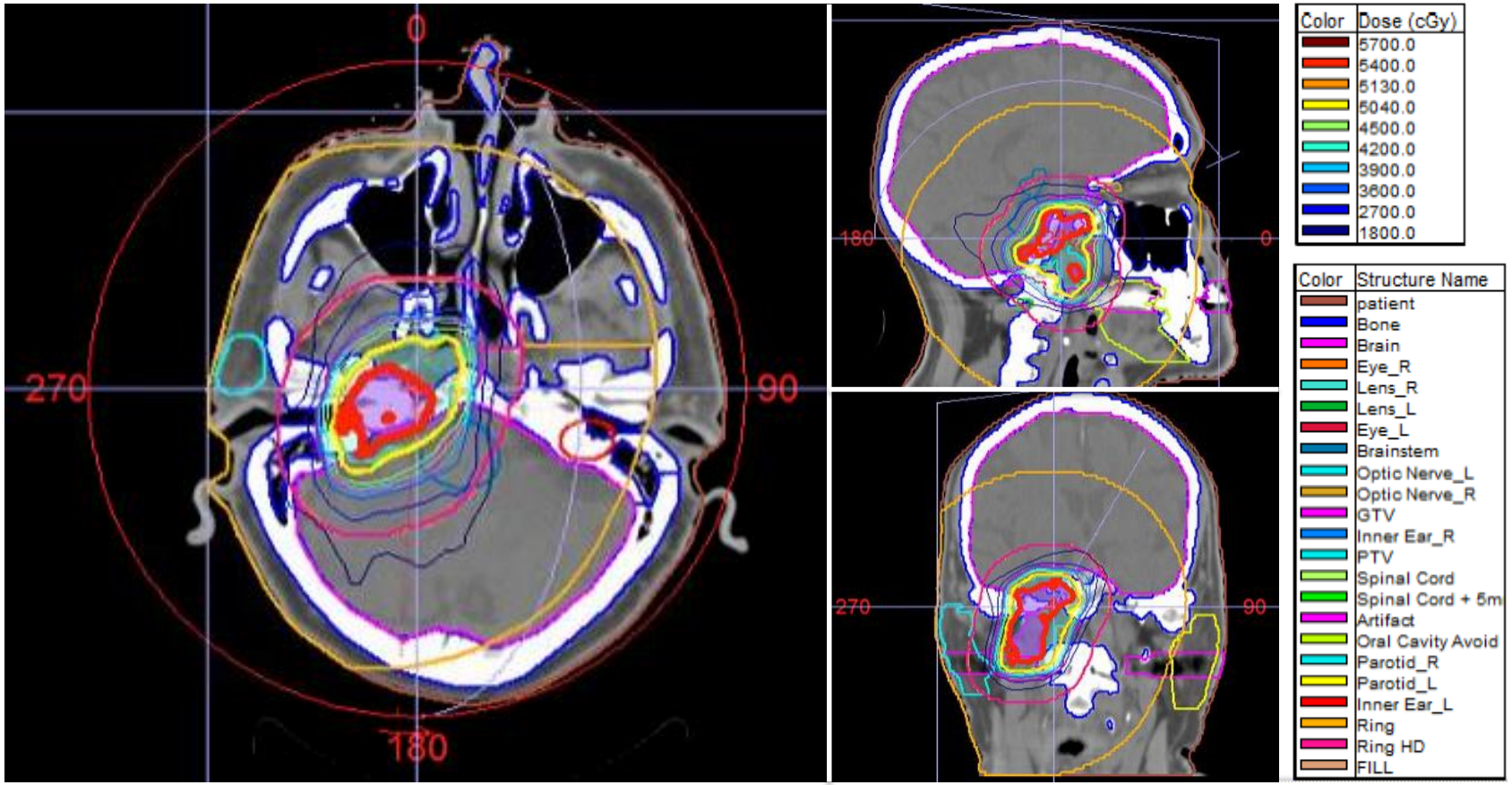
Radiotherapy: Treatment Planning

- Target Definition:
  - GTV: Grossly visible disease as defined by contrast-enhanced CT and/or MRI
  - CTV: Typically none is used unless the disease is poorly defined
  - PTV: 1-5 mm depending on image-guidance and immobilization

Case Presentation: Fractionated RT

- Given the concern for tumor delineation on MR for SRS planning, the patient underwent fractionated RT to a dose of 50.4 Gy in 28 fractions at 1.8 Gy per fraction.

Case Presentation: Treatment Planning



Case Presentation: Treatment Planning

- DVH Summary:

Structure	Constraint, #Fx
PTV Constraints	
GTV	V(5400 cGy) ≥ 95%. 28 Fx@193 cGy/Fx.
PTV	V(5040 cGy) ≥ 95%. 28 Fx@180 cGy/Fx.
OAR Constraints	
Eye_L	Dmax ≤ 2000 cGy
Eye_R	Dmax ≤ 2000 cGy
Lens_L	Dmax ≤ 300 cGy
Lens_R	Dmax ≤ 300 cGy
OpticNerve_L	Dmax ≤ 5400 cGy
OpticNerve_R	Dmax ≤ 5400 cGy
Brainstem	Dmax ≤ 5600 cGy
Inner Ear_L	Dmax ≤ 4500 cGy Dmax ≤ 4500 cGy
Inner Ear_R	Dmax ≤ 4500 cGy
Spinal Cord	Dmax ≤ 4500 cGy

Structure Name	cc	Dose cGy	Volume %/cc	Volume Delta	Min cGy	Min Delta	Mean cGy	Mean Delta	Max cGy	Max Delta
GTV	13.68	5400	95.09%	0.09	5258		5481		5662	
PTV	46.32	5040	97.56%	2.56	4462		5356		5662	
Eye_L	7.50				62		133		383	1617
Eye_R	8.87				71		242		765	1235
Lens_L	0.30				72		91		118	182
Lens_R	0.28				121		156		197	103
Brainstem	32.44				797		2624		5230	370
Inner Ear_L	2.23				479		620		790	3710
Inner Ear_R	2.36				2106		4545		5651	-1151
Spinal Cord	6.65				81		408		1647	2853
Optic Nerve_L	0.75	5400	0.00%		114		440		1299	
Optic Nerve_R	0.89	5400	0.00%		322		1154		1816	

Note: Delta is the difference between the achieved and wished values.

Toxicities

- Acute: Fatigue, skin reactions, transient mucositis, ear congestion, middle ear effusion, xerostomia
- Long-term: Decreased hearing, hypopituitarisim, xerostomia; more rarely, osteomyelitis, bone necrosis, brain necrosis, vascular compromise due to stenosis

Follow-Up

- Extrapolated from NCCN, clinical and radiographic follow up every 6-12 months for the first 3 years, then annually thereafter for 10 years, as recurrence can take several years to present

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