Paragangliomas

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Grand Rounds Presentation
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Introduction-History

• Von Haller 1743-1st paragangliomic tissue, carotid body,
• Function remained unclear for decades
• Von Luschka 1862, Marchand 1891
  – Carotid Body Tumors
• Scudder 1903-removal of carotid body tumor
Introduction-History

• Anatomists described ganglionic tissue Jacobson’s nerve 1840
• No assoc. with paraganglioma until 1941
• Guild 1953- Vascularized tissue of jugular bulb and middle ear; glomic tissue
Introduction-Nomenclature

- Glomus tumors, chemodectoma, non-chromaffin tumors, carotid body tumors
- Glenner and Grimely 1974

Table 1. CLASSIFICATION OF PARAGANGLIONIC TISSUE

<table>
<thead>
<tr>
<th>Adrenal</th>
<th>Extra-Adrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma</td>
<td>Branchiomeric</td>
</tr>
<tr>
<td></td>
<td>Aorticopulmonary</td>
</tr>
<tr>
<td></td>
<td>Coronary</td>
</tr>
<tr>
<td></td>
<td>Intercarotid</td>
</tr>
<tr>
<td></td>
<td>Jugulotympanic</td>
</tr>
<tr>
<td></td>
<td>Laryngeal</td>
</tr>
<tr>
<td></td>
<td>Nasal</td>
</tr>
<tr>
<td></td>
<td>Orbital</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td>Subclavian</td>
</tr>
<tr>
<td></td>
<td>Intravagal</td>
</tr>
<tr>
<td></td>
<td>Aorticosympathetic</td>
</tr>
<tr>
<td></td>
<td>Visceroautonomic</td>
</tr>
</tbody>
</table>
Correct terminology: paragangliomic tissue by location

Carotid body, glomus tympanicum, glomus jugulare persist
Introduction

- 90% pheochromocytoma
- 10% extra-adrenal
  - 85% abdomen
  - 12% thorax
  - 3% head and neck
- Carotid body most common
- Jugulotympanic
- Vagal
- Other
Introduction

• 1:30,000 head and neck tumors
• Malignancy determined by mets, poss all locations
  – 6% carotid body
  – 5% jugulotympanic
  – 10 to 19% vagal
  – 3% laryngeal
  – 17% sinonasal
• Survival data not accurate
  – 60% 5-year regional mets
  – Distant mets worse
Classification

• Mascorro and Yates
  – Paraganglion system- neuroectoderm-derived chromaffin cells in extra-adrenal sites

• Vital in fetal development
  – Source of catecholamines prior to adrenal medulla formation

• Secrete, store, release on neural/chemical signal
Pathology

- Type I: chief cells/granular cells
  - Organoid-nested pattern - Zellballen
- Type II: sustentacular cells
- Capillaries
Pathology

• Type I
  – Intracytoplasmic organelles, dense-core granules
  – Catecholamines, tryptophan-containing protein
  – APUD/diffuse neuroendocrine system
Pathology

- Nuclear atypia variable, no correlation with behavior
Pathology

- **Immunohistochemistry**
  - **Type I cells**
    - Neuron-specific enolase, chromogranin A, synaptophysin, serotonin
  - **Type II cells**
    - S-100, glial fibrillary acidic protein
## Differential Diagnosis

1. **WORLD HEALTH ORGANIZATION CLASSIFICATION OF ENDOCRINE NEOPLASMS**

<table>
<thead>
<tr>
<th>Origin</th>
<th>Type</th>
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<tbody>
<tr>
<td>Epithelial</td>
<td>Classical carcinoid</td>
</tr>
<tr>
<td></td>
<td>Atypical carcinoid</td>
</tr>
<tr>
<td></td>
<td>Small cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td></td>
<td>Oat cell</td>
</tr>
<tr>
<td></td>
<td>Intermediate cell</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
</tr>
<tr>
<td>Neural</td>
<td>Paraganglioma</td>
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</table>
### Differential Diagnosis

**Table 3. IMMUNOHISTOCHEMICAL MARKERS IN NEUROENDOCRINE NEOPLASM OF LARYNX**

<table>
<thead>
<tr>
<th></th>
<th>Paraganglioma</th>
<th>Typical Carcinoid Grade 1</th>
<th>Atypical Carcinoid Grade 2</th>
<th>Small Cell Neuroendocrine Carcinoma Grade 3</th>
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</thead>
<tbody>
<tr>
<td>Chromogranin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Calcitonin</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin (low molecular weight)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Carcinoembryonic antigen</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
<td>-</td>
<td>+</td>
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**Table 4. DIFFERENTIAL DIAGNOSIS OF LARYNGEAL TUMORS**

<table>
<thead>
<tr>
<th></th>
<th>Paraganglioma</th>
<th>Typical &amp; Atypical Carcinoid</th>
<th>Melanoma</th>
<th>Renal cell Carcinoma</th>
<th>MTC</th>
<th>HP</th>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>NSE</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Calcitonin</td>
<td>-</td>
<td>+</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-100</td>
<td>+*</td>
<td>+/−*</td>
<td></td>
<td>+</td>
<td></td>
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<td>Keratin</td>
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<td>CEA</td>
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<td>+</td>
<td></td>
<td>+</td>
<td></td>
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<tr>
<td>HMB-45</td>
<td>−</td>
<td>−</td>
<td></td>
<td>+</td>
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</tbody>
</table>
Figure 1. Biochemical pathway for production of epinephrine.

normal to elevate blood pressure. Patients should be as
Biology

• Paraganglioma neuropeptides
  – Norepinephrine, serotonin, vasoactive intestinal peptide, neuron specific enolase

• 1-3% functional

• Norepinephrine levels 4-5 times normal to elevate BP

• Symptoms
  – HA, palpitations, flushing, perspiration
Biology

• Labs
  – 24-hour urine
    • Norepinephrine, metabolites: vanillylmandelic acid, normetanephrine
    • Excess epinephrine, metanephrine suspect pheochromocytoma

• Treatment- alpha and beta antagonists
Syndromes

• **MEN IIA-Sipple’s syndrome**
  – RET proto-oncogene chromosome 10
  – Medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia

• **MEN IIB**
  – RET but different site
  – Mucosal neuromas

• **Von Hipple-Lindau**
  – Retinal angiomas, cerebellar hemangioblastomas

• **Carney’s complex**
  – Gastric leiomyosarcoma, pulmonary chondroma, extra-adrenal functional paragangliomas
Familial paragangliomas

- 10% of cases
- Most commonly bilateral CBP
- Chromosomes 11q13.1, 11q22-q23
- Autosomal dominant
- Genomic imprinting
  - Only expressed if father passes gene
- ? Higher incident with hypoxia due to altitude or medical conditions
Carotid Body Tumor

• Most common head and neck paraganglioma
• Most common bilateral tumor
  – 10% overall multiple
  – Familial pattern 30-50% multiple tumors
CBP multicentric/family management

- MR of entire H&N
- Long-term f/u to detect metachronous tumors
- Isolated CBP, neg family history, family PE only
- Multiple paragangliomas - entire family MRI screening
CBP

- 45 yrs- avg age presentation
- Slight female predilection
CBP

• Presentation
  – 4-7 yrs first sx and diagnosis, slow growth
  – Presents lateral cervical mass
  – Less mobile cranio-caudal
  – Pulsatile
  – Bruit-disappear with carotid compression
  – Soft and elastic to firm, non-tender
  – 10% CN palsy, most common vagal
CBP-Imaging

- MRI/MRA
  - Vascular insight
  - Occult tumors-0.8 cm
  - T1, T1 post gad, T2, axial FLAIR, FSE T2
  - Skull base to thoracic inlet
CBP-Imaging

- Angiography
  - No longer 1st line
CPB-Imaging

– Preoperative embolization
  • Controversial
  • 24-48 hrs prior to surgery
  • Avoid revascularization, edema, local inflammation
  • Balloon occlusion-EEG, technetium 99 SPECT scanning
    – 90% specificity to tolerance of collateral cerebral circulation
**CBP-Classification**

- Shamblin 1971
  - Type I
    - Localized easily resected
  - Type II
    - Adherent partially surrounding vessels
  - Type III
    - Completely encased carotids
- 70% are type II or III
CBP-Therapy

- Observation, Surgery, Radiation Therapy
- Surgery
  - < 5cm, neurologic injury 14%
  - > 5cm, vagal nerve, other complication 67%
  - Cerebrovascular complication < 5%
  - Overall CN complication 20%
  - Multidisciplinary approach
    - H&N surgeon, vascular surgeon
CBP

• Surgery
  – Proximal and distal control with vessel loops
  – Identification and preservation of neural structures if possible
  – Periadventitial, white line (plane of Gordon)
  – Preparation for vascular reconstruction if necessary
    • Suture repair, patch grafting, interposition saphenous vein graft
  – Routine shunting not recommended
    • Use only in failed balloon occlusion
    • Vascular complications 6.4%
    • Mortality 1.6 %
CBP-Radiation

- Local control-no evidence of tumor progression following therapy with long term f/u
- Most will show some regression, other remain stable
- Florida
  - 23 lesions- 19 primary, 4 post surgery
  - Most common 45 cGy 25 fractions
  - Local control 5 & 10 yrs 96% all 23
  - 22 previously unirradiated, 100%
  - One patient with previous Rx elsewhere transient CNS syndrome
CBP-Radiation

- Valdagni/Amichetti
  - 46 to 60 cGy
  - 13 lesions- local control 100%
  - No short or long term toxicity noted

- Verniers
  - 17 CB tumors
  - No recurrences
CBP Surgery vs Radiation

- Most authors continue to advocate surgery
- Especially < 5 cm
- CN deficit usually IX, X easily rehab
- Argue against XRT
  - Tumor still present so not really “cured”
  - Risk of malignant paraganglioma
  - Long-term complications of XRT
    - Microvascular disease, carotid artery disease, temporal bone ORN, XRT induced malignancy
CBP Multicentric Tumor MGMT

- Bilateral CN deficit devastating speech/swallow
- Wait and scan, annual MRI, Radiation
- Elderly deconditioned
- Pre-existing CN deficit consider XRT
CBP-Baroreflex Failure Syndrome

- Loss of carotid sinus bilaterally
- HTN 24-72 hrs post op
- Labile pressure 280/160 mm Hg
- HA, dizziness, tachycardia, diaphoresis, flushing
- Marked hypotension, bradycardia when drowsy or sedated
- Emotional lability
- Sodium Nitroprusside acutely
- Clonidine, Phenoxybenzamine long term
Vagal Paragangliomas

- Rare 5% all H&N paragangliomas
- Most commonly nodose ganglion
- 200 cases in literature
- Limited to cervical region, attached to skull base, or intracranial
Vagal Paraganglioma

• **Presentation**
  – Neck mass, pulsatile tinnitus, pharyngeal mass, hoarseness
  – 36% cranial nerve deficits at presentation
    • X-28%, XII-17%, XI-11%, IX-11%, VII-6%
Vagal Paraganglioma

- Imaging
  - MRI
  - Displace IC anteriorly and medially
  - Do not widen bifurcation
  - Skull base involvement - CT
  - Angiography - embolization >3 cm
Vagal Paraganglioma

• Surgery
  – Lateral temporal bone resection
  – Netterville 37/40 CN X sacrifice, All 40 permanent vocal cord paralysis
  – Jackson IX-39%, X-25%, XI-26%, XII-21%

• Radiation consideration same as for CBP with equal local control
Glomus Tympanicum and Jugulare

- Rosenwasser 1945 attempted resection
- Surgery limited to exploration due to morbidity and mortality
- 1970’s sporadic reports of complete removal
- 1977 Fisch infratemporal fossa exposure
- 1980 &’82 Kinney and Fisch addressed intracranial extension
- Jackson described single-stage strategy for IC extension and guidelines for reconstruction of CSF leak
Jugulotympanic paraganglioma

- Fisch classification
- Glasscock-Jackson classification
Jugulotympanic paraganglioma

- Vascular middle ear mass most common
- Differential diagnosis
  - High Jugular bulb
    - Posterior, more blue
  - Facial nerve neuroma
    - Less vascular, upper quadrants
JT paraganglioma

- Aberrant internal carotid
  - Anterior mesotympanum

- Primary neoplasms
  - Meningioma, AN not separable
Jugulotympanic paraganglioma

• Presenting symptom
  – Pulsatile tinnitus (80%)
  – Hearing loss (60%)
    • Invasion of labyrinth-SNHL
    • Ossicular invasion- CHL
  – TM erosion, bleeding- late
  – Lower cranial nerve dysfunction
    • Dysphagia, hoarseness, aspiration, tongue paralysis, shoulder drop,
  – Facial nerve weakness advanced disease and poor FN prognosis
JTP-Imaging

- CT T-bone
  - Best
  - Intact jugular bulb defined tympanicum
JT-Imaging

• MRI
  – If jugulare MR will detail IC disease and neurovascular anatomy

• Angiography
  – Evaluate further relationship to carotid artery and embolization
JT paraganglioma - Treatment

- Observation
  - Lifespan not affected by tumor morbidity or mortality
  - Annual imaging
Glomus tympanicum - Surgery

- Type I margins visible-transcanal
- Type II-IV postauricular, transmastoid approach, extended facial recess, infratympanic extended facial recess approach
- TM or ossicular involvement repair
- CWD rarely needed
Glomus Jugulare Type I & II

- Confined to infralabyrinthine chamber, only tympanic segment of carotid artery- hearing preservation surgery
  - Large C-shaped incision
GJ Type I & II

- Control vessels in neck
- Identify CN IX- XII
- Extratemporal facial nerve identified - superficial parotidectomy if needed
- Complete mastoidectomy with removal of mastoid tip
GJ Type I & II

- Extended facial recess exposure removal of inferior temporal bone, skeletonization infra/ant EAC- allows exposure of IAC to ET
- IJ ligated in neck
- Proximal bleeding controlled with surgicel packing
Glomus Jugulare Type III & IV

- Modified or extended infratemporal fossa approach
  - CHL conceded EAC, TM, middle ear lateral to stapes resected
GJ Type III & IV

- Dislocation/resection of mandible/zygoma
- Poss MF exposure
- If CSF leak may require trapezius flap or rectus abdominal free flap for recon
Glomus tympanicum results

- Jackson- 80 patients
- I-34%, II-52%, III-3%, IV-11%
- Mastoid approach 89%, CWD 16%, Transcanal 11%
- Two recurrences at 3 and 14 yrs
- Four subtotal resections
- Surgical control 92.5%
- One CVA hemiparesis resolved to cane mobility
- One facial nerve paralysis full recovery
Lateral Temporal Bone Resection

- Jackson- 152 patients GJ, 27- GV, 3-CB with skull base extension
- GJ- I-21.4%, II-20.6%, III-34.9%, IV-23%
- Subtotal resection 18 patients (9.9%)
  - 28%NED, 22% AWD, 55% yet to f/u
- Nine recurrences (5.5%)
- Time avg. 98 months, all GJ tumors
- Preoperative CN deficits 46%
  - VII-18%, VIII-13%, IX- 21%, X-30%, XI- 17%, XII – 24%
  - Assoc. with IC ext. IX-XII 50% IC ext.
Lateral Temporal Bone Resection

- Post-operative new CN deficits

**Table 1. AGGREGATE LOWER CRANIAL NERVE RESECTION**

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Glomus Jugulare N (%)</th>
<th>Glomus Vagale N (%)</th>
<th>Carotid Body Tumor N (%)</th>
<th>Total N (%)</th>
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<tbody>
<tr>
<td>9,10,11,12</td>
<td>52 (34)</td>
<td>11 (41)</td>
<td>63 (35)</td>
<td></td>
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<tr>
<td>9,10,11</td>
<td>7 (4.6)</td>
<td>1 (3.7)</td>
<td>8 (4.4)</td>
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<tr>
<td>9,10,12</td>
<td>1 (0.6)</td>
<td>1 (3.7)</td>
<td>2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4 (2.6)</td>
<td>1 (3.7)</td>
<td>5 (2.7)</td>
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<tr>
<td>9,12</td>
<td>1 (0.6)</td>
<td></td>
<td>1 (0.5)</td>
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<tr>
<td>9</td>
<td>29 (19)</td>
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<td>31 (17)</td>
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</tr>
<tr>
<td>10,11,12</td>
<td>2 (1.3)</td>
<td>1 (3.7)</td>
<td>3 (1.6)</td>
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<tr>
<td>10,11</td>
<td>1 (0.6)</td>
<td>1 (3.7)</td>
<td>2 (1.1)</td>
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</tr>
<tr>
<td>10,12</td>
<td>1 (0.6)</td>
<td>1 (3.7)</td>
<td>1 (0.5)</td>
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<tr>
<td>10</td>
<td>5 (3.2)</td>
<td>10 (37)</td>
<td>15 (8.2)</td>
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<tr>
<td>12</td>
<td>2 (1.3)</td>
<td></td>
<td>2 (1.1)</td>
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<tr>
<td>None</td>
<td>47 (31)</td>
<td></td>
<td>48 (26)</td>
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Lateral T-Bone resection

- New CN VII deficit 4.4% all reanimated
- Preoperative lower CN deficit CN resected 61%
- No preoperative lower CN deficit CN resected 11%
- Preoperative CN VII required segmental FN resection 100%
- Mortality 2.7% (5/182)
  - 3-ICA resection
  - 2-pulmonary emboli in secreting tumors
- Surgical tumor control 85%
- Complete tumor elimination when attempted 95%
LTBR- Rehabilitation

- Netterville
- 1\textsuperscript{st} postoperative week Gelfoam injection
- 3 months medialization
- Primary phonosurgery avoided
- Velopharyngeal insufficiency unilateral pharyngeal flap
- Facial nerve reanimation as needed
Jugulotympanic Radiation Therapy

• Glomus tympanicum not usually used due to excellent surgical results

• Florida
  – 42 T-bone paragangliomas
  – 42.9 cGy Mean dose
  – 10 yr avg f/u
  – 39/42 (93%) local control
    • Included nine tumors previously treated
  – No relationship with previous treatment or tumor size and local control
Jugulotympanic Radiation

- One patient surgical salvage
- Ultimate control 95%
- One patient unplanned break due to mucositis
- No other treatment complications
Jugulotympanic Radiation

- Cummings
  - 45 patients
    - 34 XRT alone, surgery local recurrence-2, subtotal resection-9
    - 35 Gy, followed 10 yrs median
    - Local control 93%
    - Three failures
      - 1 surgical salvage, 2 second course XRT
Jugulotympanic Radiation

- Symptom relief
- Complications
  - 4- chronic OE
  - 1- external canal stenosis
  - 1- surgical drainage COM
  - One death brain necrosis accidental 7,000 cGy in 26 days
  - One ORN 10 yrs later in 5,800 cGy dose

<table>
<thead>
<tr>
<th>Table 1. Response to Radiation</th>
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<tbody>
<tr>
<td>Treatment/symptom</td>
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<tr>
<td>----------------------------</td>
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<tr>
<td>3500 cGy tumor dose (41 patients)</td>
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<tr>
<td>Tinnitus</td>
</tr>
<tr>
<td>Decreased hearing</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Mass</td>
</tr>
<tr>
<td>Discharge, bleeding</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Cranial nerve abnormality</td>
</tr>
<tr>
<td>V</td>
</tr>
<tr>
<td>VI</td>
</tr>
<tr>
<td>VII</td>
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<tr>
<td>IX</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>XI</td>
</tr>
<tr>
<td>XII</td>
</tr>
<tr>
<td>Other radiation doses (4 patients)</td>
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<tr>
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<td>Mass</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Cranial nerve abnormality</td>
</tr>
<tr>
<td>VII</td>
</tr>
</tbody>
</table>

Symptom or sign present prior to irradiation in three patients who later had tumor regrowth. Patients A* and B† later developed upper
Other Paragangliomas

- Laryngeal paragangliomas
  - Supraglottic or infraglottic
  - No cases of multicentricity, familial, or secreting
Other Paragangliomas

– Supraglottic
  • hoarseness, SOB, odynophagia
  • TVC paresis not common
  • Diagnosis usually at time of surgical biopsy - brisk bleeding
    – May require tracheotomy and laryngeal packing
    – Image all submucous laryngeal lesions pre-operatively
  • Hemisupraglottic laryngectomy, lateral laryngotomy, or pharyngotomy
Other Paraganglioma

• Infraglottic - rare
  – Inner surface cricoid cartilage, outer surface, in CT membrane, in capsule of thyroid gland
  – Symptoms hoarseness, airway obstruction, hemoptysis
  – External surgical excision

• Sinonasal paragangliomas
  – Very rare
  – Sx of obstructing nasal lesion
  – Occas. Epistaxis
  – May appear as nasal polyps
  – Exision intranasally or external approach