Changing Paradigms for Paraganglioma Treatment

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Disclosures:

None

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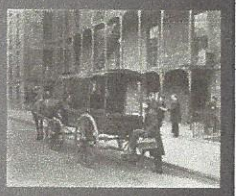

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Changing Paradigms for Paraganglioma Treatment

- Outline
  - Paraganglia
  - Paraganglioma
    - Anatomy
    - Evaluation
    - Genetics
    - Treatment Options/Sequellae

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PARAGANGLIA

- Neural Crest Origin
- Chemoreceptors
- Chief Cells

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PARAGANGLIOMAS

- CAROTID BODY TUMOR
- JUGULAR
- VAGAL
- TYMPANIC
- SYMPATHETIC GANGLIA
- LARYNGEAL, MEDIASTINAL, ABDOMINAL

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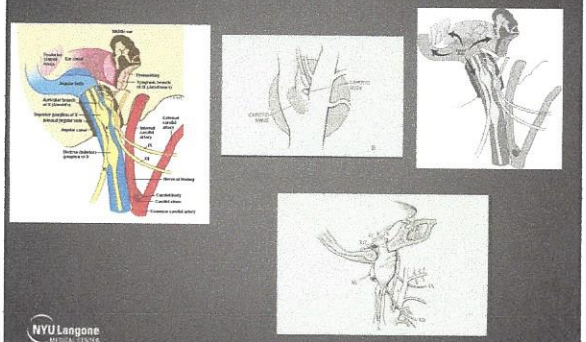
PARAGANGLIOMA



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PARAGANGLIOMAS - Facts

- MULTICENTRIC - 4% → 22%
  - Carotid Body Tumors Most Frequent
- FAMILIAL – SDH gene mutation
  - Younger age presentation
  - Autosomal Dominant - Variable Penetrance
  - Multicentric - 78% → 87%
- MALIGNANT –
- Non-Secreting – w/u should involve urinary/plasma metanephrines, vanillylmandelic acid (VMA)

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PARAGANGLIOMAS -Genetics

Table 1. Penetrance and Presence of Head and Neck Paragangliomas and Multiple Tumors, with the Likelihood of Malignancy Based on the SDH Gene Mutation.[43,52]

	SDHD (n = 164)	SDHB (n = 129)	SDHC (n = 38)
Mean age at diagnosis, y	36	37	38
Penetrance, %	50 by 31 y 86 by 50 y	50 by 35 y 77 by 50 y	N/A
Multiple tumors, %	67-74	20-31	9-31
Head and neck paragangliomas, %	79-98	31-43	88-100
Malignant tumors, %	0-3	34-38	0

Abbreviations: N/A, not applicable; SDH, succinate dehydrogenase.

Michael G. Moore et al. Otolaryngology-Head and Neck Surgery 2016;154:597-605

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PARAGANGLIOMAS -Genetics

Table 1 Clinical features (penetrance) of PGL syndromes 1–5

Syndrome	Gene	PC	TAPGL	HNPGL	Multifocal	Malignant	RCC	Other
PGL1	SDHD	~10–25%	20–25%	85%	55–60%	~4%	~8%	GIST and PA
PGL2	SDHAF2[a]	0	0	100%	0	0	0	–
PGL3	SDHC	0	Rare	?[b]	55–70%	0%	Rare	GIST
PGL4	SDHB	20–25%	50%	20–30%	20–25%	~30%	~14%	GIST and PA
PGL5	SDHA	Rare	Rare	Rare	Rare	Rare	0	GIST and PA

PC, pheochromocytoma; TAPGL, thoracoabdominal PGL; HNPGL, head and neck PGL; RCC, renal cell carcinoma; PA, pituitary adenoma; GIST, gastrointestinal stromal tumour. Neumann *et al.* (2002), Amar *et al.* (2005), Schiavi *et al.* (2005), Benn *et al.* (2006), Cascón *et al.* (2009), Hao *et al.* (2009), Mannelli *et al.* (2009), Burnichon *et al.* (2009), Ricketts *et al.* (2010), Wellander *et al.* (2011) and Giménez-Roqueplo *et al.* (2012).
[a]Paternally inherited.
[b]Lifetime prevalence not yet determined.

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-15-0268

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PARAGANGLIOMAS- IMAGING

- CT Scan - Enhancing
- MRI - "Salt and Pepper"
- MRA - Displacement of Carotid Artery
- Gallium-68 Dotatate PET Scan – incr. sensitivity/specificity over Octreotide (In111-octreotide) and MIBG (I123-MIBG)

Imaging defines:
- Extent of tumor
- Vascular/Neural Involvement
- Demonstrates Muticentric Tumors
- Defines Possible Metastases

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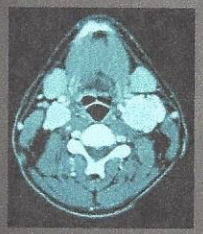
PARAGANGLIOMAS



CT

MRI

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PARAGANGLIOMAS

- Familial, multiple
  - Bilat. CBT
  - Vagal Paraganglioma
  - Jugular Paraganglioma

MRA

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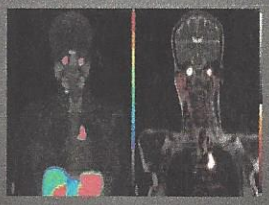
PARAGANGLIOMAS

49 yo woman with history of multiple jugular paragangliomas required study to r/o carotid body tumors. Prior imaging revealed multiple cervical level II nodes



Dotatate MRI

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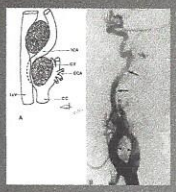
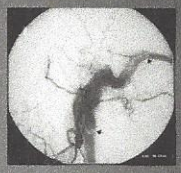
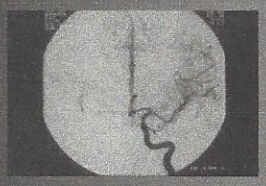
PARAGANGLIOMAS - Angiography

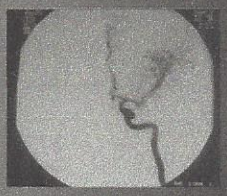




Defines flow characteristics – vascular supply, vessel displacement
Defines involvement/anastamoses with intracranial vessels

PARAGANGLIOMAS





Angiography with Carotid Occlusion

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ADVANTAGES OF EMBOLIZATION

- REDUCTION IN SIZE
- REDUCTION IN TUMOR BLOOD FLOW
  - DECREASED BLOOD LOSS
  - INCREASED EXPOSURE
  - PRESERVATION OF INTERNAL CAROTID AND CRANIAL NERVES
- AVOIDS EXTERNAL CAROTID LIGATION

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PARAGANGLIOMAS

Carotid Body Tumor

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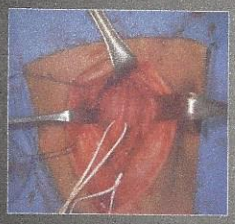
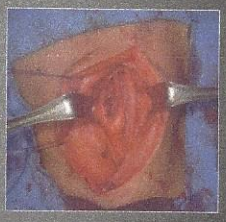
Carotid Body Tumor

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Fisch type B Infratemporal Fossa approach


Mattox, Fisch

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Postoperative Cranial Nerve Dysfunction

- Loss of Pharyngeal Sensation (CN IX)
- Aspiration, Hoarseness, Palate Paresis (CN X)
- Shoulder Weakness (CN XI)
- Tongue Dysfunction (CN XII)

Post-operative Cranial Nerve dysfunction (CBT)
< 5cm. – 14%, >5cm.- 67%
Papaspyrou et al Head&Neck 2012;34:632-637

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Surgical Considerations

- Surgical resection of skull base paragangliomas had no effect on survival and resulted in a marked increase in cranial nerve dysfunction
  - van der May, Ann Otol.Rhinol.Laryng.1992;101:635-42
- Following abrupt loss of lower cranial nerves, older patients usually do not regain full function
  Ivan,Journ.Neurosurg.2011;114:1299-1305, Wanna,Otol.H&N Surg;15,991-5
- Risk of preoperative embolization and intra-op internal carotid artery damage
- Bilat. Carotid Body Tumor resection — loss of baroreceptor feedback — severe hypertension

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PARAGANGLIOMAS
Rationale Supporting Evolution of Treatment Paradigm

- Tumor size stability, slow growth rate – JP 65% stable over 5 yrs, median growth 0.8 mm/yr
  - Prasad, Otol.Neurotol.2014;35:922-31
- Rare death due to paragangliomas
- Low incidence of malignancy
- Improved methods of surveillance – MRI, radioisotopes
- Significant symptomatic disability from surgical approaches – esp. older patients
- Radiotherapy - 90-96% effective tumor control

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Radiation Treatment

- Radiation Protocols
  - Tumors < 3cm –
    - Stereotactic Radiosurgery (SRS) 12Gy-15Gy via gamma knife or linear accelerator photon
  - Tumors > 3cm –
    - Hypofractionated Stereotatic RT -25 Gy/5 Fx's, 21Gy/3 Fx's
    - EBRT 45 Gy/5 weeks

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Radiation Treatment

- Rare total tumor resolution
- "Local control" – tumor stability or regression without progression of neurological symptoms
  - 60% demonst. tumor shrinkage with an 8-45% decrease in size
- RT →obliterative endarteritis→fibrosis⟶ shrinkage
  ↘ effect on chief cells⟶ involution

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Radiation Treatment

Cranial Neuropathy Response After Definitive Radiotherapy

Author	% Improved	% SR	% Worse
Friedland	53% (18/57)	9% (5/57)	4% (2/57)
Cummings	100% (20/20)*	9% (2/20)	0%
Dawes	28% (16/57)	NR	0%
Boyle	50% (2/4)	NR	0%
Mumaw	50% (3/6)	NR	0%
Lupert	17% (1/6)	0%	0%
Dickens	47% (14/30)	20% (6/30)	0%
Mitchell	66% (2/3)	NR	0%
Prystant	0% (0/3)	0%	0%
Powell	20% (5/25)	NR	NR
Schild	63% (5/8)	NR	0%
	33% (67/204)	10% (13/128)	1% (2/204)

Improvement in cranial nerve function is inversely related to duration of cranial neuropathy

Note: Three cases of new cranial neuropathy (2 CN VII after radiotherapy (64.4Gy))

(Powell) an alone reported a CN VI with unclear cause (Dawes)
CR=complete resolution, NR= not reported
*cranial neuropathy stable or improved, excluded from total analyses of those improved

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Radiation Treatment - Complications

- SRS – decreased hearing- 6.5%
- EBRT
  - Common – mucositis, otitis, dermatitis, xerostomia
  - Severe – osteoradionecrosis (1.5%), chronic otitis(1%), brain necrosis(0.8), cranial neuropathy(0.5%), radiation induced sarcoma(0.4%) – varies according to radiation technique and treatment site
- Experience counts –Univ. of Florida 45 yr. experience
  - 45 yr. experience treating 131 pts. With 156 tumors with mean f/u of 11.5 yrs – 0% severe complications

Gilbo, P., et al., External-beam radiation therapy for malignant paraganglioma of the head and neck. Am J Otolaryngol, 2015. 36(5): p. 692-6

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PARAGANGLIOMAS
Evolution of Treatment

- Natural History of Paragangliomas – warrants observation with serial imaging studies in select cases – no treatment
- Effectiveness of Radiation Therapy
- Development of New Medical Therapy – Peptide Receptor Radionuclide Therapy (PRRT)
  - Lutathera (lutetium177-dotatate)
  - Azedra (iobenguane [MIBG] I131) – more marrow toxic, better for secreting tumors

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Indications for Surgery

- CBT < 5cm. in younger patients
- Tympanic paragangliomas confined to middle ear
- Smaller jugular paragangliomas (experienced surgeon)
- Secreting tumors
- Malignant paragangliomas

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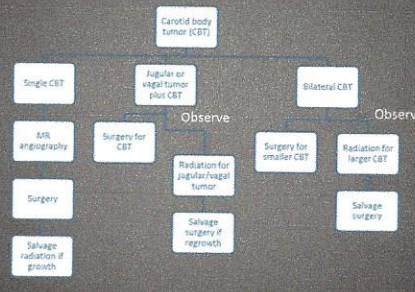
Treatment Algorithm for Carotid Body Tumors



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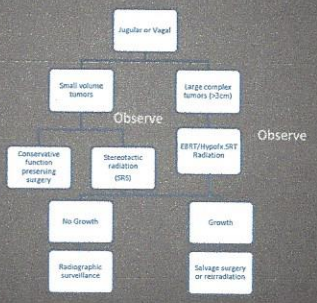
Treatment Algorithm for Jugular/VagalParagangliomas



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Conclusions

- Risks vs. Benefits

Increased emphasis on observation and non-surgical therapy

- "Do no harm"
- Individualize Treatment
  - Age/tumor extent
  - Type/multifocal
  - Neurological findings
    - None
    - Chronic dysfunction
    - Progressive
  - Malignant

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THANK YOU

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