Head and Neck Paragangliomas: A Two-Decade Institutional Experience and Algorithm for Management

Joshua D. Smith, BA; Rachel N. Harvey; Owen A. Darr, MD; Mark E. Prince, MD; Carol R. Bradford, MD; Gregory T. Wolf, MD; Tobias Else, MD; Gregory J. Basura, MD, PhD

Objectives: Paragangliomas of the head and neck and cranial base are typically benign, slow-growing tumors arising within the jugular foramen, middle ear, carotid bifurcation, or vagus nerve proper. The objective of this study was to provide a comprehensive characterization of our institutional experience with clinical management of these tumors and posit an algorithm for diagnostic evaluation and treatment.

Methods: This was a retrospective cohort study of patients undergoing treatment for paragangliomas of the head and neck and cranial base at our institution from 2000–2017. Data on tumor location, catecholamine levels, and specific imaging modalities employed in diagnostic work-up, pre-treatment cranial nerve palsy, treatment modality, utilization of preoperative angiographic embolization, complications of treatment, tumor control and recurrence, and hereditary status (ie, succinate dehydrogenase mutations) were collected and summarized.

Results: The mean (SD) age of our cohort was 51.8 (±16.1) years with 123 (63.4%) female patients and 71 (36.6%) male patients. Catecholamine-secreting lesions were found in nine (4.6%) patients. Fifty-one patients underwent genetic testing, with mutations identified in 43 (20 SDHD, 13 SDHB, 7 SDHD, 1 SDHA, SDHAF2, and NF1). Observation with serial imaging, surgical extirpation, radiation, and stereotactic radiosurgery were variably employed as treatment approaches across anatomic subsites.

Conclusion: An algorithmic approach to clinical management of these tumors, derived from our longitudinal institutional experience and current empiric evidence, may assist otolaryngologists, radiation oncologists, and geneticists in the care of these complex neoplasms.

Key Words: Paraganglioma, glomus, succinate dehydrogenase.

Level of Evidence: 4

INTRODUCTION

Paragangliomas are rare, hypervascular neoplasms arising from neural crest-derived cell clusters in the head and neck/cranial base, mediastinum, abdomen, and pelvis.\(^1\) With an overall incidence of 1 in 30,000–100,000, head and neck paragangliomas (HNPGLs) arise, in order of decreasing frequency, from the carotid body (carotid body paragangliomas, CBP), jugular bulb (JP), vagus nerve (cranial nerve [CN] X; VP), the tympanic branch of the glossopharyngeal (CN IX) or auricular branch of CN X (TP), and the cervical sympathetic chain (SCP).\(^2\)

As many as 40% of HNPGLs are now known to arise in patients with a hereditary predisposition. Most commonly implicated are germline mutations in one of the four subunits (A-D) of the succinate dehydrogenase complex of the mitochondrial electron transport chain and its flavination co-factor (SDHA-D, SDHAF2, collectively referred to as SDHx).\(^,3,4\) Screening for pathologic SDHx mutations in all patients with incident HNPGL diagnosis is now the standard of care.\(^5\) Though HNPGLs are infrequent secretors (< 3% of tumors) of catecholamines, laboratory evaluation of plasma and/or urine catecholamine metabolites should be included in the diagnostic workup to identify the rare secreting HNPGL and, far more importantly, a concomitant pheochromocytoma.\(^6\) Contrast-enhanced cross-sectional imaging by computer axial tomography (CT) or magnetic resonance imaging (MRI) of the head and neck/cranial base are essential tools to delineate the extent of disease, including great vessel involvement, expected CN anatomy, temporal bone or intracranial extension of HNPGL, and to exclude the presence of multifocal tumors.\(^,7,8\)

The principal treatment approaches for HNPGL include surgery, fractionated radiation, and stereotactic
RESULTS

Patient Demographics & Paraganglioma Localization

The mean (SD) age of our cohort was 51.8 (±16.1) years with a range of 13.7 to 85.2 years. Of 194 patients, 123 (63.4%) were female and 71 (36.6%) were male. The distribution of HNPGL sub-sites is depicted in Figure 1, panel A. A patient index and detailed localization of multi-focal and/or metastatic paragangliomas is presented in Figure 1, panel B.

Genetic Testing for Hereditary Paraganglioma-Pheochromocytoma Syndromes

Genetic testing for SDHx variants become widely adopted only after 2008. In our entire cohort of HNPGL patients, 51 (26.3%) underwent genetic counseling and testing, 44 of which were diagnosed with HNPGL in 2008 or later. Of the 51 patients undergoing genetic testing, 43 (84.3%) were confirmed to carry a pathogenic mutation in a known susceptibility gene. Mutations in SDHD were most common (20/43, 46.5%), followed by SDHB (13/43, 30.2%), and SDHC (7/43, 16.3%). Pathogenic mutations in SDHA, SDHAF2, and NF1 were identified in the final three patients with unilateral CBP, unilateral CBP, and SCP with concomitant bilateral pheochromocytoma, respectively. The highest frequency of SDHx mutations was seen in patients with SCP, multi-focal or metastatic HNPGL, and bilateral CBP (100.0% of patients tested within each cohort).

Carotid Body Paraganglioma (Unilateral)

Depicted in Figure 2 is a flow diagram detailing patient demographics, presenting signs and symptoms, diagnostic evaluation, tumor characteristics, treatment, and follow-up for our cohort of patients with solitary unilateral CBP. The most common presentation of unilateral CBP was painless, enlarging neck mass (30 patients, 48.4%). Pre-treatment CN palsy was rare, with only three patients (4.8%) presenting with cranial nerve X or XII weakness on initial physical exam. Similarly, functional CBP were rare, with notable metanephrine elevations in only four of 24 patients in whom metanephrines were assessed pre-treatment. During the study period, a single patient was diagnosed with a malignant, unilateral CBP based on aggressive soft-tissue extension into the brachial plexus and cervical nerve roots; this patient was treated with sub-total resection and adjuvant radiation.

AMMATERIALS AND METHODS

Following approval by the University of Michigan Institutional Review Board (HUM0012015), a retrospective medical record review was conducted of 194 patients with 233 paragangliomas (228 HNPGL, five concomitant mediastinal/abdominal paragangliomas or pheochromocytoma) who underwent treatment at our institution from 2000–2017. DataDirect and EMERSE search functions were utilized to identify patients from the electronic health record for inclusion in our study. Data on patient demographics, tumor characteristics, initial CN deficits and signs and symptoms at presentation, diagnostic evaluation, treatment, follow-up, and results of genetic evaluations were collected.

HNPGL size was determined by anatomic pathology or head and neck MRI, in cases of non-surgical treatment approaches. Tumors were considered functional (ie, catecholamine-secreting) when patients had plasma or urine metanephrine levels elevated ≥1.5 times our laboratory’s reference range. Duration of clinical follow-up was defined as the time interval from the date of treatment (ie, surgery or final dose of radiation) or first patient encounter (for patients observed) to the last clinical evaluation or patient death.

Descriptive statistics and student’s t-test (two-tailed, 𝛼 = 0.05) were performed using SPSS (Version 22.0, Chicago, Illinois, U.S.A.).
underwent extirpation due to CBP growth, with a mean time interval to treatment of 5.8 years.

**Carotid Body Paraganglioma (Bilateral)**

The mean (SD) age of the bilateral CBP patient cohort (14 patients) was 49.0 (±11.9) years, with a gender distribution of 8 (57.1%) females and 6 (42.9%) males. No patients with bilateral CBP exhibited CN dysfunction at presentation, and all tumors were non-secreting, benign paragangliomas. A staged surgical excision of bilateral CBP was performed in 8/14 patients with a mean (range) time interval of 11 (0.1–72) months between operations. Seven of these staged excisions began with the larger of the bilateral CBP. Staged surgical excisions of bilateral CBP resulted in development of new CN palsies in two patients (unilateral CN X weakness, unilateral CN XII weakness and bilateral Horner’s syndrome, respectively). Additionally, 5/8 patients (62.5%) were treated for new-onset hypertension due to baroreceptor dysfunction in the postoperative period.

Surgical excision of the larger CBP and observation with serial imaging of the smaller, contralateral tumor was the treatment strategy for four of 14 bilateral CBP patients. The mean (range) duration of observation for the smaller of bilateral CBP was 73 (6–140) months with
Fig. 2. Diagnostic evaluation & treatment of patients (n = 62) with solitary, unilateral carotid body tumors (CBP). † CN IX, X, XII. ‡ External carotid artery, lingual artery, superior thyroid artery, thyrocervical trunk, superior thyroid artery, and internal jugular vein. § CN VII, marginal mandibular branch: 4 patients, CN IX: 3 patients, CN X: 10 patients, CN XI: 2 patients, CN XII: 8 patients, cervical sympathetic trunk: 3 patients

| Asymptomatic at Presentation | Symptomatic at Presentation |
|-----------------------------|---------------------------|
| 28                          | 34                        |
| Incidentally Diagnosed on Head/Neck Imaging for Other Indication | With Enlarging Neck Mass/Swelling |
| 18                          | 30                        |
| Palpable Neck Mass Discovered on Physical Exam for Other Indication | With Neck Pain/Tenderness |
| 7                           | 5                         |
| Diagnosed On Initial Screening after SDHc Mutation Identified in Relative | With Evidence of Lower CN Dysfunction (CN X, XII) |
| 3                           | 3                         |

- CN IX, X, XII.
- External carotid artery, lingual artery, superior thyroid artery, thyrocervical trunk, superior thyroid artery, and internal jugular vein.
- CN VII, marginal mandibular branch: 4 patients, CN IX: 3 patients, CN X: 10 patients, CN XI: 2 patients, CN XII: 8 patients, cervical sympathetic trunk: 3 patients

| Age (Mean ± SD) | Female | Male |
|-----------------|--------|------|
| 54.0 ± 15.2     | 38 (61.3%) | 24 (38.7%) |

- 24 Had Baseline Assessment of Plasma and/or Urine Metanephrines
- 4 Had Elevated Metanephrines Consistent with a Secreting CBP
- 1 Experienced Hypertension & Palpitations & Underwent α- and β- Blockade

- 61 (98.4%) With Benign CBP
- 1 (1.6%) With Malignant CBP

- 33 Had Vascular Imaging of the Head/Neck (e.g. duplex U/S, CTA, MRA)
- 5 Had Anatomic Imaging of the Chest, Abdomen, Pelvis

- 3 Patients Had Functional Imaging (e.g. PET-CT)

- 54.0 ± 15.2 Mean (SD) Age, Years
- 38 (61.3%) Female
- 24 (38.7%) Male

- 46 Had Anatomic Imaging of the Head/Neck (e.g. CT, MRI)

- 28 (45.2%) With left-sided CBP

- 3.5 ± 1.5 Mean (SD) Tumor Size, Maximum Dimension, cm

- 20 With Temporary or Permanent Nerve Dysfunction Post-Op
- 1 With Malignant CBP Had Adjuvant Radiation (54 Gy) Due to Sub-Total Resection

- 19 (6.5 - 106) Mean (Range) Duration of Post-Op Patient Follow-Up, Months
- 0 Had CBP Recurrence During Follow-Up

- 36 (3-122) Mean (Range) Duration of Observation with Serial Imaging, Months
- 2 In Which Treatment (Surgery) was Necessary During Observation Period Due to Interval CBP Growth

- 5.8 Mean Interval from Start of Observation to Surgery in These 2 Patients, Years
no patients requiring additional treatment for CBP growth or new symptoms during the observation period. The final two patients were diagnosed with small, asymptomatic bilateral CBP within the last three years and have been observed during this time frame.

**Jugular Paraganglioma**

The flow diagram for the diagnostic evaluation and treatment of 41 patients with solitary JP is depicted in Figure 3. The highest frequency of pre-treatment CN deficits was seen in the JP cohort, with 28/41 (68.3%) patients presenting with dysfunction of one or more CNs (IX, X, XI, XII). Primary treatment modalities for JP varied: 16 (39.0%) underwent surgical excision of JP, 11 (26.8%) received conventional fractionated radiation, four (9.8%) underwent SRS, and 10 (24.4%) were followed with serial imaging. Like the CBP cohort, tumor size was similar between embolized and non-embolized JP (3.5 ± 2.0 cm vs. 3.0 ± 1.7 cm, p = 0.675). Embolization was complicated in two patients by new CN IX-X deficits and bilateral punctate thalamic strokes, respectively. In almost all cases, our surgeons opted for a subtotal resection with CN preservation (14/16 operations), with adjuvant radiation to the jugular foramen in 8/14 patients.

**Vagal Paraganglioma**

Figure 4 depicts the flow diagram for the diagnostic evaluation and treatment of 21 patients with solitary VP. Evidence of CN X palsy and unilateral vocal cord dysfunction was observed in seven (33.3%) patients at presentation. VP were the largest of any HNPGL in our cohort, with a mean (SD) tumor size of 5.3 (±1.9) cm. One patient was diagnosed with malignant VP, again due to aggressive cervical soft-tissue discovered on post-surgical pathology. Surgical excision with preoperative embolization of VP was the most common treatment path (11/2, 52.4%). Surgery resulted in complete unilateral CN X palsy in all patients, with additional postoperative deficits including CN IX, XII, and the cervical sympathetic chain in two patients.

**Tympanic Paraganglioma**

The mean (SD) age of the TP cohort (n = 22) was 60.3 (±13.8) years, with a gender distribution of 19 (86.4%) females and 3 (13.6%) males. Unilateral pulsatile tinnitus (13/22, 59.1%) and conductive hearing loss (7/22, 31.8%) were the most common presenting symptoms of TP. All TP were benign tumors, with a mean (SD) tumor size of 0.7 (±0.6) cm, the smallest HNPGL in our entire cohort. Of the 19 patients with TP undergoing surgical excision, none experienced postoperative complications or developed recurrence during the follow-up period (mean 12.1 months). The remaining three patients with TP were observed, with none requiring definitive TP treatment during a mean observation period of 24 months.

**Sympathetic Chain Paraganglioma**

The seven patients with solitary SCP were comparatively younger than other HNPGL groups, with a mean (SD) patient age of 32.7 (±10.6) years. Of six patients with symptomatic SCP at presentation, four (57.1%) had evidence of unilateral Horner’s syndrome and two (28.6%) were diagnosed during workup for new-onset hypertension caused by catecholamine-secreting lesions. The final patient with SCP was diagnosed incidentally on initial screening after an SDHx mutation was identified in a family member. The mean (SD) size of tumors in this cohort, all benign lesions, was 4.3 (±2.1) cm.

Six patients were treated primarily with angiographic embolization and excision of SCP, leading to unilateral Horner’s syndrome in five of six (83.3%) and additional CN palsies (X, XII) in four of six (66.7%). The remaining SCP patient was observed and did not require definitive treatment during 18 months of follow-up.

**Multi-Focal/Metastatic HNPGL**

The mean (SD) age of patients with multi-focal or metastatic HNPGL was 46.5 (±13.8) years. Referring to Figure 1, panel B, SDHD mutations were confirmed in five patients (patients 2, 4, 6, 17, 18), SDHB mutations in two (patients 14, 22), SDHC mutations in four (patients 8, 13, 15, 22), and NF1 mutations in one (patient 16). Four patients (patients 18, 22–24) in this cohort were diagnosed with malignant HNPGL due to the presence of metastatic disease.

**DISCUSSION**

We present a relatively large cohort of HNPGL patients, with a strong representation of particularly rare HNPGL sub-sites (eg, VP, TP, SCP), and evident diversity in genetic perturbations, diagnostic evaluation, and treatment protocols. Consistent with previous reports, there was a strong female predilection of HNPGL, a broad range of patient age at diagnosis, and a substantial proportion of patients with a hereditary predisposition to HNPGL (84.3% among those tested).20,21 Similarly, the relative prevalence of HNPGL sub-sites and SDHx mutations in our cohort (unilateral CBP and SDHD most common, SCP and SDHA least common, respectively) closely matches frequency distributions seen in other HNPGL patient cohorts.22

Across all HNPGL sub-sites at our institution, screening for functional paragangliomas with plasma or urine metanephrines was performed in a minority of HNPGL cases (Figs. 2–4), often in patients who self-reported a history of hypertension, anxiety, or palpitations or in patients with suspected or confirmed SDHx-related HNPGL. In total, we identified hypersecreting HNPGL in nine (4.6%) patients, a proportion skewed upwards slightly by two patients with paragangliomas derived from sympathetic, rather than parasympathetic, paraganglia. Elevation of metanephrines in one patient presenting with CBP (patient 14, Fig. 1, panel B) led to a diagnosis of concomitant, hypersecreting para-aortic paraganglioma. Plasma metanephrines have a marginal
Fig. 3. Diagnostic evaluation & treatment of patients (n = 41) with solitary, unilateral jugular paraganglioma (JP).† 2 patients with facial paralysis or weakness, 3 with neck/occiput pain, 1 with dysarthria, and 1 with altered vision and papilledema.‡

21 Presented with a Chief Complaint of Pulsatile Tinnitus and Hearing Loss
11 With Dysphonia/Hoarseness
9 With Dysphagia
5 With Shoulder Weakness or Pain
7 With Other Chief Complaint
3 Asymptomatic, Incidental Diagnosis on Imaging for Other Indication

28 With Dysfunction of One or More CNs at Presentation
3 With CN V Dysfunction
4 With CN VII Dysfunction
12 With CN VIII Dysfunction
20 With CN IX, X, and/or XI Dysfunction
12 With CN XII Dysfunction

24 Had Baseline Assessment of Plasma and/or Urine Metanephrines
3 Had Elevated Metanephrines Consistent with a Secreting JP
1 Experienced Hypertension & Palpitations and Underwent α- and β- Blockade

10 Patients Presented at our Multi-Disciplinary Head & Neck Tumor Board Prior to Physician Recommendation of Treatment Course

40 Had Anatomic Imaging of the Head/Neck (e.g., CT, MRI)
12 Had Vascular Imaging of the Head/Neck (e.g., MRA)
8 Had Anatomic Imaging of the Chest, Abdomen, Pelvis
4 Had Functional Imaging (e.g., PET-CT, dotatate scan)

41 (100.0 %) With Benign JP
15 (36.6 %) With right-sided JP
26 (63.4 %) With left-sided JP
3.0 (± 1.4) Mean (SD) Tumor Size, Maximum Dimension, cm

16 Initially Underwent Excision of JP
11 First Had Pre-Op Arterial Embolization of Tumor Feeding Vessels
3.4 (± 2.1) Mean (SD) Size of Embolized Tumors, Maximum Dimension, cm
3 With Intra-Op Nerve Injury or Intentional Sacrifice (of CN VII)
2 Patients Required Ligation of Vessels of Neck

6 With New CN Palsy Post-Op
14 With Residual Tumor in Jugular Foramen Post-Op Due to Sub-Total Resection
8 With Residual Tumor Given Adjuvant RT
34 (1-96) Mean (Range) Interval to RT, Months
67 (11-156) Mean (Range) Duration of Post-Op Patient Follow-Up, Months

11 Initially Received Radiation (RT) to JP
30 – 50.4 Range of Total Radiation Dose Given, Gray (Gy)
1.8 – 6.0 Range of Single Dose Fractionations Given, Gy
4 Initially Underwent Stereotactic Radiosurgery (SRS) to JP
12 – 45 Range of Single SRS Dose Given, Gy

31 (2-132) Mean (Range) Duration of Observation with Serial Imaging, Months
0 With JP Treated During Observation Period
1 In Which Treatment (RT) was Recommended Due to Interval JP Growth
11.4 Interval to Treatment Recommendation in this Patient, Years

385
Fig. 4. Diagnostic evaluation & treatment of patients (n = 21) with solitary, unilateral vagal paraganglioma (VP). 1 patient with painless neck swelling/fullness, 1 with pulsatile tinnitus, 1 with dysphagia. † Ascending pharyngeal artery, facial artery, internal carotid artery, external carotid artery.

47.7 (± 19.9) Mean (SD) Age, Years
9 (42.9 %) Female
12 (57.1 %) Male

13 Asymptomatic at Presentation
5 Incidentally Diagnosed on Head/Neck Imaging for Other Indication
6 Palpable Neck Mass Discovered on Physical Exam for Other Indication
2 Diagnosed On Initial Screening after SDHx Mutation Identified in Relative

8 Symptomatic at Presentation
3 With Unilateral Neck Pain/Soreness
2 With Dysphonia/Hoarseness
3 With Other Chief Complaints
7 With CN IX Palsy & Unilateral Vocal Fold Palsy at Presentation

7 Had Baseline Assessment of Plasma and/or Urine Metanephrines
0 Had Elevated Metanephrines Consistent with a Secreting VP

21 Had Anatomic Imaging of the Head/Neck (e.g. CT, MRI)
8 Had Vascular Imaging of the Head/Neck (e.g. CTA/MRA, duplex US)
1 Had Anatomic Imaging of the Chest, Abdomen, Pelvis
2 Had Functional Imaging (e.g. PET-CT)

7 Patients Presented at our Multi-Disciplinary Head & Neck Tumor Board Prior to Physician Recommendation of Treatment Course

20 (95.2 %) With Benign VP
1 (4.8 %) With Malignant VP
12 (57.1 %) With right-sided VP
9 (42.9 %) With left-sided VP
5.3 (± 1.9) Mean (SD) Tumor Size, Maximum Dimension, cm

11 Initially Underwent Excision of VP
11 First Had Pre-Op Arterial Embolization of Tumor Feeding Vessels
5.9 (± 1.9) Mean (SD) Size of Embolized Tumors, Maximum Dimension, cm
9 With CN Sacrifice (X; 7, IX; 2, X; 2, Cervical Sympathetic Chain: 1)
3 Required Ligation of Vessels of Neck

2 Initially Received Radiation (RT) to VP
50 – 56.4 Range of Total Radiation Dose Given, Gray (Gy)
1.8 – 2.0 Range of Single Dose Fractionations Given, Gy

8 Initially Observed with Serial Imaging
7 Observed Due to VP Causing Minimal/No Symptoms, with Likely Surgical Morbidity
1 Observed Due to Significant Comorbidities and Advanced Age

3.5 (2-5.3) Mean (Range) Duration of Patient Follow-Up Post-RT, Months
2 (100 %) Patients Initially Treated with RT or SRS Had Minimal Growth of VP and Required No Additional Treatment During Follow-Up Period

26 (3-59) Mean (Range) Duration of Observation with Serial Imaging, Months
2 With VP Developed New CN (IX, X, XI, XII) Dysfunction During Observation Period
1 Underwent VP Excision with CN IX Sacrifice due to Development of Neck Pain
Fig. 5. Proposed clinical algorithm for diagnostic evaluation & treatment of HNPGL. Panel A: Beginning with suspected HNPGL, diagnostic evaluation should commence with patient history and physical exam (1), followed by head and neck imaging (2) to confirm diagnosis of HNPGL and case presentation at Tumor Board (3). Panel B: Following comprehensive diagnostic evaluation as in panel A, providers should consider a number of tumor- and patient-related factors when choosing between observation and protocols for active treatment of HNPGL.
sensitivity of roughly 22% for HNPGl, though their utility lies in their near 100% sensitivity for diagnosing a concomitant catecholamine-secreting paragangliomas at other sites in SDHx mutation carriers that would demand prioritized treatment.23,34 Thus, a baseline assessment of plasma metanephrines should be performed in all patients with HNPGl.

Multimodal imaging techniques were often employed (Figs. 2–4) in our cohort. Angiography commonly supplemented initial contrast-enhanced CT and MRI in all HNPGl subsites except for TP. Angiography allowed for mapping of dominant tumor feeding vessels (eg, ascending pharyngeal artery) in preparation for embolization and was useful in identifying important collateral vessels from the internal carotid and vertebral arteries requiring preservation during surgical extirpation.8 Baseline and post-treatment audiometry was uniformly employed in JP and TP cases to assess long-term hearing outcomes in these patients.25

In our entire HNPGl cohort, observation with serial imaging was a popular approach for patients with small, asymptomatic HNPGl (Figs. 2–4) to define tumor growth pattern and avoid operative morbidity to lower cranial nerves. A “watchful waiting” protocol was employed in 40/194 patients (20.6%) with HNPGl over a range of 24–73 months of follow-up. A switch to active treatment planning occurred in seven (17.5%) patients due to radiologic growth of HNPGl (two CBP, one JP), pain (one VP), or new cranial nerve dysfunction (two VP, one SCP). A dearth of retrospective evidence supports “watchful waiting” as a viable initial management in appropriately selected HNPGl patients due to indolent growth patterns and exceedingly low rates of malignant degeneration or death due to HNPGl progression.26–29

Iatrogenic damage to lower cranial nerves is the foremost risk in surgical extirpation of HNPGl.30,31 New cranial nerve dysfunction after surgery was seen in 20/49 (40.8%) patients with unilateral CBP and 6/16 (37.5%) patients with JP. The former is a considerably higher number than in other published reports likely due to a referral bias favoring a greater number of Shamblin III tumors treated at our institution.32 Permane nt CN X palsy and unilateral Homer’s syndrome was virtually universal in VP (11/11 patients) and SCP (5/6 patients) cohorts undergoing surgery. Nevertheless, cure rates afforded by surgery were excellent across all HNPGl subsites. In the JP cohort, function-preserving, sub-total resection was followed by adjuvant radiation in 8/14 (51.7%) patients (Fig. 3). In five of these cases, adjuvant radiation was administered expeditiously after resection. Conversely, radiation was prompted by tumor recurrence/regrowth in three cases (roughly one in five JP patients undergoing sub-total resection) validating rates of recurrence/regrowth seen in other JP cohorts.33 Increased utilization of this function-preserving approach to JP treatment may therefore necessitate patient counseling regarding likelihood of adjuvant treatment and/or timely adjuvant radiation therapy to preempt tumor recurrence/regrowth.

At our institution, unilateral and bilateral CBP, JP, VP, and SCP frequently undergo angiographic embolization 24–72 hours prior to surgery, though our data suggest larger size does not reliably influence surgeon preference for embolization. At present, there remains a paucity of strong data on which HNPGl characteristics (eg, size, subsite) predict greater benefit of preoperative embolization on outcomes.34,35 Therefore, a best practices approach to HNPGl embolization should involve a case-based consideration of institutional preferences, level of interventional/vascular radiology expertise, and tumor-specific factors such as size, subsite, and proximity to lower CNs.

Fractioned radiation (RT) and stereotactic radiosurgery (SRS) produce long-term, durable HNPGl control and were most commonly employed in our JP and VP cohorts, providing excellent tumor control over 2–119 months of follow-up and causing no treatment complications (Figs. 3 and 4). These therapies are clearly highly-efficacious, safe alternatives to surgery and are best suited for patients with large CBP, JP, VP, or multifocal HNPGl who have a high likelihood of operative morbidity to lower cranial nerves or contraindications to surgery (eg, medical comorbidities).13

Genetic testing for hereditary predisposition to HNPGl is crucial for active treatment planning, screening for co-occurring pheochromocytoma and multifocal tumors, evaluation of at-risk relatives, and in determining protocols for life-long surveillance.3 Some have posited a step-by-step strategy for genetic testing based on clinical features of HNPGl (eg, begin with SDHD or SDHB testing in multi-focal or malignant HNPGl, respectively).36 However, although some genotype-phenotype correlations in specific SDHx-related HNPGl are evident, there is a significant clinical overlap of syndromes caused by different SDHx mutations. For this reason, and as genetic testing becomes more accessible and affordable,38 initial screening for known pathogenic mutations in all 12 of the known hereditary susceptibility genes likely improves sensitivity and patient care in this population.

CONCLUSIONS
Management of each HNPGl case should be individualized and tailored to specific patient-, tumor-, and genetic-factors. However, an algorithmic approach to management, as we posit (Figure 5) based on our extensive institutional expertise, can provide a general framework for best practices of current HNPGl evaluation and management.

ACKNOWLEDGMENTS
The authors would like to thank the diverse faculty and staff of the Departments of Otolaryngology—Head and Neck Surgery, Radiology, Radiation Oncology, and Genetics at the University of Michigan who see and care for these patients. JDS received funding support from an NIH T32 Training Grant (T32 DC 5356-15).

AUTHOR CONTRIBUTIONS
Conception or Design of Study: JDS, TE, GJB. Acquisition, Analysis, or Interpretation of Data: JDS,
BIBLIOGRAPHY

1. Fishbein L. Pheochromocytoma and paraganglioma: Genetics, diagnosis, and treatment. *Hematol Oncol Clin North Am* 2016;30:135–150.

2. Pellitteri PK, Rinaldo A, Mysiaszek D, et al. Paragangliomas of the head and neck. *Oral Oncol* 2004;40:563–575.

3. Dahia PLM. Pheochromocytoma and paraganglioma pathogenesis: Learning from genetic heterogeneity. *Nat Rev Cancer* 2014;14:108–119.

4. Piccini V, Rapizzi E, Bacca A, et al. Head and neck paragangliomas: Genetic spectrum and clinical variability in 79 consecutive patients. *Endoor Relat Cancer* 2012;19:2:149–155.

5. Boedeker CC, Hensen EF, Neumann HPH, et al. Genetics of hereditary head and neck paragangliomas. *Head Neck* 2014;36:907–916.

6. Van duinen N, Corssmit EP, de Jong WH, Broekman D, Kema IP, Romijn JA. Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. *Eur J Endocrinol* 2013;169:3:377–382.

7. Corrales CE, Fishbein N, Jackler RK. Imaging innovations in temporal bone disorders. *Otologyng Clin North Am* 2015;48:2:263–280.

8. Woden S, Gmejte JF. Paragangliomas of the head and neck. *Neuroimag Clin N Am* 2016;26:259–278.

9. Mendenhall WM, Amdur RJ, Vaysberg M, et al. Head and neck paragangliomas. *Head Neck* 2011;33:1530–1534.

10. Jansen JC, van den Berg R, Kaiper A, van der Mey AG, Zijnderman AH, Cornelisse CJ. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer* 2000;88:2811–2816.

11. Michalowska I, Cwikla JB, Michalski W, et al. Growth rate of paragangliomas related to germline mutations of the SDHX genes. *Endoor Pract* 2017;23:3:342–352.

12. Timmers HJ, Ginernez-Roqueplo AP, Mannelli M, Pacak K. Clinical aspects of SDHx-related pheochromocytoma and paraganglioma. *Endoor Relat Cancer* 2009;16:2:391–400.

13. Gillo P, Morris CG, Amdur RJ, et al. Radiotherapy for benign head and neck paragangliomas: A 45-year experience. *Cancer* 2014;120:3738–3743.

14. Antilla T, Hayry V, Nicoli T, et al. A two-decade experience of head and neck paragangliomas in a whole population-based single centre cohort. *Eur Arch Otorhinolaryngol* 2015;272:2045–2053.

15. Ngwenya LB, Chiacca EA. Treatment for paragangliomas: Passing the test of time. *World Neurosurg* 2012;77:639–641.

16. Kollett M, Minovi AA, Draft W, Bockmuhl U. Cervical paragangliomas—results from genetic heterogeneity. *Eur J Endocrinol* 2017;177:2:103–113.

17. Medina M, Praasad SC, Pataenik U, et al. The effects of tyraminomastoid paragangliomas on hearing and the audiological outcomes after surgery over a long-term follow-up. *Audiol Neurootol* 2014;19:5:342–350.

18. Carlson ML, Sweeney AD, Wanna GB, Netterville JL, Haynes DS. Natural history of glomus jugulare: A review of 16 tumors managed with primary observation. *Otolaryngol Head Neck Surg* 2015;152:1:98–105.

19. Langerman A, Athavale SM, Ranganaraj SM, Sinard RJ, Netterville JL. Natural history of cervical paragangliomas: Outcomes of observation of 45 patients. *Arch Otolaryngol Head Neck Surg* 2012;138:4:341–345.

20. Jansen TTG, Timmers HIJLM, Marres HAM, et al. Feasibility of a wait-and-scan period as initial management strategy for head and neck paragangliomas. *Head Neck* 2017;39:10:2988–2994.

21. Praasad SC, Mimoune HA, D’Orazio F, et al. The role of wait-and-scan and the efficacy of radiotherapy in the treatment of temporal bone paragangliomas. *Otol Neurotol* 2014;35:5:922–931.

22. Baccia A, Medina M, Ait Mimoune H, et al. Lower cranial nerves function after surgical treatment of Fisch Class C and D tympanojugular paragangliomas. *Eur Arch Otorhinolaryngol* 2015;272:311–319.

23. Lope Ahmad RA, Sivalingam S, Kenzushi M, et al. Oncologic outcome in surgical management of jugular paraganglioma and factors influencing outcomes. *Head Neck* 2013;35:4:527–534.

24. Anand VK, Alemar GO, Sanders TS. Management of the internal carotid artery during carotid body tumor surgery. *Laryngoscope* 1995;105:231–235.

25. Li D, Zeng XJ, Hao SY, et al. Less-aggressive surgical management and long-term outcomes of jugular foramen paragangliomas: a neurosurgical perspective. *J Neurosurg* 2016;125:5:1135–1154.

26. Power AH, Bower TC, Kasperbauer J, et al. Impact of preoperative embolization on outcomes of carotid body tumor resections. *J Vasc Surg* 2012;56:979–988.

27. Jackson RS, Myhill JA, Mhaskar RS. The effects of preoperative embolization on carotid body paraganglioma surgery: A systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2015;153:6:943–950.

28. Neumann HPH, Eric Z, Boedeker CC, et al. Clinical predictors for germ-line mutations in head and neck paraganglioma patients: cost reduction strategy in genetic diagnostic process as fall-out. *Cancer Res* 2009;69:3650–3656.

29. Ricketts CJ, Forman JR, Rattenberry E, et al. Tumor risks and genotype-phenotype analysis in 358 patients with germline mutations in SDHB and SDHD. *Hum Mutat* 2010;31:41–51.

30. Uhlmann WR, Schwalm K, Raymon VA. Development of a streamlined work flow for handling patients’ genetic testing insurance authorizations. *J Genet Couns* 2017;26:4:657–668.