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

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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

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radiosurgery, although observation with serial imaging may also be considered.[9] Recommendations for HNPGL treatment depend on a number of factors. First, HNPGLs exhibit an indolent growth pattern, with an average tumor-doubling time of 4.2–5.5 years,[10,11] and are seldom malignant.[12] Second, fractionated radiation therapy (eg, 45–50 Gy), stereotactic radiosurgery (SRS), and surgery offer comparable 10-year control rates, HNPGL-specific survival, and distant-metastasis free survival, all in excess of 97%.[13,14] As operative morbidity to CNs VII–XII is often unavoidable, radiation or SRS may offer improved functional outcomes with regard to speech, swallowing, and facial nerve and shoulder function. As such, a steadily-increasing proportion of patients with HNPGL are being treated with non-curative or debulking surgery with preservation of CNs followed by adjuvant radiation, or exclusively by non-surgical therapies.[15,16] Finally, patient-related factors, including age and goals of care, medical comorbidities, and genetic status also serve as critical factors to consider before embarking on any specific treatment path.

Ultimately, clinical management of these tumors remains challenging owing to heterogeneity in clinical presentation, existence of multiple treatment alternatives, and potential to cause serious detriment to critical functions of the head and neck.[17] Herein, we provide a report of our institutional experience with 194 patients with HNPGLs from 2000–2017, with an emphasis on our approach to clinical evaluation, treatment, and genetic investigation of CBP, JP, VP, TP, SCP, and multi-focal HNPGL patient cohorts. Finally, we posit an evidence-based algorithm for multidisciplinary clinical evaluation and management of these diverse neoplasms.

MATERIALS AND METHODS

Following approval by the University of Michigan Institutional Review Board (HUM00120115), 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[18] and EMERSE[19] 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 $\geq$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, $\alpha = 0.05$) were performed using SPSS (Version 22.0, Chicago, Illinois, U.S.A.).

RESULTS

Patient Demographics & Paraganglioma Localization

The mean (SD) age of our cohort was 51.8 ($\pm$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

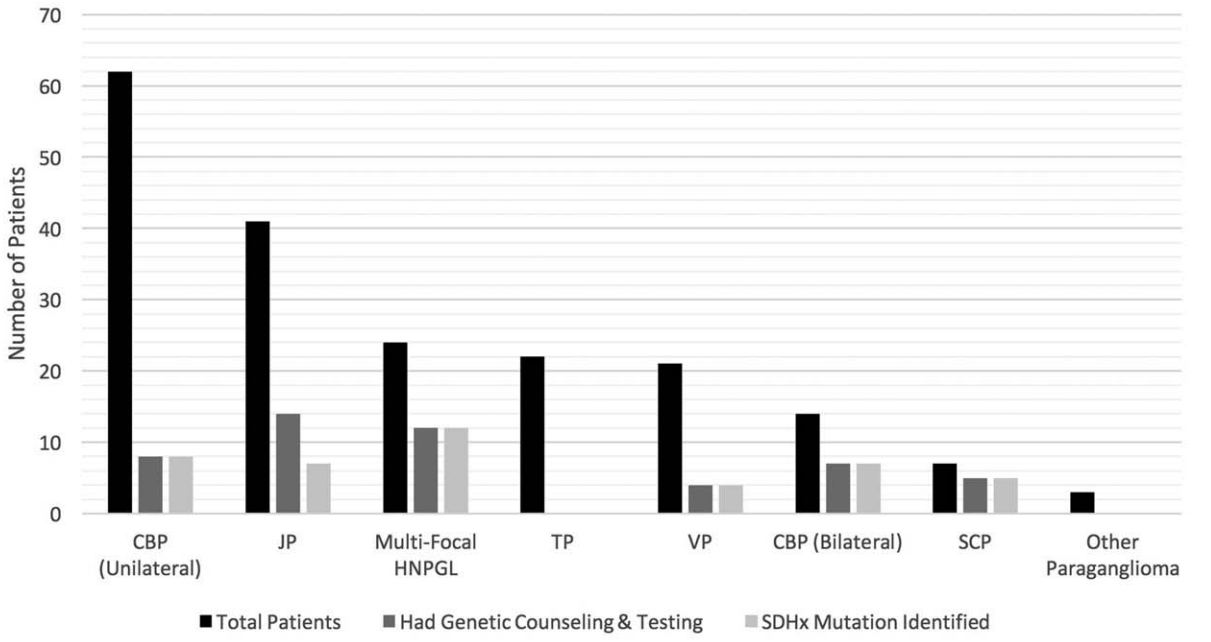
Genetic testing for *SDHx* variants become widely adopted only after 2008. In our entire cohort of HNPGL patients, 51 (26.3%) underwent genetic counseling and testing, 44 of which were diagnosed with HNPGL in 2008 or later. Of the 51 patients undergoing genetic testing, 43 (84.3%) were confirmed to carry 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.

Among 49 patients with CBP treated initially with surgery, 25 patients first underwent preoperative angiographic embolization. There was no difference in CBP size between patients undergoing preoperative embolization versus those that did not (3.8 ± 1.2 cm vs. 3.4 ± 1.6 cm, $p = 0.337$). Preoperative tumor embolization was complicated by new CN weakness in two patients (CN X, XII, respectively) and a right, fronto-parietal ischemic stroke in one patient, precluding definitive treatment of CBP. Among the 12 patients with CBP initially undergoing a "wait and scan" approach, 2 (16.7%) eventually

A



B

Patient #	Paraganglioma Localization	Patient #	Paraganglioma Localization
1	CBP (R), CBP (R)	14	CBP (L), PAP
2-3	CBP (L), VP (L)	15	JP (L), MP
4	CBP (L), VP (L)†	16	SCP (R), bilat Pheo
5	CBP (R), VP (R)	17	bilat CBP, VP (L)
6	CBP (L), VP (R)	18	bilat CBP, CNM, MP‡
7	VP (L), VP (R)†	19	CBP (L), JP (R), VP (R)
8	CBP (R), JP (R)	20	CBP (R), JP (L), SLNP (R)
9-10	CBP (L), JP (R)	21	bilat CBP, JP (R), SGP (L)
11	JP (L), TP (L)	22	CBP (L), CNM‡
12	VP (R), GPP (R)†	23	CBP (L), CNM, VM, PM‡
13	CBP (L), MP	24	bilat CBP, JP (L), MP, PM, FLM‡

Fig. 1. Localization of paraganglioma (s) of the head and neck in 194 patients at our institution from 2000–2017. Panel A: Frequency histogram depicting total patients and patients with confirmed mutations in *SDHx* gene by paraganglioma location (*Other paraganglioma*: includes parotid gland/CN VII paraganglioma, infratemporal-pterygopalatine paraganglioma, and gangliocytic paraganglioma of skull base. Panel B: Index and localization of 24 patients with multi-focal or metastatic paragangliomas. bilat = bilateral; CBP = carotid body paraganglioma; CNM = cervical nodal metastases; FLM = frontal lobe metastases; GPP = glossopharyngeal paraganglioma; JP = jugular paraganglioma; L = left-sided; MP = mediastinal paraganglioma; PAP = para-aortic paraganglioma; Pheo = pheochromocytoma; PM = pulmonary metastases; R = right-sided; SCP = sympathetic chain paraganglioma; SGP = supraglottic paraganglioma; SLNP = superior laryngeal nerve paraganglioma; TP = tympanic paraganglioma; VM = vertebral body metastases; VP = vagal paraganglioma. † Paragangliomas developed sequentially. ‡ Metastatic disease

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 nonsecreting, 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

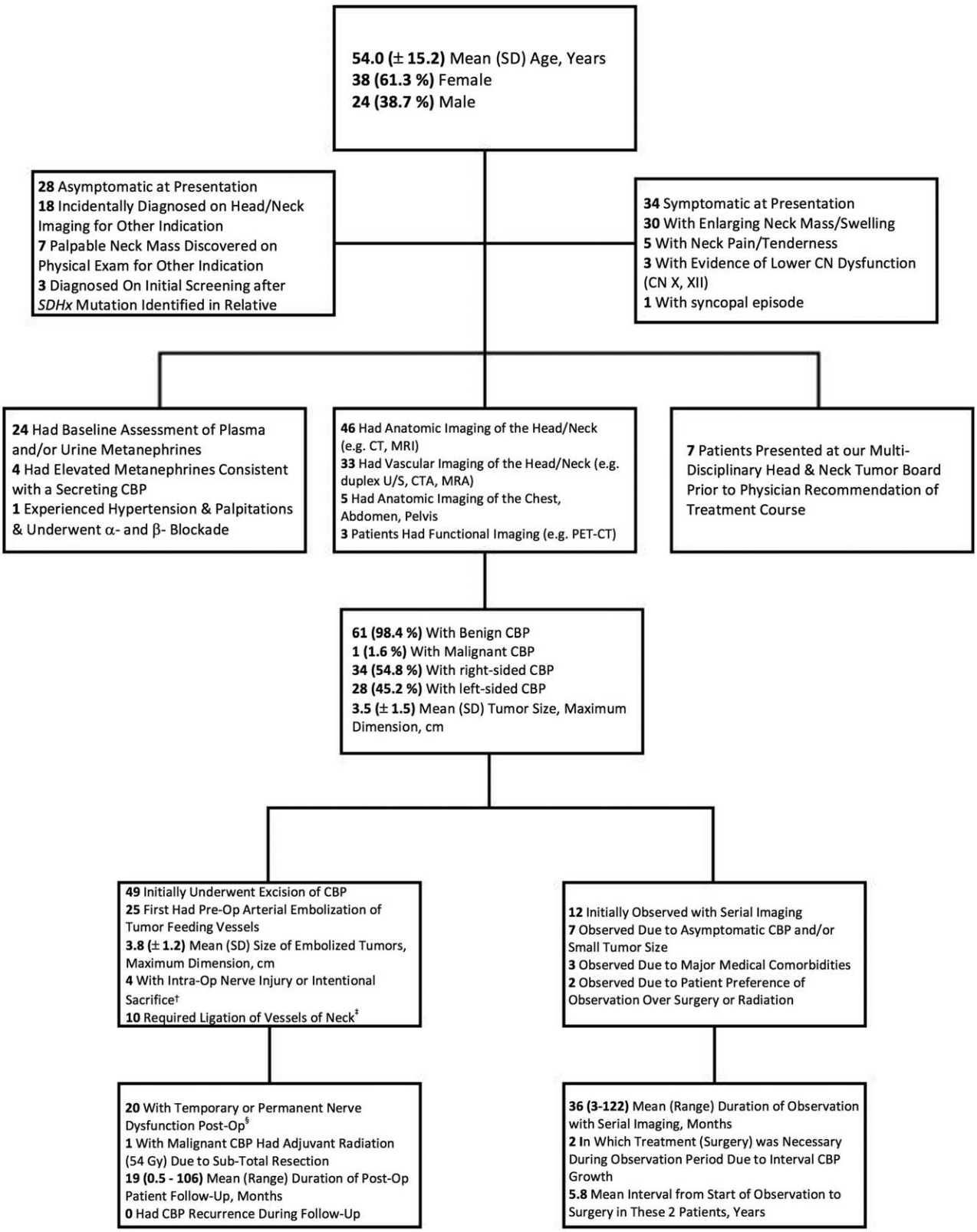


Fig. 2. Diagnostic evaluation & treatment of patients (n = 62) with solitary, unilateral carotid body tumors (CBP). † CN IX, X, XII. ‡ External carotid artery, lingual artery, superior thyroid artery, thyrocervical trunk, superior thyroid artery, and internal jugular vein. § CN VII, marginal mandibular branch: 4 patients, CN IX: 3 patients, CN X: 10 patients, CN XI: 2 patients, CN XII: 8 patients, cervical sympathetic trunk: 3 patients

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 subsites 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 subsites 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

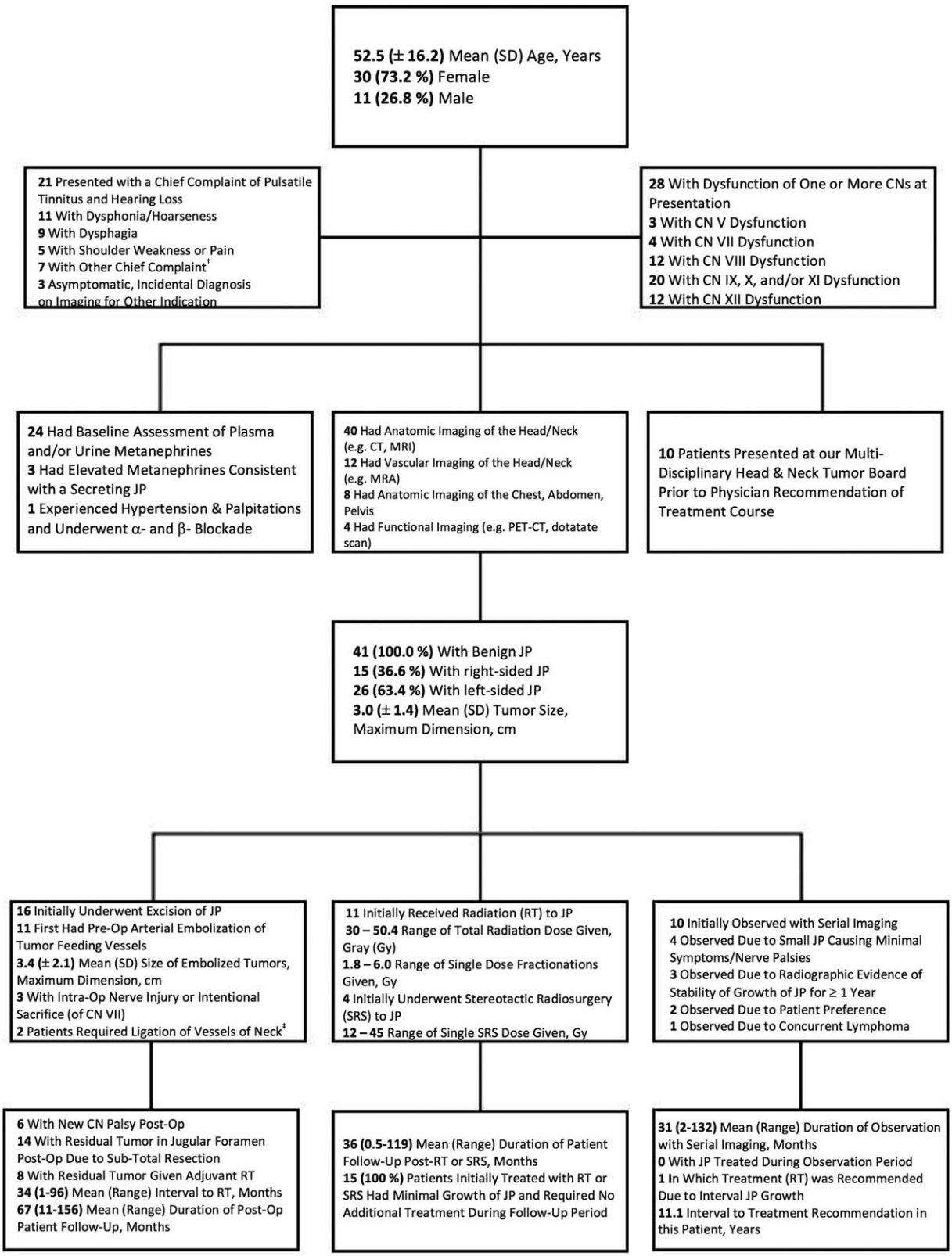


Fig. 3. Diagnostic evaluation & treatment of patients (n = 41) with solitary, unilateral jugular paraganglioma (JP). † 2 patients with facial paralysis or weakness, 3 with neck/occiput pain, 1 with dysarthria, and 1 with altered vision and papilledema. ‡ External carotid artery, occipital artery, and internal jugular vein

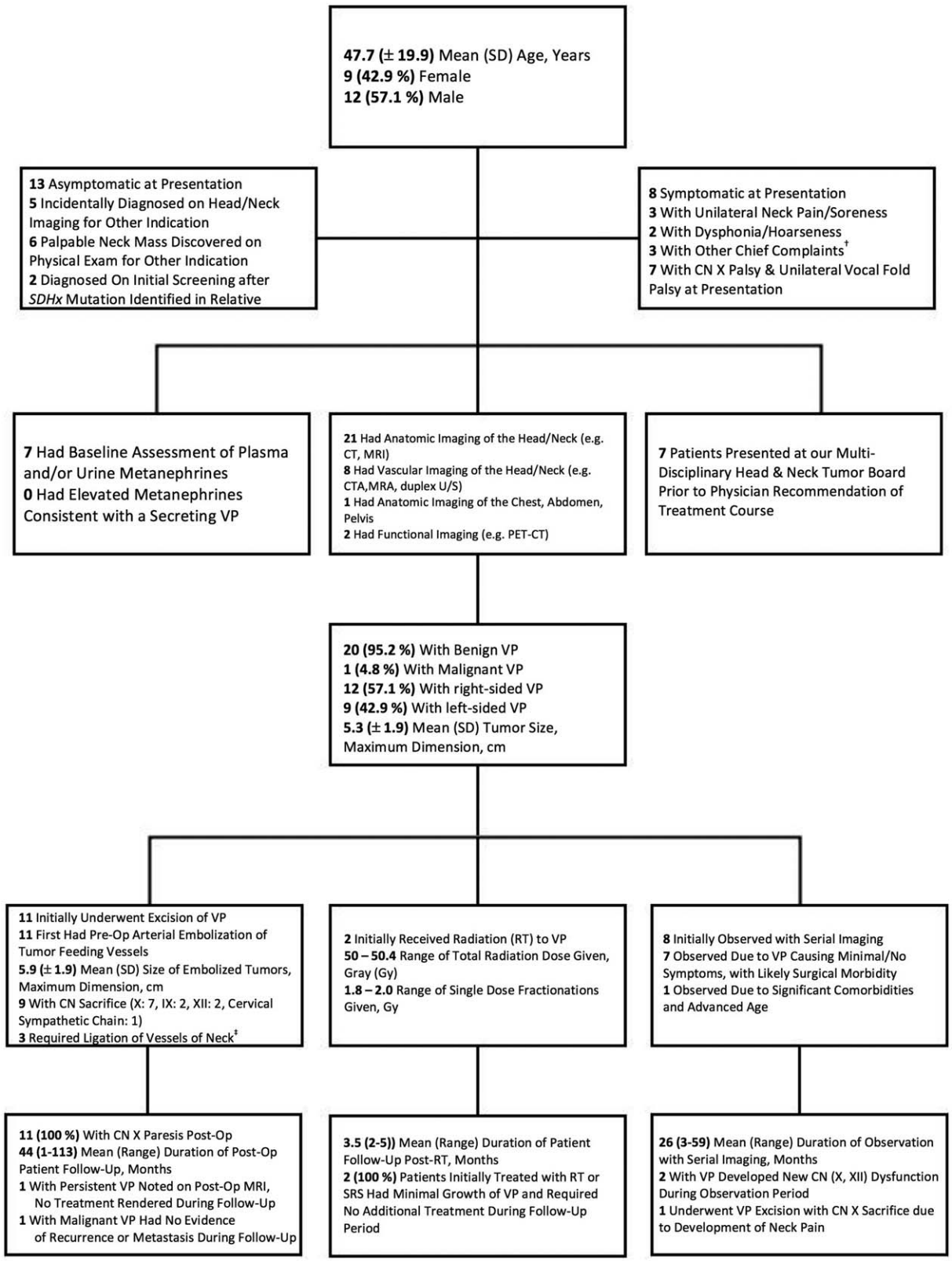


Fig. 4. Diagnostic evaluation & treatment of patients (n = 21) with solitary, unilateral vagal paraganglioma (VP). † 1 patient with painless neck swelling/fullness, 1 with pulsatile tinnitus, 1 with dysphagia. ‡ Ascending pharyngeal artery, facial artery, internal carotid artery, external carotid artery

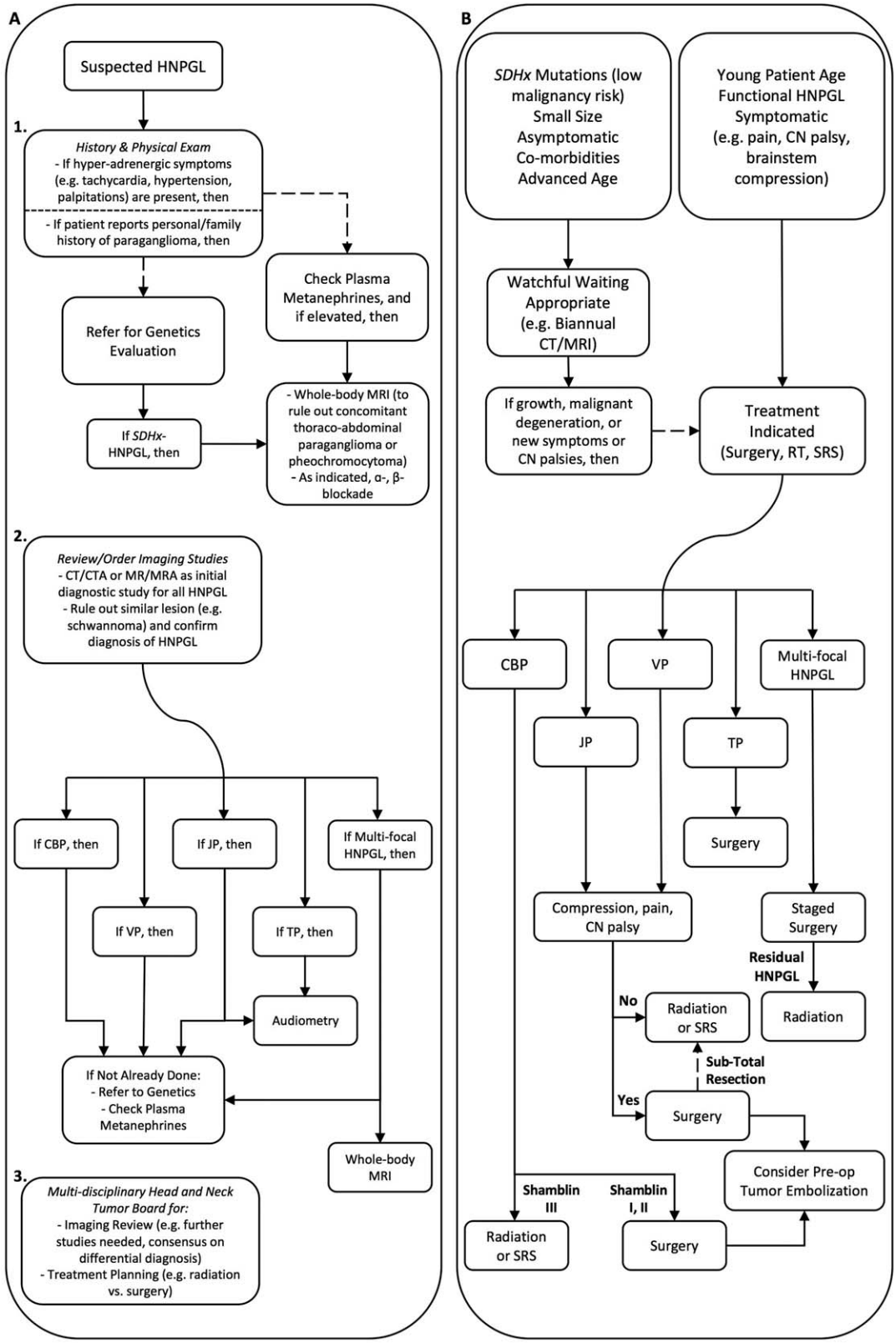


Fig. 5. Proposed clinical algorithm for diagnostic evaluation & treatment of HNPGL. Panel A: Beginning with suspected HNPGL, diagnostic evaluation should commence with patient history and physical exam (1), followed by head and neck imaging (2) to confirm diagnosis of HNPGL and case presentation at Tumor 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.[23,24] 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] Permanent CN X palsy and unilateral Horner'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,[37] 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.

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AUTHOR CONTRIBUTIONS

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

RNH, OAD, TE, GJB. Preparation and Revision of Manuscript: JDS, RNH, OAD, MEP, CRB, GTW, TE, GJB. Approval of the Manuscript: JDS, RNH, OAD, MEP, CRB, GTW, TE, GJB.

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