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*When treatment for paragangliomas of the head and neck is indicated, an algorithm-based approach can help optimize outcomes.*

## Treatment of Head and Neck Paragangliomas

Kenneth Hu, MD, and Mark S. Persky, MD

**Background:** Commonly occurring in the head and neck, paragangliomas are typically benign, highly vascular neoplasms embryologically originating from the extra-adrenal paraganglia of the neural crest. Frequently, these tumors are associated with the vagus, tympanic plexus nerve, the carotid artery, or jugular bulb. Their clinical presentation can vary across a wide spectrum of signs and symptoms.

**Methods:** We reviewed and compared standard treatment approaches for paragangliomas of the head and neck.

**Results:** In general, surgery is the first-line choice of therapy for carotid body tumors, whereas radiotherapy is the first-line option for jugular and vagal paragangliomas.

**Conclusions:** Because of the complexity of clinical scenarios and treatment options for paragangliomas, a multidisciplinary algorithmic approach should be used for treating paragangliomas. The approach should emphasize single-modality treatment that yields excellent rates of tumor control, low rates of severe, iatrogenic morbidity, and the preservation of long-term function in this patient population.

### Introduction

Commonly occurring in the head and neck, paragangliomas are typically benign, highly vascular neoplasms embryologically originating from the extra-adrenal paraganglia of the neural crest, and they are typically associated with the vagus, tympanic plexus nerve, the carotid artery, or jugular bulb.<sup>1-3</sup> Clinically, patients with paragangliomas present with diverse signs and symptoms. They may have a family history of paragangliomas and can present with multicentric tumors regardless of sporadic or familial origin.<sup>1-3</sup>

In the era of safe embolization protocols and sophisticated surgical approaches to the skull base, surgery has become the preferred treatment method for paragangliomas.<sup>1-5</sup> Historically, health care professionals relied on radiotherapy to treat debilitated or elderly patients with unresectable, extensive tumors or paragangliomas, but long-term experience and advances in the field of radiation oncology have demonstrated that first-line radiotherapy for the treatment of paragangliomas has low rates of long-term complications and high rates of tumor control.<sup>1-3</sup> Thus, radiotherapy now plays an important role in treatment algorithms.<sup>1-3</sup> In addition, individualized treatment strategies may also include observation.

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### Multicentricity

Rarely, sporadic cases (10%) will present with a concurrent second paraganglioma, and multicentricity may be present in up to 85% of those with a genetic predisposition.<sup>6-8</sup> A second carotid body tumor is by far the most common pattern of a synchronous secondary paran-

glioma (20% of carotid body tumors).<sup>6-8</sup> An additional contralateral or ipsilateral paraganglioma, as well as bilateral carotid body tumors, poses significant and challenging treatment problems for the clinician, because patients undergoing resection of bilateral carotid body tumors may experience baroreceptor function loss and deficits in the cranial nerves resulting in labile hypertension.<sup>1,2,9</sup> These tumors may be metachronous, indicating that surveillance may be appropriate for select paraganglioma cases. Routine follow-up imaging with magnetic resonance imaging (MRI) or fluorodeoxyglucose/fluorodopa or indium pentetretotide positron emission tomography (PET) is warranted in multicentric, metachronous tumors.<sup>1-3</sup>

## Malignancy

Paragangliomas are rarely malignant, representing a small subset of extra-adrenal paragangliomas with a propensity for regional lymph-node and distant metastatic disease, primarily to bone, the lungs, and liver.<sup>1-3</sup> A higher rate of malignancy has been observed in sporadic paragangliomas compared with the familial type, with the exception of the familial syndrome associated with *SDHB* mutation (rate of malignancy, 30%–70%).<sup>10,11</sup> The rate of malignancy depends on the site of origin: Although rare, orbital and laryngeal paragangliomas have a 25% rate of malignancy, which is the highest rate of any paraganglioma.<sup>1-3</sup> By comparison, the rate of malignancy for vagal paragangliomas is between 16% and 19%, between 5% and 6% for jugulotympanic paragangliomas, and between 3% and 4% for carotid body tumors.<sup>10</sup> No histological criteria exist to diagnose malignancy in primary tumors. The health care professional can make the diagnosis only if malignancy is confirmed by the presence of a tumor in the lymph nodes or the disease has metastatically spread to distant sites.<sup>1-3</sup>

It is worth emphasizing that the implications for treatment are significant when malignant disease is present.<sup>11-13</sup> Locoregional control is best achieved with primary resection followed by adjuvant radiotherapy.<sup>1-3</sup> The disease is known to recur for up to 20 years.<sup>1-3</sup> The 5-year survival rates are 50% to 80% for those with nodal disease and up to 11% for those with distant spread.<sup>14</sup>

## Anatomy and Physiology

Diffusely distributed throughout the upper part of the body, paraganglia facilitate the chemoreceptive reflexes of the cardiovascular system. They contain chief cells with the capacity to secrete neuropeptides (eg, norepinephrine), which, in turn, influence vascular reflexes.<sup>1-3</sup>

The carotid body, which is a type of paraganglion, can sense changes in pH, arterial oxygen pressure, and level of carbon dioxide.<sup>1-3</sup> Located within

the carotid bifurcation, the carotid body is a discrete, oval structure that directly receives its blood supply from the carotid bifurcation via the glomic arteries (Fig 1).<sup>3</sup> The afferent reflex is mediated by a glossopharyngeal nerve branch called the nerve of Hering. Expanding tumors that originate from here can impair sympathetic nerve chain function as well as cranial nerves X and XII.<sup>1-3</sup>

Distributed within the temporal bone in close association with the Jacobsen nerve, which is the tympanic branch of the glossopharyngeal nerve (see Fig 1), are the jugulotympanic paraganglia.<sup>3</sup> Typically, temporal bone paraganglia are located in the jugular fossa, and symptoms may involve early functional impairment of cranial nerves IX, X, XI within the jugular foramen, and XII as it exits the hypoglossal canal.<sup>1-3</sup>

Vagal paraganglia are distinctly separate from jugulotympanic paraganglia because they do not form discrete bodies; in addition, they may be interspersed within the vagal nerve fibers in the pars nervosa of the jugular foramen (which transmits lower cranial nerves IX, X, and XI) or located within the vagus nerve beneath the perineurium.<sup>1-3</sup> The superior vagal ganglion is visible at the level of the jugular foramen. The ori-

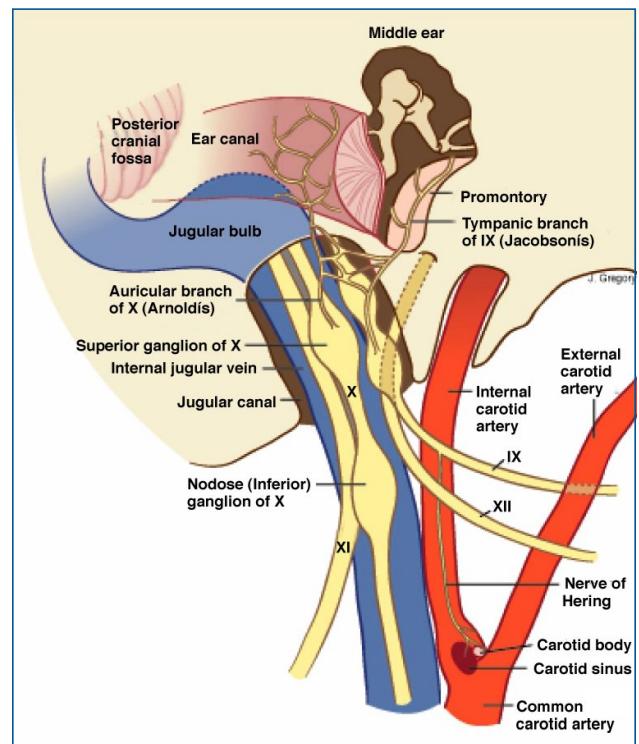


Fig 1. — Schematic representation of common sites of head and neck paragangliomas and their relationship to the lower cranial nerves and major vessels.

From Persky MS, Hu KS. Paragangliomas of the head and neck. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. 3rd ed. Lippincott Williams and Wilkins, Philadelphia, PA; 2009. Reprinted with permission by Wolters Kluwer.

gin of most vagal paragangliomas is the nodose vagal ganglion, which is located approximately 1 to 2 cm below the jugular foramen (see Fig 1).<sup>3</sup> Both the superior and nodose vagal ganglia are proximal to the pars venosa of the jugular foramen, cranial nerves IX to XII, and the ascending portion of the petrous internal carotid artery.<sup>15</sup> Therefore, vagal paragangliomas have distinct therapeutic sequela based on their close anatomical association with the superior portion of the vagal nerve and other adjacent neurovascular structures.<sup>1-3</sup>

Extra-adrenal paraganglia lack methyltransferase, a requirement for converting norepinephrine to epinephrine; the metabolic breakdown of catecholamines to metanephrine (from epinephrine) and normetanephrine (from norepinephrine) as well as vanillylmandelic acid can be detected in urine. Thus, appropriate urine and serum analysis can be used to detect actively secreting paragangliomas.<sup>1-3</sup>

## Workup

### History and Physical Examination

The health care professional should obtain a thorough history and perform a physical examination for any patient presenting with a paraganglioma, evaluating for cranial nerve dysfunction, possible signs and symptoms related to catecholamine secretion as well as evidence of malignant transformation.<sup>1-3</sup> Typically, carotid body tumors present as an enlarging asymptomatic mass at the level of the carotid bifurcation. Dysfunction of the cranial nerve may be indicative of the presence of large tumors extending into the jugular foramen.<sup>1-3</sup> Patients with jugulotympanic tumors may present with pulsatile tinnitus or conductive hearing loss. Otoloscopic examination may reveal the Brown sign involving a red-blue lesion in the middle ear that blanches with positive pressure.<sup>1-3</sup> For patients with more advanced disease, lower cranial nerve deficits may become apparent. Frequently (< 50% of cases), vagal paragangliomas present with multiple cranial neuropathies involving the hypoglossal, vagus, and spinal accessory nerves.<sup>3,13,16,17</sup>

Attention should be given to a possible familial history of paragangliomas, von Hippel-Lindau syndrome, and type 2 multiple endocrine neoplasia.<sup>1-3</sup> Sweating, hypertension, tachycardia, and nervousness may be symptoms of secreting tumors. Laboratory studies, including 24-hour urinalysis and serum catecholamine screening (norepinephrine, epinephrine, and metanephrine), should be ordered for all patients with suspected paraganglioma.<sup>1-3</sup>

### Diagnostic Imaging

In general, fine needle biopsy is not indicated because radiographic studies are pathognomonic.<sup>1-3,16,18</sup> The

health care professional can obtain computed tomography (CT) with contrast for delineating paragangliomas because the contrast enhances these highly vascular tumors.<sup>1-3</sup> In addition, CT is frequently diagnostic given the characteristic patterns tumors displace to the internal and external carotid arteries.<sup>3</sup> CT can be utilized to define the erosion and any possible skull-base involvement, including in the temporal bone. A well-circumscribed mass occupying the carotid bifurcation that has splayed the external and internal carotid arteries is characteristic of carotid body tumors, which posterolaterally displace the internal carotid artery. Typically, when vagal paragangliomas are present, the internal carotid artery is anteriorly/medially displaced, occupying the superior parapharyngeal space (with or without skull-base involvement).<sup>1-3</sup> In the early disease stage, jugulotympanic paragangliomas can be distinguished — in particular when a paraganglioma is located in the tympanic cavity alone — and bone destruction patterns typical for this type of paraganglioma are observed.<sup>1-3</sup>

MRI with gadolinium contrast is a complementary imaging modality that the health care professional can also employ for evaluating head and neck paragangliomas.<sup>1-3</sup> Gadolinium should be used, if available, because paragangliomas show intense signal enhancement in this medium.<sup>19</sup> Similar to CT, use of contrast for MRI aids the health care professional in the delineation of the tumor, and it also helps to survey and detect synchronous paragangliomas of the head and neck as well as confirm the diagnosis. On T2-weighted MRI, the characteristic “salt and pepper” appearance observed is essentially pathognomonic and is related to the high-flow vascular voids within the vascular tumor.

Findings on magnetic resonance angiography that demonstrate the patency of the circle of Willis provide the surgeon with critical information about intracranial circulation. Angiography can be used to detail the features of tumor flow dynamics (the venous drainage and blood supply of the tumor venous drainage) as well as the vascular anatomy of the intracranial space and head and neck (Fig 2).<sup>3</sup> If carotid artery sacrifice is anticipated, then cerebral angiography with ipsilateral internal carotid balloon occlusion can be obtained to define the intracranial cerebral circulation. However, because techniques in high-resolution MRI and CT have evolved, the role of magnetic resonance angiography is limited in diagnosis, although it does remain important for use in preoperative planning for tumor resection. Obtaining superselective angiography and performing embolization of the arterial supply can decrease the risk for intraoperative blood loss.

Radionuclide imaging can be used to target the biochemical pathways of catecholamine synthesis. Such imaging techniques include fluorodeoxyglucose

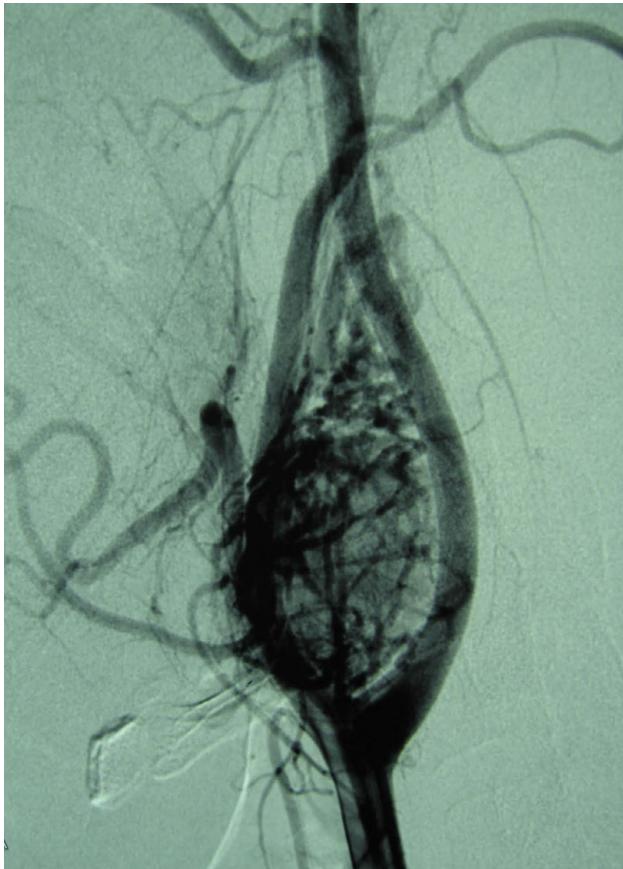


Fig 2. — Carotid body tumor splaying the carotid bifurcation.

From Persky MS, Hu KS. Paragangliomas of the head and neck. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. 3rd ed. Lippincott Williams and Wilkins, Philadelphia, PA; 2009. Reprinted with permission by Wolters Kluwer.

with or without metaiodobenzylguanidine, dihydroxyphenylalanine, fluorodopamine, fluorodopa, or indium octreotide for use with PET.<sup>20,21</sup>

## Surgery

Prior to surgery, the health care professional should typically perform an angiographic evaluation. To evaluate for use of anesthesia, the presence of catecholamine-secreting tumors should be considered because they require an alpha- and beta-adrenergic blockade. Continuous arterial pressure monitoring is ideal, and preparing for possible blood transfusions should be expected.

Based on our experience with paragangliomas, any proposed treatment must be individualized to each patient. Issues to be considered include patient age, medical comorbidities, location and size of the tumor, possible presence of synchronous tumors, and a history of progressive neurological dysfunction.

## Angiographic Evaluation

An important preoperative adjunct for the surgical approach to paragangliomas is superselective angiography

because it can be used for arterial mapping to identify tumor blood supply, tumor flow dynamics, and — perhaps the most important — the displacement of major vessels. Angiography is particularly useful for patients whose tumors are large and are supplied by the external and internal carotid arteries and anastomoses are present between the internal and external carotid systems.<sup>22</sup> The health care professional should evaluate the internal carotid artery for areas of irregularity or constriction as well as the structural integrity of the vessels, because either may indicate that removal could be necessary. Equally important is the venous phase of angiography because it can help the health care professional identify draining vessels, and evaluate the amount of invasion and occlusion of the lumen of the jugular bulb, jugular vein, and sigmoid sinus — which are characteristic findings of jugulotympanic paragangliomas.

If the surgeon anticipates that disruption or removal of the internal carotid artery might be necessary during surgery, then he or she must evaluate for adequate contralateral cerebral circulation; several methods can be used for this purpose. Although it is not available in all settings, xenon CT in conjunction with ipsilateral balloon occlusion can be useful to measure cerebral flow.<sup>23,24</sup> While monitoring the clinical neurological status of the patient, temporary balloon occlusion of the internal carotid artery if a patent circle of Willis is present may be easier to perform. In addition, this method is reliable: Approximately 93% of patients can tolerate removal of their ipsilateral internal carotid artery based on findings from the angiographic evaluation.<sup>9</sup> It is worth noting that conditions in the operating room and the angiographic suite may differ in terms of the cerebral delivery of oxygen.<sup>9</sup> A patient's tolerance for the temporary occlusion of the internal carotid does not preclude the possibility that a delayed cerebrovascular ischemic event may occur following surgery. Particularly among patients with jugulotympanic paragangliomas, venous outflow of the contralateral and ipsilateral transverse sinus and jugular systems should be evaluated. Because anatomical variations exist, an absent or contralateral hypoplastic jugular system may be a contraindication for surgery because of an increased risk of venous stroke after surgery.<sup>25-27</sup>

## Embolization

Embolization is important adjunct therapy, and this is especially true for surgery to treat large paragangliomas. Experienced interventional radiology teams are necessary to avoid surgical complications. Embolization carries the risk of the potential migration of embolization particles into the cerebral circulation, thus resulting in stroke, and it is known to occur in the presence of anastomoses between the internal and exter-

nal carotid systems or flow reversal from the arterial blood supply of the tumor. Advantages to embolization include tumor shrinkage, decreased blood flow, and additional surgical benefits. A decrease in the rate of intraoperative bleeding after embolization results in fewer transfusions, making for more effective tumor dissection with more well-defined tissue planes and more effective identification and preservation of normal anatomical structures, including the cranial nerves. Larger paragangliomas usually demonstrate multiple arterial feeding vessels that should be individually addressed through superselective angiography. With progressive embolization of these vessels, additional compartments of the tumor are devascularized until a tumor “blush” is absent. Surgery should be performed within 48 hours of embolization to avoid collateral or intracranial arterial supply, and steroids should be administered to reduce the inflammatory response following embolization.<sup>28,29</sup>

### Observation

Judicious observation may be appropriate for select patients prior to performing surgery or providing radiotherapy. Small- or moderate-sized, unilateral carotid body tumors can be easily and safely resected; however, enlarging tumors or progressive neurological dysfunction warrants intervention.

### Carotid Body Tumors

The surgeon can make an oblique vertical incision along the anterior border of the sternocleidomastoid muscle to visualize large-sized tumors; by contrast, a transverse neck incision across the sternocleidomastoid muscle should be made to approach small-sized carotid body tumors. Dissection distal and proximal to the tumor helps the surgeon identify the common, internal, and external carotid arteries, and vessel loop control must be applied to anticipate possible injury to the carotid. Precautions related to carotid bypass must be available.

The surgeon should expose the most superior and inferior extent of the internal carotid artery; typically, the vessel is posterolaterally displaced. Because hemostasis is generally feasible with paragangliomas, tumor embolization prior to surgery is unwarranted.<sup>1-3</sup> The surgeon should use caution when dissecting the tumor in the subadventitial plane. Although it should be avoided in most cases, external carotid artery sacrifice may be required if the artery is encased and infiltrated by the tumor. The last surgical step when dissecting the tumor (at the bifurcation of the common carotid artery) occurs when the artery is at its most vulnerable point for damage.<sup>1-3</sup> The surrounding cranial nerves in carotid body tumors may have marked hyperemia of the vasa nervosum of their nerve sheath. In larger tumors, these nerves may be

involved and their dissection may cause dysfunction of the hypoglossal, vagus, and glossopharyngeal nerves. Ligation of the external carotid artery has been previously reported as a way to control blood flow to the tumor, but this maneuver should be avoided because it does not affect blood flow to the tumor and collateral circulation may be profuse.<sup>1-3</sup>

### Jugulotympanic Paragangliomas

The surgeon can perform tympanotomy to approach small-sized tympanic paragangliomas through the external auditory canal. Embolization of these small tumors is not required. Larger-sized tympanic paragangliomas that are confined to the mastoid, middle ear, or both places without breaching the bone across the jugular bulb or the jugulo carotid spine can be exposed through a combined postauricular/endaural approach.

The surgeon is required to combine the temporal and cervical approaches when the jugular bulb is involved. Because intraluminal vascular invasion will be present, the surgeon is required to pack or ligate the internal jugular ligation located inferior and the sigmoid sinus located superior to tumor involvement. The surgeon must also proximally and distally trace and identify cranial nerves IX, X, and XI. More advanced tumors with the potential to involve various branches of the petrous carotid artery that may also extend into the intracranial area might require a postauricular infratemporal fossa approach.

The modes of spread for jugular paragangliomas are shown in Fig 3.<sup>3</sup>

### Vagal Paragangliomas

Located below the jugular foramen (~ 2 cm), vagal paragangliomas typically begin in the inferior (nodose) vagal ganglion. They have also been known to originate in the middle and superior ganglia, situated within the jugular foramen; this location results in early skull-base invasion and, in some cases, extends to the intracranial space. Growth of tumors bidirectionally along the vagus nerve will also inferiorly and superiorly involve the poststyloid parapharyngeal space and jugular foramen, respectively. In general, the internal carotid artery is medially and anteriorly displaced.<sup>7</sup> The surgical approach for jugulotympanic paragangliomas involving the skull base is similar to vagal paragangliomas.

The modes of spread for vagal paragangliomas are shown in Fig 4.<sup>3</sup>

## Complications

### Vascular Injury

The incidence rate for stroke following surgery for paragangliomas has been reported to be as high as 20% and as low as 2% or less.<sup>1-3</sup> With the evolution of

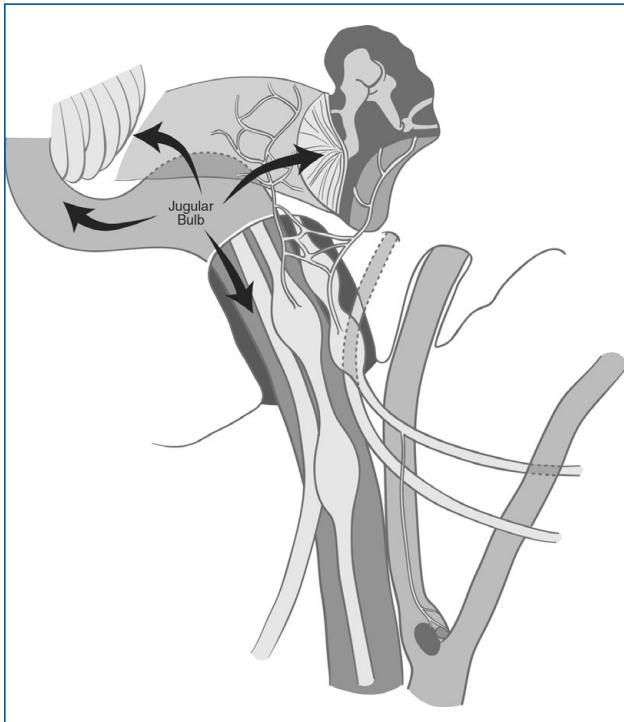


Fig 3. — Modes of spread for jugular paragangliomas.

From Persky MS, Hu KS. Paragangliomas of the head and neck. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. 3rd ed. Lippincott Williams and Wilkins, Philadelphia, PA; 2009. Reprinted with permission by Wolters Kluwer.

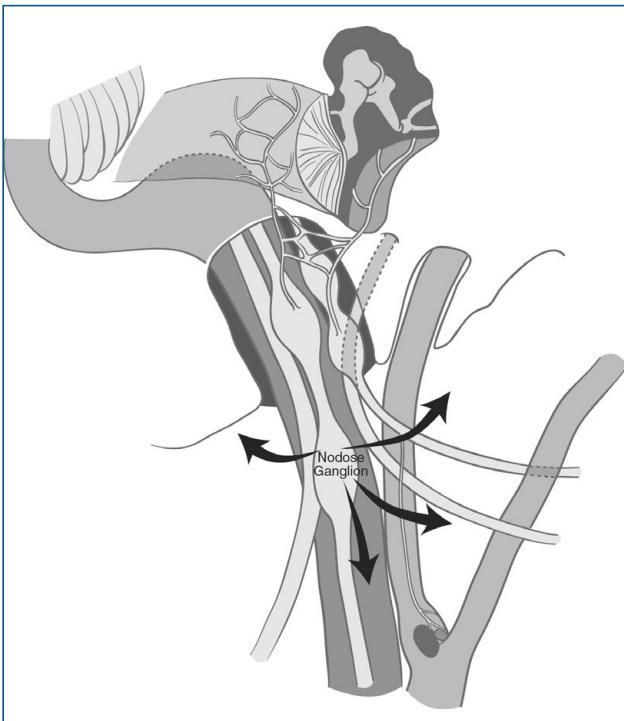


Fig 4. — Modes of spread for vagal paragangliomas.

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preoperative planning, surgical techniques, and diagnostic evaluations, the need to sacrifice the internal carotid and the risk of injury are minimal. The risk of injury to the carotid artery or need for sacrifice following treatment of carotid body tumors is size specific: tumors larger than 5 cm are likely to require carotid reconstruction.

Unlike jugulotympanic paragangliomas and carotid body tumors, vagal paragangliomas are not closely associated with the carotid artery, although the internal carotid artery may be involved in its petrous portion in advanced disease. Rarely, injury may occur, even with adequate surgical exposure and microsurgical technique. If the patient is at high risk for vessel injury within the petrous carotid portion and balloon occlusion testing has been safely and satisfactorily performed, then the surgeon may consider permanent preoperative occlusion of the carotid distal to the tumor.<sup>1-3</sup>

### Baroreflex Failure

Following the resection of bilateral carotid body tumors, the baroreceptor reflex is lost and bilateral denervation of the carotid sinus is unavoidable, resulting in postoperative labile refractory hypertension, tachycardia, diaphoresis, and headache.<sup>30</sup> The long-term treatment of choice is clonidine.<sup>31</sup> Algorithms have been created for the management of bilateral carotid body tumors to avoid long-term postoperative hypertensive issues.<sup>1-3</sup>

### Cranial Nerve Injury

The surgical risk to the lower cranial nerves for the treatment of paragangliomas is site specific and directly related to tumor size. Vagal, jugulotympanic, and carotid body paragangliomas represent, in decreasing order, risk of injury to the cranial nerves. The size of the tumor is especially important in vagal and jugulotympanic paragangliomas. Tumors presenting with extensive skull-base involvement are likely to have extensive lower cranial nerve involvement and often preoperatively present with multiple cranial nerve deficits. Facial nerve involvement in conjunction with preoperative paralysis is a sign of such extensive involvement.<sup>16,30,32-34</sup>

Following surgery, deficits in the cranial nerve may involve impaired aspiration, deglutition, tongue motion, and phonation. Patients with more than 1 cranial nerve deficit do not respond well to treatment because these deficits have additive effects. Those who are older may experience difficulty in recovery because vocal cord medialization may be necessary if a risk of aspiration is present. In such patients, tracheostomy or gastrostomy may be necessary — this is especially true for patients with injuries to the high vagus nerve.

Injury to the accessory nerve results in func-

tional loss of the sternocleidomastoid and trapezius muscles. Patients with such injury should be referred to physical therapy to help avoid shoulder pain secondary to shoulder “drop” and limited range of motion. If the nerve is injured below the jugular foramen, then primary repair or nerve grafting may be performed.<sup>17</sup>

Hypoglossal nerve injury results in paralysis of the ipsilateral tongue. Long-term hypoglossal nerve paralysis results in hemiatrophy of the tongue within a few months. If this occurs in combination with other lower cranial nerve injuries, then swallowing therapy will be required to prevent aspiration. Swallowing therapy is usually focused on educating the patient to direct the bolus to the functioning side.<sup>17</sup> More significant, persistent swallowing and aspiration issues may require feeding via tracheostomy and gastrostomy tubes.

## Radiotherapy

Traditionally, radiotherapy was offered to those with postoperative recurrence or for those patients who were not surgical candidates due to technical unresectability issues, patient refusal, age, or illness. Unlike surgery, concern exists with radiotherapy because lesions may remain dormant as they rarely regress completely after this treatment modality. Yet, evidence supports the long-term efficacy of moderate doses of radiation to prevent tumor progression while also preserving cranial nerve function.<sup>1-3</sup> Thus, radiotherapy has become a first-line treatment for these largely benign tumors, and it is commonly considered for skull-base tumors of a jugulotympanic origin as well as vagal tumors.<sup>1-3</sup> Given the demonstrable and favorable long-term outcomes, successful treatment is typically defined as lack of tumor progression on serial radiographic follow-up and includes stability of tumor size or partial regression.<sup>1-3</sup>

Primary radiotherapy may be delivered with conventional external beam radiotherapy (EBRT), stereotactic radiosurgery, or hypofractionated stereotactic radiotherapy — all of these approaches have excellent rates of local control and outcomes.<sup>1-3</sup> Typically, doses of 45 Gy in 5 weeks are given with conventional EBRT, 12 to 15 Gy with stereotactic radiosurgery, and 21 Gy for 3 fractions or 25 Gy for 5 fractions with hypofractionated stereotactic radiotherapy.<sup>1-3</sup> Patients whose intracranial tumors measure less than 3 cm are the best candidates for stereotactic approaches, whereas those whose tumors are larger or have a component of extracranial spread are best suited for EBRT.<sup>1-3</sup> The ablative nature of stereotactic radiosurgery can cause a small increase or exacerbation in the rate of cranial neuropathy, and, thus, a more fractionated approach with stereotactic radiotherapy or conventional EBRT may be considered in those whose baseline cranial nerve function is excellent.<sup>1-3</sup>

## Histopathological Changes

Multiple reports have described the histopathological impact of radiation on paragangliomas.<sup>35-37</sup> Gardner et al<sup>36</sup> studied 6 irradiated tumor specimens resected 4 to 6 weeks following radiotherapy and found evidence of vascular endarteritis with mural thrombi as well as necrotic infarct and pyknotic cellular death. Fibrosis around nests of the pathognomonic chief cells has been reported at 6 months post-treatment with diminished vascularity.<sup>35,38-40</sup> Chief cells may show evidence of senescence such as nuclear pleomorphism, irregular nuclear outlines, and chromatin clumping.<sup>36,37,40</sup> Thus, radiation appears to create sclerosing endarteritis with subsequent fibrosis, which in turn prevents tumor growth and involution while also causing a loss of reproductive capacity of the chief cells.<sup>22,35,41</sup>

## External Beam Radiotherapy

Ever since the first major review was published more than 50 years ago of 106 cases of paragangliomas that demonstrated similar rates of efficacy between radiotherapy and surgery, numerous retrospective studies have confirmed the effectiveness of radiation for managing head and neck paragangliomas.<sup>35,42-68</sup> Reflecting a wide variety of delivery techniques, beam energies, and dosing schedules, cumulative rates of local control average 90% (range, 65%–100%) and are based on more than 1,000 cases (median follow-up time, 10 years).<sup>35,42-68</sup>

Primary radiotherapy may be delivered with conventional fractionation, the results of which have the largest and longest experience. Typically, a dose of 45 Gy in 5 weeks is given with conventional fractionation (Fig 5).<sup>3</sup> The effectiveness of radiotherapy is not affected by site of origin, whether it be the jugulotemporal, carotid body, or vagal space.<sup>43,48,62,69</sup> Gilbo et al<sup>63</sup> reported on a 45-year experience with conventional fractionation and prescribed a dose of 45 Gy. A total of 131 patients were enrolled and 156 paragangliomas were studied. The 5- and 10-year rates of local control were 99% and 96%, respectively, at a median follow-up of 8.7 years.<sup>63</sup> Five tumors recurred between approximately 1 and 8 years following treatment.<sup>63</sup>

**Compared With Surgery:** The effectiveness of surgery compared with EBRT is difficult to ascertain because of the retrospective nature of data from authors at single institutions, who report small patient numbers confounded with selection bias and other conflicting outcomes.<sup>66,70-73</sup> To extract meaningful comparative outcomes based on a common staging system, an analysis of 5 studies was performed to report on the outcomes of temporal bone tumors using McCabe/Fletcher staging.<sup>43,47,51,60,68</sup> That analysis demonstrated that study patients treated with radiotherapy, surgery, or a combination of both had average rates of local

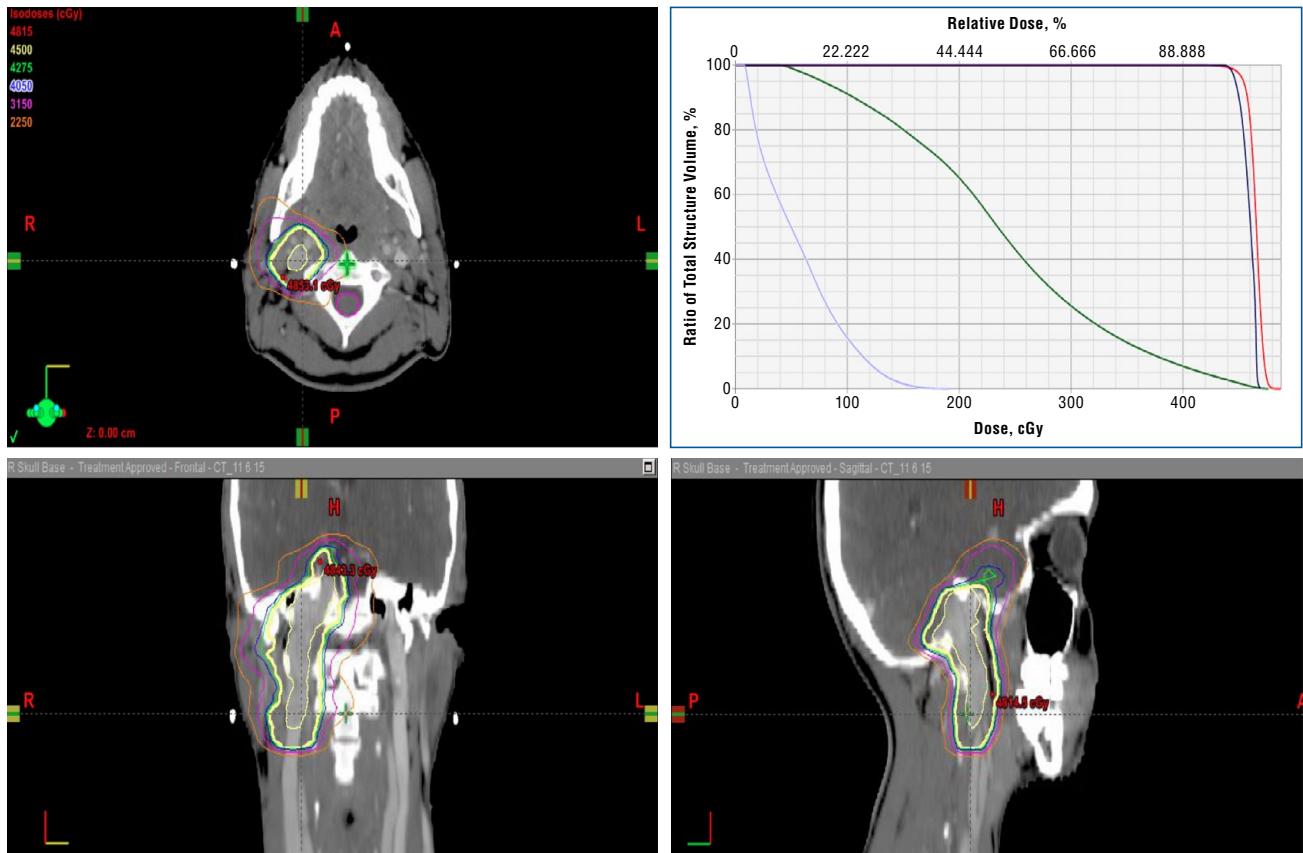


Fig 5. — Jugular paraganglioma treated with external beam radiotherapy. A man aged 27 years presented with diplopia and tinnitus and was found to have paraganglioma of the jugular area that extended extracranially and to the cavernous sinus. He was treated with definitive intensity-modulated radiotherapy (dose of 45 Gy in 25 fractions). Both symptoms resolved by the end of radiotherapy.

control of 93%, 78%, and 85%, respectively, for a median follow-up period of 11 to 16 years.<sup>43,47,51,60,68</sup> Despite a larger number of advanced tumors in the radiotherapy group, the rate of local control was similar or better than those undergoing surgery alone or receiving combination treatment.<sup>43,47,51,60,68</sup> Others have shown debulking surgery does not improve outcomes when patients are treated with radiotherapy.<sup>60</sup>

In a systematic literature review, Suarez et al<sup>10</sup> reported on the role of surgery and EBRT in the treatment of carotid body paragangliomas. The mean follow-up times were 80.6 months for surgery (n = 2,175) and 99.9 months for those receiving EBRT (n = 127).<sup>10</sup> No difference was seen in local control in the surgery and EBRT arms (93.8% vs 94.5%, respectively).<sup>10</sup> Reduction in tumor size was reported in 25.2% of study patients treated with EBRT. All received conventional doses of radiotherapy (40–65 Gy); 44% received doses between 40 and 50 Gy.<sup>10</sup> Iatrogenic cranial neuropathy — primarily occurring in cranial nerves X and XII — occurred in 22.2% of patients treated with surgery vs 0% in those treating with EBRT ( $P = .004$ ).<sup>10</sup> Iatrogenic Horner syndrome occurred in 2.5% of patients treated with surgery.<sup>10</sup> The carotid artery was resected in 12.5% because of injury or tumor encase-

ment, 3% developed permanent stroke, and 1.3% died because of postoperative complications.<sup>73</sup> The rates of iatrogenic cranial neuropathy and vascular complications were 2.3% for Shamblin class 1/2 tumors and 35.7% for Shamblin class 3 tumors ( $P < .001$ ).<sup>74</sup> With use of EBRT, a potential increased risk of ischemic stroke of approximately 12% has been observed with long-term follow-up of 15 years.<sup>75,76</sup>

Suarez et al<sup>73</sup> also studied patients with jugular or vagal paragangliomas treated with surgery (n = 1,310), EBRT (n = 461), or stereotactic radiosurgery (n = 261). The median follow-up times for surgery, EBRT, and stereotactic radiosurgery were 66 months, 113 months, and 41 months, respectively.<sup>73</sup> Among patients with jugular paragangliomas, better rates of local control were observed with radiotherapy compared with surgery (91.5% vs 78.1%;  $P = .002$ ), and fewer major complications were seen with radiotherapy compared with surgery (11% vs 26%;  $P = .02$ ) — in particular, lower iatrogenic cranial neuropathy (0.08 vs 1.0/per patient;  $P < .001$ ).<sup>73</sup> Perioperative complications of major importance were, in order of decreasing incidence, cerebrospinal fluid leak, aspiration/pneumonia, wound infection, meningitis, and stroke.<sup>73</sup> A rate of perioperative mortal-

ity was reported to be 1.6%.<sup>73</sup> Severe complications from radiotherapy included, in order of decreasing incidence, deafness, osteonecrosis, death, and brain necrosis.<sup>73</sup> No significant difference was observed in rates of local control between EBRT and stereotactic radiosurgery.<sup>73</sup>

### **Impact on Neurological Function**

In the majority of patients with jugulotympanic tumors who present with tinnitus, EBRT can be used to reduce or resolve it.<sup>48,55</sup> Cummings et al<sup>55</sup> demonstrated complete resolution of tinnitus in 79% and stable or partial relief in 21% of the cases they studied. With regard to sensorineural hearing loss, they found that 5% of patients reported a return to normal hearing, 30% reported some improvement, and 62% noted no change after radiotherapy.<sup>55</sup> Improvement of other cranial neuropathies after radiotherapy has been reported in approximately one-third of patients.<sup>44,47,48,50,51,53,55,62,69</sup> Complete restoration of cranial nerve function is less common, occurring in about 10% (range, 8%–20%).<sup>44,47,48,50,51,53,55,62,69</sup> The probability that cranial nerve function will improve following radiotherapy is most likely inversely related to the duration of cranial neuropathy.<sup>48,73</sup> Suarez et al<sup>73</sup> reported improvement of cranial nerve function in 8.8% of patients after stereotactic radiosurgery compared with 4.1% in those treated with EBRT. Hearing loss occurred in 6.5% patients treated with stereotactic radiosurgery.<sup>73</sup>

Radiation-induced cranial neuropathy following EBRT is rare and has been associated with doses above what are recommended.<sup>48,53,62</sup> Four such cases have been reported: 2 cases of cranial nerve VII palsy, 1 case of cranial nerve VIII dysfunction occurring after a high dose of radiotherapy (64–66 Gy), and 1 case of cranial nerve VI palsy that the authors stated had an “unclear etiology.”<sup>48,53,62</sup>

### **Impact on Radiographic Tumor Regression**

Results of the radiographic follow-up of patients after EBRT demonstrate stability in tumor size or modest tumor regression.<sup>51,60,77</sup> Mukherji et al<sup>78</sup> reported on 17 patients with 18 paragangliomas treated with definitive radiotherapy who underwent pre-treatment and post-treatment imaging using CT or MRI. A total of 61% showed a decrease in tumor size, with an average reduction of 23% (range, 8%–45%) at a median follow-up of 2.5 years. Postradiotherapy findings on MRI included reduction in flow voids, decreased heterogeneous enhancement, and a reduced T2 signal.<sup>78</sup> Other studies have demonstrated tumor regression in 57% to 73% of patients followed by CT.<sup>47,49</sup> Thus, paragangliomas will show modest radiographic change or stable tumor in the majority of cases.

van Hulsteijn et al<sup>79</sup> performed a meta-analysis of 15 studies involving 283 jugulotympanic paraganglio-

mas in 276 patients to evaluate the proportion of patients whose tumors had regressed after stereotactic radiosurgery or conventional EBRT. All studies had to have a minimum of 12 months of follow-up with adequate radiologic evaluation.<sup>79</sup> The percentages of patients demonstrating some regression after stereotactic techniques and treated with definitive intent, combined modality, and salvage treatment were 21%, 33%, and 52%, respectively; for those receiving conventional EBRT, the corresponding outcomes were 4%, 0%, and 64%.<sup>79</sup> No differences in local control were noted between the 2 treatment techniques nor in those with tumor regression vs those without.<sup>79</sup>

### **Fractionated Radiotherapy**

Rates of morbidity following radiotherapy vary according to the radiation technique and treatment site.<sup>1-3</sup> Common toxicities related to radiotherapy include mucositis, fatigue, otitis, dermatitis, nausea, xerostomia, epilation, skin dryness, fibrosis, and cerumen build up.<sup>1-3</sup> Severe complications after radiotherapy have been reported in 30 series and occur in approximately 6% of patients; the rate of treatment-related mortality has been observed to be 0.6%.<sup>35,42-68</sup> Severe morbidity primarily consists of osteoradionecrosis, chronic otitis, brain necrosis, radiation-related cranial neuropathy, radiation-induced sarcoma, external auditory canal stenosis, and trismus.<sup>1</sup>

Most of these severe complications are related to radiotherapy that exceed the current recommended dose, use outdated treatment techniques, or are due to toxicity from reirradiation.<sup>1</sup> For example, of the 4 reported cranial neuropathies related to radiotherapy, 3 occurred after receiving 64 to 66 Gy of radiation.<sup>48</sup> Cole et al<sup>45</sup> reported that all of the severe complications seen in their series occurred in patients treated with orthovoltage; none occurred in those treated with megavoltage. It is worth noting that the reported incidence of radiation-induced secondary malignancies was low (0.4%).<sup>45</sup> These included 2 fibrosarcomas occurring 15 and 25 years after treatment and 1 osteosarcoma occurring 5 years post-treatment.<sup>45</sup> In 2015, Gilbo et al<sup>65</sup> reported on 131 patients (156 benign paragangliomas) in a 45-year report. The patients were treated for paragangliomas of the jugular bulb, vagal area, temporal bone, and carotid body. At nearly 12 years of median follow-up, they observed no severe (grade 4/5) complications, and none of their study patients developed iatrogenic cranial neuropathy/malignancy.<sup>63</sup> Thus, with current recommended dosing guidelines and modern treatment techniques, definitive radiotherapy can be well tolerated in patients with paragangliomas.

### **Stereotactic Radiosurgery**

Stereotactic radiosurgery is a successful first-line treatment for paragangliomas and as salvage therapy

for treatment failure. Stereotactic radiosurgery uses a highly focused, single ablative dose of radiation to a small target with a steep dose gradient to spare as much surrounding normal tissue as possible. For most patients, the plan for treatment and the treatment itself are performed in a single session. Radiation is delivered using non-coplanar beams, rigid immobilization, and MRI-based treatment planning.

Multiple series have reported on the success of this approach to treat jugular paragangliomas and have observed generally high rates of local control.<sup>77,80-84</sup> A wide range of median doses has also been reported between 15 and 32 Gy, with 15 Gy being the most common.<sup>77,80-84</sup> Chen et al<sup>85</sup> reported on a 15-patient series and found that 13 Gy was associated with higher rates of failure than 15 Gy ( $P = .08$ ). Treatments appeared to be well tolerated, with low incidence rates of transient facial neuropathy, hearing impairment, and vertigo.<sup>85</sup> Stereotactic radiosurgery does have limitations, which include the location of the intracranial tumor and tumor size.<sup>80</sup> Tumors are typically no larger than 3 cm to achieve tight dose conformality.

A population-based meta-analysis of 19 studies comprising 335 glomus jugulare cases treated with radiosurgery was reported by Guss et al.<sup>86</sup> For all of the 19 studies, the rate of tumor control was 97%; among 8 reports studied whose median follow-up times were longer than 36 months, the rate of control achieved was 95%.<sup>86</sup> No difference in outcome was reported by radiosurgical technique used.<sup>86</sup>

**Compared With Surgery:** Gottfried et al<sup>87</sup> performed a meta-analysis of 109 studies comprising 869 glomus jugulare cases treated either by gross total resection, subtotal resection, stereotactic radiosurgery alone, or subtotal resection combined with stereotactic radiosurgery. The median follow-up times for gross total resection, subtotal resection, subtotal resection in combination with stereotactic radiosurgery, and stereotactic radiosurgery were 88 months, 72 months, 96 months, and 71 months, respectively.<sup>87</sup> The rates of tumor control for gross total resection, subtotal resection, subtotal resection in combination with stereotactic radiosurgery, and stereotactic radiosurgery were 86%, 69%, 71%, and 95%, respectively.<sup>87</sup> The study patients undergoing stereotactic radiosurgery alone had the best tumor control rates ( $P < .001$ ).<sup>87</sup> Those undergoing gross total resection had worse deficits in cranial nerves IX to XI compared with those assigned to stereotactic radiosurgery, although deficits in cranial nerve XII were comparable in the 2 groups.<sup>87</sup>

Gottfried et al<sup>87</sup> also performed a comprehensive literature review comparing stereotactic radiosurgery and conventional surgery for the treatment of jugular paragangliomas in 576 patients. They reviewed 8 radiosurgery series reporting outcomes on 142 patients and 7 conventional surgical series that detailed outcomes on

374 patients.<sup>87</sup> The mean age for patients undergoing surgery was 47 vs 57 years of age for those treated with stereotactic radiosurgery.<sup>87</sup> A total of 48% of patients underwent first-line radiosurgery and 52% underwent salvage or adjuvant radiosurgery.<sup>87</sup> Tumor shrinkage was reported in 36% of patients treated with radiosurgery while 61% remained unchanged.<sup>87</sup> With regard to neurological symptoms, 39% showed improvement, 58% showed no change, and 3% had worsening symptoms; moreover, most study patients experiencing neurological improvement did so within the first 12 months.<sup>87</sup> At a follow-up period of 49 and 39 months (range, 20.0–86.4 months) for the surgical and radiosurgical groups, respectively, the rates of local control in the surgical group were 92% and 98% for the radiosurgical group.<sup>87</sup> The neurological complication rate after stereotactic radiosurgery was 8.5% (6.4% transient, 2.1% permanent).<sup>87</sup> Transient complications included exacerbation of pre-existing cranial nerve deficits, tinnitus, or vertigo; permanent complications were reported as worsening facial nerve function ( $n = 3$ ), worsening vertigo ( $n = 1$ ), and progressive hearing loss to deafness ( $n = 1$ ).<sup>87</sup> No patients experienced new deficits in the lower cranial nerves.<sup>87</sup> Meningitis, wound infection, pneumonia, ischemia, cerebrospinal fluid leak, and aspiration were the major surgical complications reported.<sup>87</sup> Iatrogenic cranial nerve deficits were reported in several surgical series and involved cranial nerves VII and IX to XII.<sup>87</sup> The rate of perioperative mortality was 1.3%.<sup>87</sup>

### **Hypofractionated Stereotactic Radiotherapy**

Hypofractionated stereotactic radiotherapy combines the high precision of stereotactic planning, the function preservation advantages of fractionation, and the convenience of short-course treatment. Some authors have reported excellent outcomes with low rates of severe toxicity. For example, Wegner et al<sup>88</sup> reported an early experience of 18 glomus jugulare cases treated with linear accelerator-based stereotactic radiotherapy; 8 had persistent tumors after prior surgery, 1 had recurrence after EBRT, and 2 were treated with combined extracranial stereotactic radiotherapy with intracranial Gamma Knife (Elekta, Crawley, UK) radiotherapy.<sup>88</sup> The median radiation dose was 21 Gy delivered in 3 fractions (16–25 Gy in 1–5 fractions) to the 80% isodose line.<sup>88</sup> At a median follow-up of 22 months, the observed rate of local control was 100%. No cases of new or worsening pre-existing neurological deficits were observed.<sup>88</sup>

Chun et al<sup>89</sup> reported on 31 patients with jugular paragangliomas ( $n = 30$ ) or carotid body tumors ( $n = 1$ ) treated with CyberKnife (Accuray, Sunnyvale, California) fractionated stereotactic radiotherapy at a dose of 25 Gy in 5 fractions.<sup>89</sup> Mean tumor size was reported as 10.7 mL, which is twice the size of the typical volumes used in Gamma Knife series.<sup>88,89</sup> At a median follow-

up time of 24 months, the rate of local control was reported as 100%.<sup>89</sup> Tumor volume was reduced for the entire study population by 37%; at 2 years, that rate was 49%.<sup>89</sup> A total of 60% of patients reported improvement in tinnitus.<sup>89</sup> Grade 1/2 adverse events (primarily headache) were reported in 19% of the patients studied.<sup>89</sup>

Liebersson et al<sup>90</sup> reported on 36 patients (41 paragangliomas): 17 of whom were treated with fractionated stereotactic radiotherapy, and 19 were treated with surgery. They reported that, on average, smaller lesions (< 8 mL) were treated with 18 Gy in 1 fraction, moderately sized lesions (8–16 mL) were treated with 20 Gy in 2 fractions, and larger-sized lesions (≥ 16 mL) were treated with 22 Gy in 3 fractions (median lesion size = 1.64 mL).<sup>90</sup> One large lesion measuring 69 mL received 25 Gy in 5 fractions, and another measuring 42 mL received 24 Gy in 3 fractions.<sup>90</sup> Five of the 19 patients treated with single-dose radiation had worsening of their pretreatment deficit, 2 patients had transient worsening of cranial nerve deficits, and 7 patients had an improvement of their pretreatment deficit, including 4 treated with stereotactic radiosurgery and 3 treated with stereotactic radiotherapy.<sup>90</sup>

## Malignant and Catecholamine-Secreting Paragangliomas

The diagnosis of malignant tumors is radiographically determined, because no distinguishing histological features of transformation exist. The standard treatment for malignant paragangliomas is resection of the primary tumor and neck dissection.<sup>91</sup> Data regarding the outcomes of malignant paragangliomas after definitive radiotherapy are rare.<sup>37,43</sup> Hinerman et al<sup>43</sup> reported on 3 patients with malignant carotid body tumors and neck metastases who underwent definitive radiotherapy (64.8–70 Gy) who were without evidence of disease at 15 months, 4 years, and 6 years. Catecholamine-secreting tumors should be treated with resection as results from case reports indicate poor functional control in patients treated with radiotherapy despite lack of tumor progression.<sup>37</sup>

## Multidisciplinary Treatment Algorithms

The management of paragangliomas is challenging given the complexity of possible presentations, the availability of multiple treatment options, and the nature of these tumors to indolently grow but with the potential to severely impact functioning of the head and neck.

Observation without treatment is an appropriate initial option in patients who are asymptomatic, particularly among older individuals with comorbidities who are willing to undergo watchful surveillance. Some authors indicate that paragangliomas can remain stable for long periods of time and, if growth is detected, then the rate of expansion is generally slow

and more sensitive imaging techniques can detect and accurately follow the progress of these tumors.<sup>92</sup> In an observational study of 47 tumors followed for 5 years, the researchers found that 38% progressed at an annual growth of 2 mm while 42% were stable and 20% decreased in size.<sup>92</sup> Others have reported a higher rate of progression (≤ 60%) and an annual average growth rate of 1 mm, with variable doubling times between 6 months and 21 years.<sup>93</sup> Whether observation for all asymptomatic patients is the best initial strategy remains to be determined. Moreover, additional research is needed to identify the following:

- Optimal surveillance strategies across a long time period
- Thresholds for active treatment with regard to symptom onset or changes in tumor size that impact morbidity
- Reversibility of symptoms that develop from active surveillance with subsequent treatment

If treatment is to be pursued, then we propose multidisciplinary algorithms that take into account multiple factors, such as type of paraganglioma, malignant status, whether the tumor is catecholamine-secreting, presence of synchronous tumors, and extent of pre-treatment cranial neuropathy (Figs 6 and 7).<sup>1-3</sup> Patient factors include age, presence of comorbidities, potential for rehabilitation, lifestyle, and wishes. The focus of the treatment algorithms is unimodality treatment to control the tumor, minimize iatrogenic morbidity, and preserve cranial nerve function as optimally as possible.

First-line surgery is preferred for patients with carotid body tumors, especially those whose tumors are less than 5 cm in size and also lack carotid artery encasement, because these tumors are usually excised with a low associated risk of carotid artery sacrifice. In cases of bilateral synchronous carotid body tumors, bilateral resection is contraindicated due to baroreflex failure syndrome. Rather, resection of the smaller tumor and radiotherapy to the larger tumor are recommended.

For patients with catecholamine-secreting or malignant tumors, first-line resection is recommended with adjuvant radiotherapy as needed based on pathological factors.

Radiotherapy is the preferred modality for the treatment of jugular and vagal paragangliomas because this therapeutic option offers the opportunity for high rates of local control combined with likely resolution of pre-existing tinnitus and possibly improvement in cranial neuropathy. First-line surgery may be considered for small tympanic tumors and in those with advanced jugular/vagal paragangliomas in which resection would not worsen any pre-existing cranial nerve palsy.

First-line radiotherapy should be considered in patients who are elderly, those with multiple comorbidities, and in those whose tumors have advanced

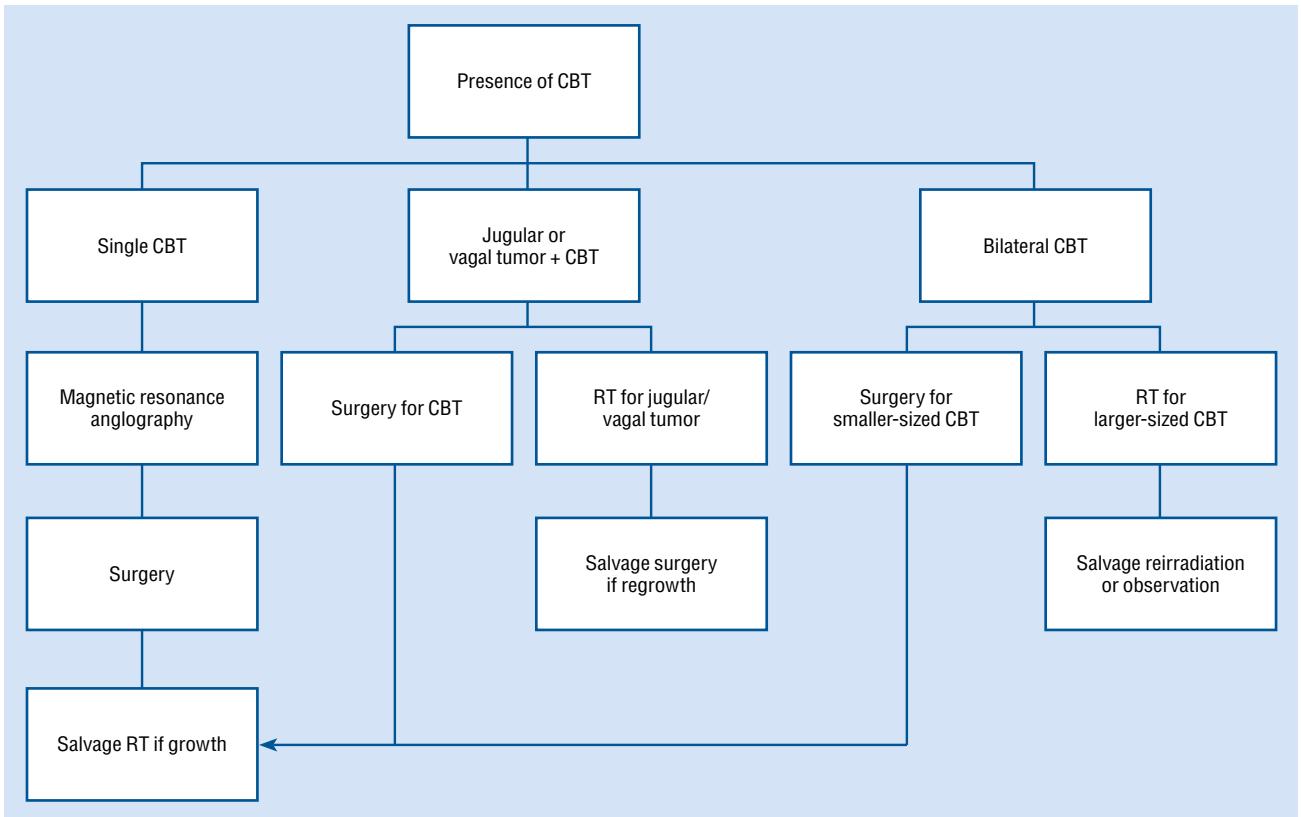


Fig 6. — Algorithm for the treatment of CBTs. CBT = carotid body tumor, RT = radiotherapy.

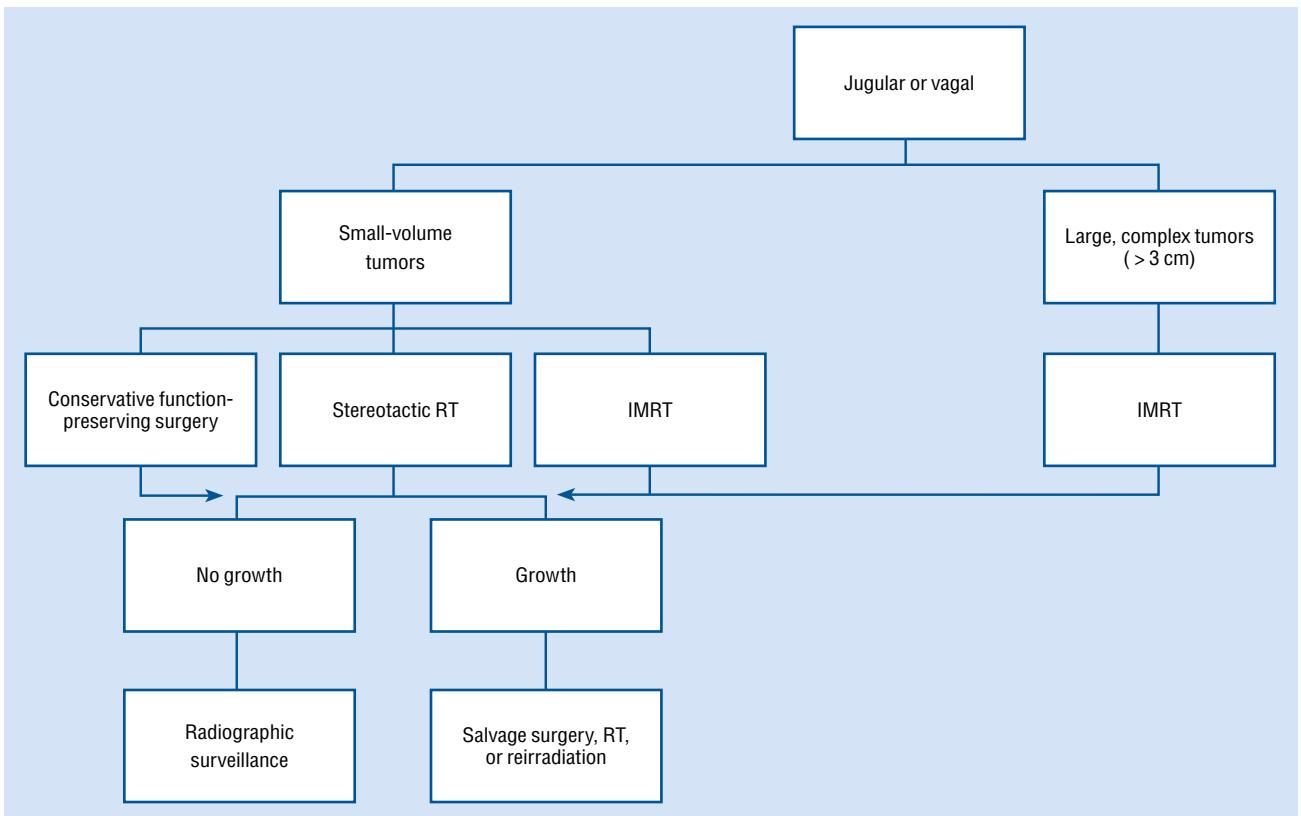


Fig 7. — Algorithm for the treatment of vagal and jugular paragangliomas. IMRT = intensity-modulated radiotherapy, RT = radiotherapy.

into the skull base or extended into the intracranial space.

## Conclusions

Management of head and neck paragangliomas has evolved with advances in the understanding of the natural history of the disease, genetic testing, and the improvements of multiple treatment options. Because paragangliomas are benign in the vast majority of cases, survival is not a common end point reported in studies. Rather, the primary focus of study is preserving function and the prevention of morbidity from progressive disease. Watchful waiting represents an initial management strategy that may be appropriate for select patients whose tumors are incidentally found and remain asymptomatic. For those who require treatment, a multidisciplinary approach that emphasizes single-modality therapy offers optimal outcomes.

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