Important observations made managing carotid body tumors during a 25-year experience

Allan J. Kruger, FRACS, MBBS, DDU,[a] Philip J. Walker, FRACS, MBBS,[a,b] Wallace J. Foster, FRACS, MBBS,[a] Jason S. Jenkins, FRACS, MBBS,[a] Nicholas S. Boyne, FRACS BBS,[a] and Julie Jenkins, RN,[b] *Brisbane and Queensland, Australia*

Objectives: **Our objective was to assess the short- and long-term outcome for patients after carotid body tumor (CBT) resection and discuss the potential pitfalls of the treatment.**
Methods: **An analysis was undertaken of all patients who underwent CBT resection at Royal Brisbane and Women's Hospital and Greenslopes Private Hospital between 1982 and 2007. Primary tumor characteristics, surgical technique, and outcomes were recorded and analyzed.**
Results: **A total of 49 consecutive CBT resections (2 recurrent tumors) were carried out in 39 patients (26 women [56%]) who were a mean age of 49 years (range, 17-75 years). A nontender neck mass was the presenting complaint in 85%, followed by screening in familial or contralateral tumors in 26%. Familial cases occurred in 11 patients (28%). There were no operative deaths. Complications occurred in 13 of the 49 operations (27%), predominantly temporary nerve palsies and were more likely to occur in tumors of large volume or in cases of removal of coexisting vagal tumors. Malignant disease was present in seven cases (15%). All patients have been followed-up postoperatively for a mean of 11 years (range, 2-26 years). Metachronous paragangliomas have been discovered in six patients, all with familial disease.**
Conclusions: **Early resection of carotid body tumors should be undertaken while still small to minimize the risk of neural injury, which increases with tumor size. In cases of bilateral CBT, we recommend that the smaller tumor be resected first, before the staged resection of the larger contralateral tumor. In familial or bilateral tumor cases, other synchronous and metachronous paragangliomas should be excluded. Mandatory lifelong follow-up is essential. (J Vasc Surg 2010;52:1518-24.)**

Paragangliomas of the neck are rare, with the most common form being the carotid body tumor (CBT). The carotid body is a small cluster of chemoreceptors and supporting cells located near the carotid bifurcation that was first anatomically described in 1743 by Albrecht von Haller.[1,2] The glomus cells of the carotid body are derived from neural crest cell lines, which in turn are derived from neuroectoderm. Although CBTs are rare tumors, diagnosed with an incidence of about 1:30,000 in the general population,[3] they account for >50% of head and neck paragangliomas.[4] It is generally considered that approximately 90% of CBTs are sporadic and 10% are familial.[5] A family history of paraganglioma syndrome should be considered in all cases but particularly if bilateral tumors exist. Vagal paragangliomas (VP) are the other rarer form of paragangliomas that the vascular surgeon might encounter and account for 5% of all head and neck paragangliomas. In this report, we review our experience with the clinical presentation and management of these tumors, with special emphasis on the pitfalls in management that can occur and insights learned from managing a sizable series of patients during a 25-year period.

From the Department of Vascular Surgery, Royal Brisbane and Women's Hospital;[a] and the Department of Surgery, University of Queensland Centre for Clinical Research, University of Queensland.[b]

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Correspondence: Allan J. Kruger, FRACS, MBBS, DDU, Royal Brisbane and Women's Hospital, Department of Vascular Surgery, Butterfield St, Herston, Brisbane, Queensland, Australia (e-mail: allan_kruger@health.qld.gov.au).

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METHODS

All patients who underwent CBT resection of cervical paragangliomas by vascular surgeons at the Royal Brisbane and Women's Hospital Vascular Unit and Greenslopes Private Hospital between 1982 and 2007 were identified by hospital admission codes and vascular unit audit data and were cross-referenced to operative theater procedural codes. All patients have been monitored from the time of their tumor resection.

Patients and presenting symptoms. A total of 47 primary CBTs and 2 recurrent tumors were diagnosed in 39 patients (26 women [56%]) who were a mean age of 49 years (range, 17-75 years). All 49 tumors were histologically proven CBT. Six patients underwent VP resections concurrently with the CBT procedure. Sporadic CBT were found in 28 patients (72%), and 11 (28%) had familial CBT. Bilateral tumors, which were found incidentally in most cases, were seen in 14 patients (36%). These 39 patients underwent 49 operative procedures, of which 47 procedures were for primary tumors and 2 for recurrent disease. Eight patients underwent staged bilateral CBT resection, and a further four patients had previously undergone contralateral CBT excision at other institutions.

The presenting symptoms for the 49 CBT in these 39 patients are listed in Table I and are tabulated for 41 patients presenting with CBTs alone, 6 patients with con-

Table I. Presenting symptoms for 49 cervical paragangliomas (in 39 patients) before surgical resection

Presenting symptom	*CBT only (n = 41) No. (%)*	*CBT and VP (n = 6) No. (%)*	*Recurrent CBT (n = 2) No. (%)*
Mass	27 (66)	4 (66)	2 (100)
Screening	14 (34)	2 (33)	2 (100)
Pain	4 (10)	. . .	. . .
FNAB	4 (10)	. . .	. . .
Cranial nerve palsy[a]	4 (10)	2 (33)	2 (100)
Dysphagia/dysphonia/SOB	3 (7)	. . .	. . .
Fainting	3 (7)	. . .	. . .
Metastasis	3 (7)	. . .	. . .
Palpitations	2 (5)	. . .	. . .
Flushes	2 (5)	. . .	. . .
Tinnitus	1 (2)	1 (17)	. . .

CBT, Carotid body tumor; *FNAB,* fine-needle aspiration biopsy; *SOB,* shortness of breath; *VP,* vagal paragangliomas.
[a]All vagal nerve palsy.

current CBT and VP, and for the 2 patients with recurrent CBT. A number of patients presented with multiple symptoms. A neck mass was the most common initial presenting complaint, evident in approximately two-thirds of patients with primary tumors. If the patient whose paragangliomas were detected by screening and the two recurrent CBTs are excluded, this figure rises to 100% (31 of 31). This was uniform across the 25 years of the study.

The mass was usually painless, although four patients with CBT only (10%) reported pain associated with the mass. Cranial nerve palsies, which in all cases were vagal (XII) nerve palsies, were present in 10% of patients with CBT alone and in one-third of patients with concurrent CBT and VP. Although three patients (5%) presented with palpitations or flushes, no CBT was hormonally functional on the basis of endocrine studies that were undertaken selectively in patients where there was a clinical suspicion.

Screening of family members identified 16 additional tumors. Metastatic spread of the CBT was documented in three patients (8%) at the time of initial presentation. A confirmed histologic diagnosis of CBT was made at the referring institution by fine-needle aspiration biopsy in four cases. This delayed treatment in one patient by 13 years because she had been warned of hemorrhagic risk with surgery.

Four of the familial cases had undergone previous surgery for their paraganglioma before presentation at our unit. These patients represented two distinct families. The other two family groups had not been diagnosed with other paragangliomas before their initial CBT diagnosis at our institution.

Investigations. The investigations undertaken in these patients are listed in Table II. Many patients had multiple investigations. Computed tomography angiography (CTA) was the most commonly used imaging modality, followed by duplex ultrasound (DUS) imaging. Angiography was used frequently in the early years in this series but is now rarely used, having been superseded by CTA and DUS. No preoperative embolization was used.

Table II. Diagnostic modalities used in the diagnosis of 47 primary carotid body tumors

Diagnostic modality	*No. (%)*
Total tumors	47 (100)
Computed tomography angiography	40 (85)
Duplex ultrasound imaging	34 (72)
Digital subtraction angiography	19 (40)
Magnetic resonance arteriography	2 (4)
Fine-needle aspiration biopsy	4 (9)

Treatment. All patients were managed by surgical resection of the CBT, with most of the procedures performed by a single surgeon. The intent of surgery was palliative in the three patients who presented with metastatic disease and curative in the remaining cases. At the time of surgery in one patient, there was direct extension of tumor to the base of the skull with bony erosion, and surgery was noncurative in this case. This patient was offered adjuvant radiotherapy but refused. The tumor mass enlarged to again cause compressive symptoms 8 years later, and a further debulking procedure was done. The patient was once again offered radiotherapy and agreed.

All procedures were performed under general anesthesia, and nasoendotracheal intubation was used liberally when there were preoperative concerns about the cranial extent of the tumor. One patient required emergency cricothyroidotomy and formal tracheostomy before reoperation for tumor resection because of the tumor size. A second patient required tracheostomy after the resection of a larger second CBT and vagal tumor; this was reversed after 3 months.

The tumors were approached through a standard endarterectomy incision along the anterior border of the sternocleidomastoid. As a general principle, CBT resection was achieved using a craniocaudal approach with conventional monopolar diathermy. In patients earlier in the series, dissection was commenced at the bifurcation, but this was modified to the above approach to avoid the arterial plexus often present in the fork of the bifurcation and to avoid the ascending pharyngeal branch of the external carotid artery, which often tethers the tumor.

Early identification of neural structures is paramount. In particular, the superior laryngeal nerve on the deep aspect is best found from a posterolateral approach and the hypoglossal nerve dissected from the peritumor fibrous "capsule" superiorly. Early looping of the common carotid artery (CCA) is followed by dissection at the cranial (distal) extent of the internal carotid artery (ICA). If possible, the tumor is then peeled down off the vessels with diathermy, leaving the carotid bifurcation dissection until last.

The CBTs in this series were not routinely assigned a Shamblin classification using preoperative imaging or the intraoperative findings, and the retrospective nature of this series makes post hoc classification hazardous. Neverthe-

Table III. Complications of 49 tumor resection procedures[a]

Complication	*CBT Only (n = 41) No. (%)—P/T*	*CBT & VP (n = 6) No. (%)—P/T*	*Recurrent CBT (n = 2) No. (%)—P/T*
Nerve injury			
Vagal	5 (12)—3/2	6 (expected)	. . .
Glossopharyngeal	1 (2)—1/0	. . .	. . .
Hypoglossal	5 (12)—3/2	2 (33)—0/2	1 (50)—1/0
Facial (MMN)	2 (5)—0/2	. . .	. . .
External laryngeal	1 (2)—1/0	. . .	. . .
Labile blood pressure[b]	4 (10)—0/4	1 (2)—0/1	—
Tracheostomy[b]	2 (5)—1/1	. . .	. . .
Jaw ache	1 (2)—0/1	. . .	. . .
Aspiration[b]	1 (2)	. . .	1 (50)
Hemorrhage postop	1 (2)	. . .	1 (50)

CBT, Carotid body tumor; *MMN,* marginal mandibular nerve; *P,* permanent nerve palsy; *T,* temporary nerve palsy; *VP,* vagal paragangliomas.

[a]In cases complicated by cranial nerve palsies, often more than one nerve was affected.

[b]These patients all had bilateral CBT resections, and the complication occurred after resection of the second, contralateral CBT.

less, the CBT could be dissected free of the carotid vessels without the need for adjunctive operative procedures in 42 of the 49 (85%) operative cases. This could be consistent with Shamblin group 1 or 2 tumors. The ICA and CCA bifurcation was resected in five cases (10%). These cases would be consistent with Shamblin group 3 tumors. An Argyle shunt (Covidien, Mansfield, Mass) was used in each of these five cases, and the ICA was reconstructed using a reversed long saphenous vein interposition graft; however, external carotid artery (ECA) reconstruction was not done. In the final two cases, the ECA alone was resected. There were no adverse effects from ECA resection without reconstruction.

Six patients underwent resection of VPs concurrently with the CBT resection. Five of these were in patients with familial cases of CBT. Enlarged or adherent lymph nodes were resected for histology. Two operative cases required transfusions, both in the same patient with an extremely large CBT. At the initial operation, the styloid process perforated the distal ICA at the skull base. Temporary balloon occlusion was used for control while the artery was repaired by simple suture. At reoperation 8 years later, the CCA/ICA confluence was resected and a long saphenous vein interposition graft was inserted. This procedure was complicated by a postoperative anastomotic hemorrhage.

There were no operative deaths. Complications occurred in 13 of the 49 operations (27%), and these are summarized in Table III. Unplanned permanent cranial nerve palsies occurred in six operations (12%), whereas a further five (10%) resulted in temporary cranial nerve deficits. These data exclude vagal palsies in the six patients who underwent concurrent VP resection where vagal nerve palsy was expected. Tumor volume, as measured by CT, was assessed in 40 cases (85%). The excised CBTs had a mean volume of 23.6 cm^3 (range, 0.5-350 cm^3). There was no statistically significant difference between the volumes of the pathologic specimens and the volumes measured on CT ($P > .1$). The mean volume of the CBTs in the cases resulting in nerve palsy was significantly larger than in those procedures in which nerve palsy did not occur (52.2 v 16.1 cm^3; $P = .04$).

Table IV. New tumors diagnosed in six patients during follow-up after prior resection of carotid body tumor *(CBT)*

Tumor type	*No. diagnosed*
Adrenal tumor	4
Phaeochromocytoma	3
Adenoma	1
Vagal paraganglioma	4
Stellate ganglion paraganglioma	1
Glomus jugulare tumor	2
New contralateral CBT	1

Histologically proven CBT was seen in all 49 operations. In addition, VPs were confirmed in the six cases where these were concurrently resected. Three cases had microscopic lymph node spread and one had perivascular spread. Direct extension of tumor into surrounding tissue was seen in three cases at the level of the skull base. Two of these patients had known metastatic disease.

Five patients received adjuvant radiotherapy. This included the three patients who presented with metastatic disease and one patient who had direct extension of tumor to the base of skull with associated bony erosion. A further patient had radiotherapy upon resection of a recurrent CBT. Those patients with micrometastasis to lymph nodes and positive soft-tissue margins were not given adjuvant therapy. No tumor recurrence has been seen during follow-up.

Three patients died from proven metastatic CBT during follow-up (mean, 11 years; range, 2-26 years). Recurrent CBT developed in the neck in two of these patients before death, and one underwent reoperation for debulking. Another patient required reoperation for recurrent CBT 12 years after the primary resection and remains free of further recurrence now 26 years after the initial resection.

New tumors have been diagnosed during follow-up in six patients, at a mean interval of 5 years (range, 2-18 years) after resection of their primary tumor. All these are familial cases (Table IV).

DISCUSSION

This is a sizeable series of patients with cervical paragangliomas (39 patients, 49 procedures) who have been managed during a 25-year period, predominantly by one vascular surgeon, allowing a uniquely personal reflection on management issues for patients with this rare condition. This series had a high incidence of familial CBT (30%)

compared with 10% in other series.[6] A familial incidence was even more evident in those with bilateral tumors (80%), a finding that has also been reported by other groups.[7] Other non-CBT paragangliomas must be excluded in these patients with familial CBT, because 75% also had concurrent vagal tumors as well as other synchronous and metachronous tumors. Because of this, we recommend screening of all family members of patients who have bilateral CBTs or other neuroendocrine tumors.

Most of the tumors in our series presented as a painless neck mass, as has been reported by others.[3,8] Because some patients will present with cranial nerve palsies and because of the risk of operative cranial nerve injury, it is imperative to carefully assess and document the patient's cranial nerve status preoperatively. Preoperative neurologic involvement generally indicates more challenging surgery as well as the likelihood of increased complications. In the presence of a clear preexisting neurologic deficit or when the likelihood of operative neurologic injury is highest, such as with recurrent or bilateral tumors and in large tumors where more difficult dissection can be anticipated with greater accompanying risk to the surrounding nerves, more rigorous assessment should be undertaken. This involves formal otolaryngology review and indirect laryngoscopy, which might uncover vocal cord palsy. Some surgeons advocate more rigorous assessment for all cases, but this is not part of our standard workup for small and uncomplicated tumors.

The tumors are highly vascular, and the experience of the patient who hemorrhaged severely after fine-needle aspiration biopsy—a procedure that we would not recommend—is testament to the danger of performing a biopsy of these tumors. If CBT is suspected clinically, appropriate imaging almost always will confirm the diagnosis. Typically, a CBT causes splaying of the carotid bifurcation that can be observed on diagnostic imaging. Early in our series, angiography was used routinely before undertaking tumor resection. With the advances in DUS and CT imaging, angiography is no longer required for diagnosis, and in our hands, is rarely performed for preoperative planning. Color DUS imaging can usually provide information about the vascularity of the tumor, its dimensions, and its location in relation to the carotid bifurcation. Modern CT or magnetic resonance imaging (MRI) can provide definitive imaging for preoperative planning, including information about tumor extent as well as predicting vessel wall involvement. Angiography may be used in instances where ICA ligation may be required to perform a preoperative balloon occlusion test.

Preoperative embolization was initially introduced to decrease the size and vascularity of large tumors and is advocated by some authors as being extremely important to avoid major surgical complications for high-risk large Shamblin group 2 or 3 tumors. It has also been used to treat midsized tumors.[9] No preoperative embolization was used in any of the patients in this series, and we question its role. Proponents advocate preoperative embolization, preferably the day before the resection, thus avoiding any inflammation that may occur with waiting[10] and claim the benefits of a reduction in the technical difficulty of the procedure, reduced operative time, reduced bleeding, reduced operative cranial nerve morbidity, and decreased length of hospital stay.[11-14] Other authors have found no benefit,[9] and most importantly, embolization is associated with a definable neurologic complication rate, reported to be as high as 18% in one series.[9,11,15] We are not convinced that the perceived but unproven benefits of preoperative embolization outweigh the potential complications. In our series of 49 procedures, bleeding requiring transfusion was encountered in only one patient at two separate procedures. On neither occasion was bleeding related to tumor vascularity.

Endocrine assessment was undertaken selectively in a small number of patients whose symptoms raised the possibility of functional tumors. None of the CBTs tested had evidence of endocrine function. Routine testing of all patients is common practice in some centers, but our experience suggests that such an approach is not warranted. We do recommend additional imaging of the abdomen and chest with CT, MRI, or iodine-131-meta-iodobenzylguanidine (MIBG) scintigraphy in patients with familial, multiple, or functional paragangliomas. A better test when the tumor is nonfunctional is a pentetreotide scan, which uses a radiolabelled somatostatin analogue.[16,17] This scan is based on the tumor containing somatostatin receptors. In addition to detecting small tumors, these studies can be useful in evaluating residual or recurrent tumor and possible metastasis.[17,18]

A CBT classification system proposed by Shamblin[19] is extensively used when describing these tumors. Shamblin suggested a surgical classification of CBTs into three groups according to the gross tumor-vessel relationship, the intraoperative findings, and the postoperative specimen examination. Advances in imaging have led to attempts to assign this classification preoperatively; however, some authors have stated that CBTs can only be given a Shamblin classification at or after surgery.[20]A recent small study of nine CBTs suggested that MRI can accurately predict Shamblin group preoperatively, and the maximum degree of circumferential contact of the CBT with the ICA on axial images is the criterion to predict the Shamblin group. In that study, tumor size and Shamblin group did not have a uniformly predictable relationship.[21] Some have found the size of the tumor is more useful when considering risk of surgery[22-24] because the Shamblin group classification is only useful in predicting vascular morbidity and not neurologic morbidity.[20] The tumors in our series were not assigned a Shamblin classification. Tumor volume was measured in 40 cases (85%) with CT and from the resected specimens. Volume was significantly larger in those cases in which nerve palsies occurred (52.2 vs 16.1 cm^3; $P < .05$).

Alternative surgical strategies have been proposed for the resection of CBT. The traditional surgical approach commences at the bifurcation,[24] but we believe this is more likely to result in vessel injury and hemorrhage, making the surgery more difficult. We recommend early control, but not clamping of the CCA proximal to the lesion, followed by dissection at the distal extent of the ICA, if possible, and

peeling the tumor down with diathermy, leaving the carotid bifurcation dissection until last. In our experience, this "craniocaudal" approach results in a low risk to the vessels and minimal bleeding. Others have also advocated this approach.[25] The early identification of neural structures is paramount. By staying close to the tumor and dissecting posteriorly around the ICA, identification of the superior laryngeal nerve can be made early. This can be difficult to identify with an anteromedial approach to the ECA. The vagus nerve, which may be enlarged or edematous with large perineural vessels—even when not directly involved—is best identified away from the tumor area and followed into the area of dissection. This minimizes risk of injury from direct trauma, but retraction injury can still occur.

Early in our series, partial resection of the vagus nerve during removal of vagus vagale tumors was undertaken in an attempt to preserve nerve function. This approach has been abandoned because palsy almost always occurs and there is a risk of inadequate resection of the tumor. For this reason, we now recommend complete nerve resection for these cases. Patients need to be carefully counseled about the consequences of vagal palsy, which can be a very debilitating injury, with slow adjustment to the debility over many months to years.

In patients with bilateral tumors, consideration of potential neural dysfunction should be taken into account when planning which side to resect first. The approach in the earlier years of this series was to deal with the larger tumor first and stage the resection of the contralateral smaller tumor. Our policy has changed in the latter years. Now, our strategy is to resect the smaller tumor first because this can generally be done with minimal or only temporary risk of cranial nerve injury. This allows the later, staged removal of the larger tumor, where the risk of nerve injury is greater, to be undertaken without the risk of leaving the patient with bilateral nerve palsies.

Malignancy is rare in CBTs, thought to occur in 6%.[26,27] Malignant potential is not readily determined, however, and only the discovery of neural crest cells in nonneuroendocrine sites is diagnostic. Compression or erosion of local structures may result in nonresectability but not true malignancy, as suggested by some authors.[28-31] We documented a 15% malignancy rate in our series, and we believe this is higher than reported by some authors[17,32] because of our practice of routine excision of surrounding abnormal lymph nodes. For this reason, we advocate the excision of any large or closely approximated lymph nodes for definitive histology in patients undergoing tumor resection because unsuspected micrometastasis may well be present.

Cranial nerve deficits have been reported to occur in 11% to 49% after CBT resection.[23,32-34] Unexpected cranial nerve palsies occurred after CBT resection in 11 operations (22%) in our series, and 54% of these were permanent. Cranial nerve palsy occurred more often in those patients with large tumors than in those with smaller tumors, and because of the increased nerve injury rate with large tumors as well as the potential for malignancy (albeit low), we advocate an aggressive approach to early resection unless there are compelling contraindications to surgery.

CONCLUSIONS

During the 25-year period during which 49 procedures were performed on 39 patients with carotid body paraganglioma, some changes in management and strategy evolved as technologies developed and experience accumulated. From this experience, we draw the following conclusions:

- Routine diagnostic and planning angiography is obsolete and has been replaced with high-definition CT and MRI. More sophisticated and functional imaging now allows detection of smaller and multiple cervical tumors and should be used in patients with familial, bilateral, or functional paragangliomas.
- Endocrine function in cervical paragangliomas is rare, and we therefore favor a selective approach to endocrine testing for patients in whom symptoms suggest function rather than routine endocrine testing for all.
- Early surgical resection while the CBT is small is recommended to limit the rate of permanent neurologic disability, which increases dramatically with larger tumors. Where tumors are bilateral, we recommend resection of the smaller tumor first, followed by later staged resection of the larger tumor, which has higher operative risk.
- When confronted with VP, we favor complete resection of the nerve rather than partial removal, which in our hands is associated uniformly with vagal palsy and a high risk of recurrence.
- We have found no need for preoperative embolization and remain unconvinced that its touted benefits outweigh the inherent stroke risk.
- We are comfortable with a craniocaudal method of resection, which in our hands allows safe resection of most tumors with minimal blood loss and low morbidity.
- Because of the risk of unsuspected micrometastasis, any large or closely adjacent lymph nodes should be excised for definitive histology.
- Ongoing surveillance is mandatory in familial cases or in patients with bilateral tumors because they are at higher risk of having metachronous tumors and they may represent the first of a new genetic line. Patients with incomplete resections should also have ongoing surveillance for the assessment of tumor enlargement.

AUTHOR CONTRIBUTIONS

Conception and design: AK
Analysis and interpretation: AK, PW
Data collection: AK, WF, JJ
Writing the article: AK, PW
Critical revision of the article: PW, JSJ, WF, NB
Final approval of the article: AK, PW, WF, NB, JSJ
Statistical analysis: AK, JJ

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AK and PW participated equally and share first authorship.

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INVITED COMMENTARY

Glenn M. LaMuraglia, MD, *Boston, Mass*

This single center, retrospective study adds some important caveats to the scant clinical knowledge relating to the approach of patients with carotid body tumors (CBT) or paragangliomas. CBTs are known to occur in either sporadic or familial cases, the latter resulting from a mutation of the succinate dehydrogenase gene with a greater phenotypic penetration when altitude or hypoxia is present.[1] In patients with CBT, it has therefore been customary to empirically recommend the careful evaluation for multifocal disease and screen patient families to identify latent familial cases. However, it is this 25-year longitudinal study that has provided clear evidence to support the benefit of this practice.

Though the patients in this study were not genetically evaluated, the data nicely elucidate the relevance of a field defect in the glomus cells of the paragangliomas. The identification in the study of concurrent vagal paragangliomas (15%) or concurrent bilateral CBT (21%) emphasizes the synchronous nature of the disease, and the importance of bilateral neck evaluation with Duplex ultrasound or contrast computed tomography. However, this study took this a step further with careful evaluation of the proband's family