

# Carotid body paragangliomas – clinical variety and management (RCD code: I-O)

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## Abstract

Paragangliomas (PGLs) are a group of rare, slow-growing tumours which are found between the base of the skull and the pelvis. The tumour is often asymptomatic, although a lump on the neck, cranial nerve palsy, or neck pain may be present. The treatment of choice is surgical resection. We present the cases of 7 patients (6 females) diagnosed with 9 PGLs of the carotid body (carotid body tumours – CBTs). These include: one case with known genetic burden, one of an advanced bilateral and recurrent tumour, and one with a malignant tumour. All presented CBTs were surgically removed. The size of a tumour correlates with postoperative complications. Resection of the largest lesion was associated with persistent left recurrent laryngeal, hypoglossal, and partial facial nerve paralysis. Other complications included single cranial nerve palsy and temporary Horner syndrome. JRC D 2018; 4 (1): 9–14

**Key words:** rare disease, carotid body paraganglioma, carotid body tumour, carotid body, paraganglioma, bifurcation of the common carotid artery

## Introduction

Carotid body tumours (CBTs), also known as chemodectomas, are rare, slow-growing, typically painless, and non-malignant tumours which are often present for years prior to the patient's seeking of medical attention [1,2,3]. The most common symptoms are presence of a lump in the neck, cranial nerve palsy, and neck pain, and apart from the lump, tumours are usually asymptomatic [4,5,6].

CBTs are the most common cervical paragangliomas (PGL) (60–65%) followed by jugular foramen and vagal tumours [2,5,6]. They are localised in the bifurcation of the common carotid artery [1,5]. CBTs develop from paraganglial cells of a carotid body [3], are well-supplied with blood, and appear as sharply circumscribed dark red polypoid masses with a rubber texture which can reach a large size [1,5]. About 5% of CBTs are malignant [4]. The treatment of choice is surgical resection [1,2,5]. CBTs are very rare, therefore, few reports describing their clinical course exist. The aim of this paper is to present the clinical course of 9 CBTs in 7 patients,

evaluate their comorbidities, and to discuss the surgical outcomes of tumour removal from a single centre experience.

## Material and methods

We searched the electronic database of medical records of all patients admitted to the Department of Vascular Surgery and Endovascular Interventions between 2009 and 2017. The following diagnoses were queried: 'D75.4 Malignant neoplasm of carotid body', 'D35.5 Benign neoplasm of carotid body', and 'D44.6 Neoplasm of uncertain or unknown behaviour of carotid body'. Out of 15 664 hospitalisations, 8 patients were selected, of which 7 were diagnosed with a carotid body tumour.

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**Table 1. Characteristic of the studied group (M – male, F – female; L – left, R – right)**

Case No.	Year of resection	Age at diagnosis	Sex	Symptoms	Genetic burden	Side	Tumors size [mm]	Malignancy	Surgical complications	Recurrence
1	2009	57	F	Palpable tumor on the neck	–	Right	52x30x27 (42.1cm <sup>3</sup> )	No	–	–
2	2010	26	M	Palpable tumor on the neck	SDHD and RET mutation	Left	10x10x10 (1cm <sup>3</sup> )	No	–	–
3	2011	42	F	Palpable tumor on the neck, blurred vision, swelling of the right eye socket region, palpation causing coughing, change of vocal timbre	–	Right	50x50x40 (100cm <sup>3</sup> )	Yes, metastatic cells in 2/6 removed lymphatic nodes	transient – hoarseness	–
4	2012	58	F	Palpable tumor on the neck, dyspnea, fainting	–	Both	L:42x40x75 (126cm <sup>3</sup> ) R:36x36x61 (79.1cm <sup>3</sup> )	No	L: paralysis of recurrent laryngeal and hypoglossal nerves (hoarseness, mildly impaired swallowing) partial left facial nerve palsy (drop of mouth corner)	R: palpable tumor on the neck 25x15x11mm (4.1cm <sup>3</sup> ), transient complication – Horner syndrome
5	2013	77	F	Palpable tumor on the neck	–	Right	18x11x14 (2.8cm <sup>3</sup> )	No	–	–
6	2015	77	F	Palpable tumor on the neck	–	Left	37x42x35 (54.4cm <sup>3</sup> )	No	–	–
7	2017	72	F	Palpable tumor on the neck	–	Right	20x15x15 (4.5cm <sup>3</sup> )	No	transient – hoarseness	–

## Statistical analysis

Data are presented as means  $\pm$  standard deviations, medians, numbers and percentages. Statistical analysis was performed using Microsoft Excel 16.0 software for Windows (Microsoft Corp., Redmond, WA, USA).

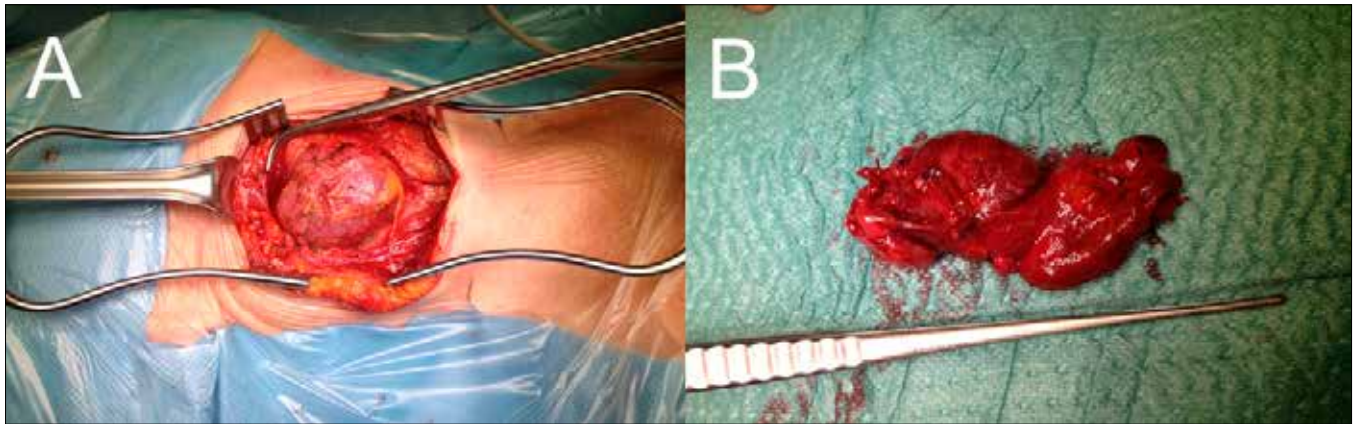
## Results

We present a series of 7 CBT cases diagnosed and surgically removed in our department. The study group consisted of 6 females (85.7%) aged 42–77, and one 26-year-old male with a genetic burden. The median age of the whole group was 58 (mean: 58.4  $\pm$  19.1 years of age). All tumours were palpable (100%). Six (66.7%) out of 9 tumours were located on the right side. Tumour volume varied widely (1–126 cm<sup>3</sup>), with a mean of 46  $\pm$  47.3 cm<sup>3</sup> and median of 42.1 cm<sup>3</sup>. Other symptoms included blurred vision (11.1%), swelling of the right eye socket region (11.1%), coughing and change in vocal timbre upon palpation (11.1%), dyspnoea (11.1%), and fainting (11.1%). Temporary paresis of the recurrent laryngeal nerve (transient hoarseness) was the most common

postoperative complication (22.2%). Other complications included recurrent laryngeal nerve paralysis (permanent hoarseness, 11.1%), hypoglossal nerve paralysis (mildly impaired swallowing, 11.1%), partial left facial nerve palsy (slight drop of mouth corner, 11.1%), and transient Horner syndrome (11.1%). Hence, transient or permanent hoarseness was the most common symptom, and occurred in 1 out of every 3 postoperative courses. Furthermore, the study group included one case of bilateral tumours, one malignant, one inherited, and one recurrent.

## Case No. 1

A 57-year-old female was diagnosed with PGL of the right carotid body. Computed tomography angiography (CT-angio) revealed a tumour with dimensions of 52  $\times$  30  $\times$  27 mm and the Lyre sign (internal and external carotid arteries drawn aside by the tumour), which is typical for carotid body tumours [2]. Moreover, the tumour significantly compressed the right internal jugular vein, and to a lesser extent, the internal carotid artery. There was neither pain during cervical palpation nor any other typical symptoms of CBTs. Concomitant diseases included hyperten-



**Figure 1.** Paraganglioma of right carotid body (Case No. 3): **A.** CBT before the removal; **B.** Removed CBT

sion and nontoxic goitre. One year prior to admission, the patient underwent a hysterectomy. The tumour was surgically removed without any complications, and histopathological examination confirmed the diagnosis of PGL. No lymph nodes were resected.

### Case No. 2

A 26-year-old male was admitted to our department and presented with PGL of the left carotid body. This patient underwent a laparoscopic removal of pheochromocytoma of the abdominal aorta in the same year. His father's family history was positive for genetic abnormalities. The mutation 33N TGC> TGA of the SDHD gene and polymorphism CTT> CTG at codon 769 of the RET proto-oncogene were diagnosed. Surgical removal of the mass (10 mm in diameter) was successful and without any complications. Extensive S-100 protein and chromogranin expression were found in the histopathological samples. Lymph nodes showed no evidence of tumour cells.

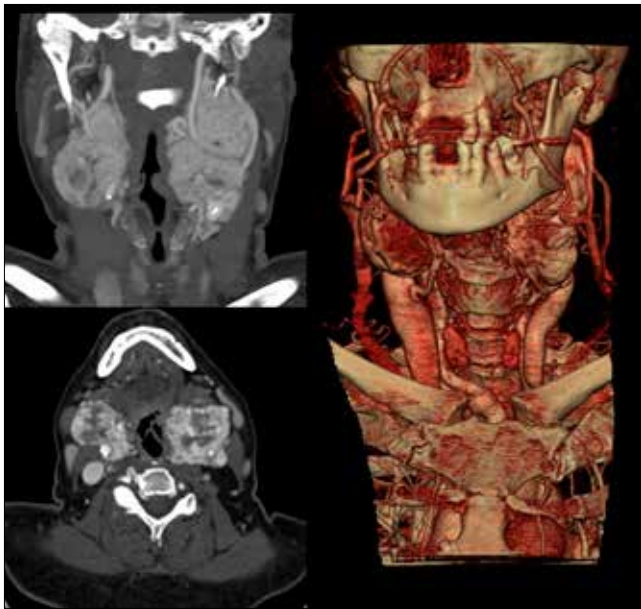
### Case No. 3

A 42-year-old female, suffering from hypertension and hyperlipidaemia, consulted her ophthalmologist due to blurred vision and swelling of the right eye socket region. A thyroid gland pathology was suspected. Neck ultrasound revealed a 50×50×40 mm mass in the area of the right common carotid artery bifurcation (Fig. 1). Following computed tomography, PGL of the right carotid body was diagnosed. The CBT infiltrated vagus, accessory, and phrenic nerves. The hypoglossal nerve, internal jugular vein, and mastoid process adhered to the tumour. Palpation of the tumour resulted in coughing and a change in vocal timbre. After surgical removal of the CBT, hoarseness occurred. In the histopathological examination, chromogranin and Ki-67 protein expressions were found. Two out of 6 excised lymph nodes contained tumour cells. The tumour was classified as malignant.

### Case No. 4

A 58-year-old female was referred to the vascular surgery out-patient clinic due to bilateral neck tumours with tenderness on palpation. CBTs were compressing the trachea causing dyspnoea. The patient suffered from hypertension, hyperlipidaemia, and was a smoker. Past medical history included hysterectomy, strumectomy, and pacemaker implantation due to sick sinus syndrome. Small lumps in the neck were already detected four years earlier but remained undiagnosed until the patient was referred to our facility. The appearance and increasing size of these lumps were associated with incidents of fainting. The diagnosis was established using colour Doppler ultrasound of the neck, which revealed the characteristic Lyre sign [2], followed by CT-angiography for optimal spatial reconstruction and surgical planning. Two large tumours were visualised in the bifurcations of the carotid arteries (42×40×75 mm on the left and 36×36×61 mm on the right), with infiltration of carotid vessels reaching the base of the skull on the left side. The patient underwent two-stage surgical removal, starting from the larger and more locally advanced tumour on the left side. Treatment was difficult due to the size of the tumour (Fig. 2). Surgery was complicated by paralysis of the left recurrent laryngeal and hypoglossal nerves, resulting in hoarseness and mildly impaired swallowing. Moreover, a slight drop of a mouth corner was observed due to partial left facial nerve palsy. The histopathological examination revealed a PGL containing chromogranin-expressing cells and sustentacular cells expressing the S-100 protein, with areas of hyalinization and haemorrhages without necrosis or increased mitotic activity. Resection of the tumour on the right side was uncomplicated. PGL was confirmed by histopathological examination. Regional lymph nodes were removed and found to be negative for tumour cells on both sides.

Eight months after the second operation, the patient was re-admitted due to recurrence of the PGL on the right side. A CBT measuring 25×15×12 mm was removed with a similar histopathological result as previously excised tumours. Horner syndrome was present postoperatively for 3 days, without long-term nerve damage (aside from persistent damage on the left side).



**Figure 2.** Computed tomography scan of bilateral CBTs shows compression on right internal jugular vein and internal carotid artery and areas of hyalinization and hemorrhages (A,B) (Case No. 4): **A.** Frontal scan; **B.** Transversal scan; **C.** 3D reconstruction

### Case No. 5

A 77-year-old female was diagnosed with a right-sided CBT. Characteristic symptoms of CBTs were absent. Tumour size was  $18 \times 11 \times 14$  mm based on ultrasound and CT-imaging studies (Fig. 3). The CBT was well-vascularised and had a well-demarcated border. The patient was suffering from hypothyroidism, dyslipidaemia, and chronic leukopenia. The CBT was removed together with 2 regional lymph nodes without any complications. No tumour cells were found in the excised nodes. One year later, ultrasound

imaging showed progressive calcification of the bifurcation of the right common carotid artery.

### Case No. 6

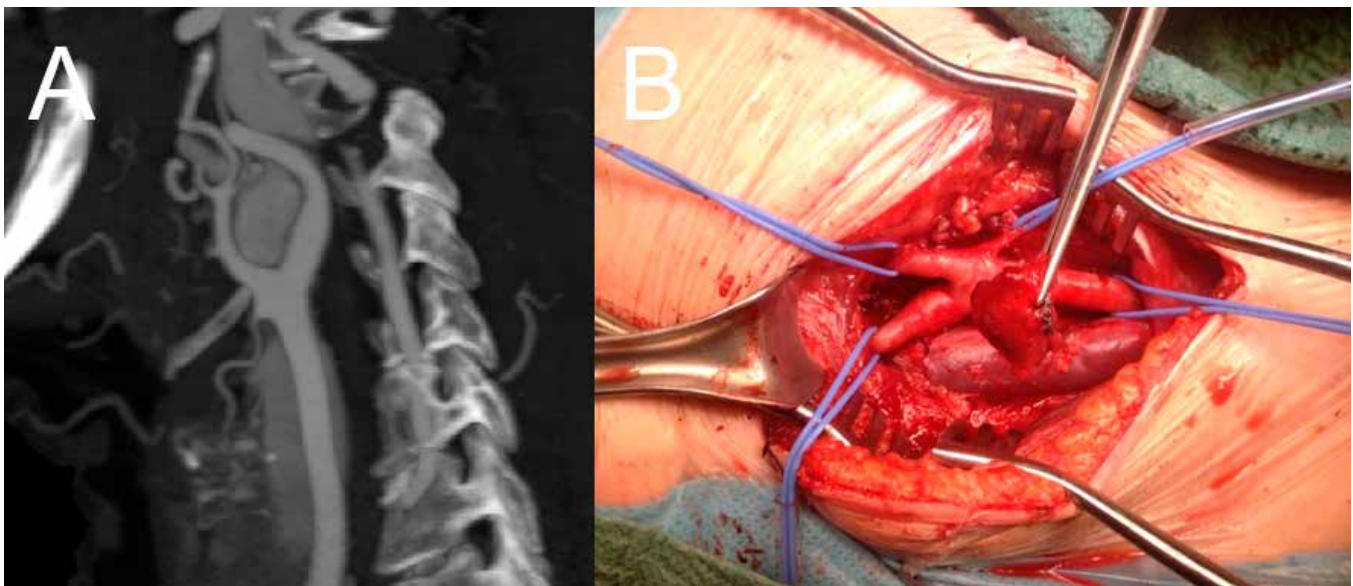
A 77-year-old female was diagnosed with CBT located in the bifurcation of the left common carotid artery. The size of the tumour was  $37 \times 42 \times 35$  mm. She did not present with any typical signs of CBT. Comorbidities included diabetes mellitus type II. No complications occurred following surgery. The histopathological examination indicated PGL. Three regional lymph nodes were negative for tumour cells.

### Case No. 7

A 72-year-old female was diagnosed with PGL of the right carotid body after routine ultrasound examination of the carotid arteries revealed a mass 20 mm in diameter. In addition, the patient suffered from an anxiety disorder. Six months prior to operation, the patient underwent tumour embolization. Hoarseness was a complication of the surgery. The tumour had a well-demarcated border surrounded by fibrofatty tissue and a size of  $20 \times 15 \times 15$  mm.

## Discussion

PGLs arise predominantly from adrenal glands (pheochromocytoma, 90%), however, only 0.3% of them occur in the head and neck area. CBT are the most common head and neck paragangliomas [1,5]. Although some studies have suggested that CBTs are more common in males [7,8], it appears that women are more often affected [2,4,5,6,9,10,11], constituting up to 95% of patients [10]. Unsurprisingly, a large systematic review of 19 studies con-



**Figure 3.** CBT of right carotid body (Case No. 5): **A.** Computed tomography sagittal scan; **B.** Removed CBT

firmed that female patients are more likely to be affected [12]. In our study, only Case No. 2 featured a male patient. CBTs have been reported to occur throughout adulthood (between 18–94 years of age) [4], with the median age of diagnosis between the 4<sup>th</sup> and 6<sup>th</sup> decades of life [2,4,9,10,11]. Cases No. 5 and 6 were outliers, as both patients were 77 years old at the time of diagnosis. Case No. 2 was not a sporadic PGL.

Apart from the presence of a lump in the neck, CBTs are mostly asymptomatic (Cases no. 1, 5, 6, 7) [4,5,6]. In most cases they are only noticeable during palpation, so in the setting of a positive family history, it is advisable to perform regular inspections of the region. Palpation may trigger pain [10]. Moreover, symptoms caused by especially large tumours include autonomic nervous system disorders, dysphagia, and dyspnoea [2,5,6]. Symptoms such as hypertension, sweating, tachycardia, and nervousness may appear if the tumour is secreting catecholamines [4,5,13]. Nevertheless, only up to 4% of head and neck paragangliomas secrete hormones [11]. None of our patients had a confirmed secreting tumour, however, patients in Cases No. 1, 3, and 4 were treated due to hypertension. Additionally, the patient in Case No. 3 had visual disturbances, which might be a rare symptom of a secreting pheochromocytoma [14]. It is worth mentioning that 3 out of 7 of the presented patients had thyroid diseases (Cases No. 1, 4 – nontoxic goitre, 5 – hypothyroidism). The patient in Case No. 6 had diabetes mellitus type II.

Recent studies suggest that head and neck PGLs are, in more than 30% of cases, heritable due to mutations within the succinate dehydrogenase genes (SDHD, SDHA, SDHC, SDHB) [15,16]. In most cases, such mutations lead to formation of tumours in multiple locations [5,16]. In our study group, only the patient in Case No. 2 had a confirmed mutation in the SDHD gene and was diagnosed with pheochromocytoma and PGL of the carotid body.

In approximately 60% of cases, head and neck PGLs [5,6] localise to the bifurcation of the common carotid artery as a CBT, and these are mostly unilateral (70–95%) [4,9–11]. Two of our cases featured tumours on the left side (Cases no. 2, 6), four on the right side (Cases no. 1, 3, 5, 7), and one was bilateral (4). CBTs exhibit greater mobility in the horizontal than vertical plane, which is known as the Fontaine sign (due to adhesion of the lower pole of the tumour to the carotid bifurcation) [17]. Carotid bodies have physiological sizes ranging from 1.1 to 3.9 mm on CT imaging [18]. Depending on a CBT's size it may affect the position of the neighbouring vessels (common carotid artery, internal, and external carotid artery) or cause cranial nerve palsy (Patients in Cases No. 1, 3, 4) [4].

On gross examination, the tumours are usually well-circumscribed. The cut surface is typically solid with a smooth, rubbery texture but may display some areas of haemorrhage. Actual size of the tumours vary greatly [1], some as large as 8×7 cm have been reported [19]. Histologically, a carotid body's glomus consists of Type I and Type II cells [20]. Type I cells are part of the Amine Precursor Uptake and Decarboxylation (APUD) group and are responsible for catecholamine secretion. Type II cells are modified Schwann cells and have sustentacular function [20,21]. CBT cells are characterised by specific, nest-like (*Zellballen*) growth and these cells show reactivity with chromogranin staining (Samples from Cases No. 2, 3, and 4 were positive). Type II cells are usually present peripherally or outside the *nest* and can be visualised with S-100 protein staining

(2, 4) [1]. Currently, no histological criteria exist to diagnose malignancy in primary tumours [13]. Initial CBT metastases may first occur in the lymph nodes, therefore, regional lymph node removal is a common procedure, however, findings may be ambiguous (lack of changes – Cases no. 2, 4, 5, 6, reactive change – Case no. 3, not removed – Cases no. 1, 7) [15].

A CBT classification system was developed by Shamblin, which is based on their size, involvement of the carotid arteries, surrounding nerves and vessels, and indicates possible complications after surgical removal [18]. CBTs of the first type slightly affect the neighbouring neck vessels and total resection is possible. Risk of damage to the surrounding vessels and nerves associated with the surgical procedure is minimal. The second type of CBTs include cases in which the body of the tumour surrounds the main neck vessels and infiltrates adventitia but does not entirely encase the carotid vessels. Total removal is possible but difficult, with the risk of complications. CBTs of the third type occur when neck vessels are significantly infiltrated and encased by the tumour. Involvement and stenosis of the vessel wall, involvement of the hypoglossal nerve and superior laryngeal nerve can be observed. Total resection is very difficult, often results in complete to temporary interruption of the cerebral circulation, and is usually complicated by damage to the vessels, requiring complex reconstructive procedures [17,18]. Recently, a modification to the classification system has been suggested. The newly added class IIIb represents a tumour of any size if it is intimately adherent to the vessels [22].

Paraganglioma of the carotid body is a slow-growing, rarely malignant tumour (5%) [4] which doubles in size usually in a period of 4 years. Other cancers of the same area require approximately 100 days to double in size [23]. The treatment of choice is surgical resection, which was performed in all of the described cases in this paper [1,4]. A large meta-analysis reports that nearly half of the patients may have a cranial nerve complication, and that more than a third of these impairments are permanent (Case No. 4) [12]. Early diagnosis and management appear to have a crucial role in avoiding postoperative complications [24]. Due to the slow-growing character of CBTs, an alternative treatment, radiotherapy, may be preferred in the group of patients with short life expectancy [15].

## Conclusions

CBTs are typically slow-growing and rarely malignant tumours, which cause symptoms related to compression of surrounding structures. Early detection is crucial as postoperative complications correlate with the tumour size. The most common symptom is a lump on the neck, and the procedure of choice is surgical resection often combined with local lymph node removal due to the unpredictable nature of the neoplasm. In our case series, we found a high association of CBTs with thyroid disease in past medical history (42.9%), which may indicate a relationship. In addition, we presented the case of a patient with an SDHD gene mutation which likely led to CBT formation.

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