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Level of plasma catecholamine predicts surgical outcomes of carotid body tumors: Retrospective cohort study

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Abstract

Backgrounds: Carotid body tumors (CBTs) are rare neoplasms and some of them produce catecholamine. Although operations for catecholamine-producing CBTs are safe, the relationship between prognosis and endocrine function has not been analyzed before.

Methods: Patients diagnosed with CBTs in our department between 2009 and 2018 were analyzed. Plasma catecholamine was examined as a variable of surgical outcomes and prognosis by using statistical methods.

Results: Patients who suffered CBTs and underwent operations were divided into two groups according to their plasma catecholamine. Patients in the normal group had more or heavier surgical complications, such as neurological complications ($P = .008$) and blood loss ($P = .03$), than those in the high group. However, overall survival, local recurrence, and remote metastasis were not varied significantly in both groups.

Conclusions: A high level of plasma catecholamine was a predictor for the improved operative outcomes of CBTs. Hence, nonfunctional CBTs had further short-term surgical complications.

KEYWORDS
carotid body tumor, cohort study, plasma catecholamine, prognosis, surgery outcomes

1 | INTRODUCTION

Carotid body tumor (CBT) is a rare neuroendocrine neoplasm located at carotid bifurcates. CBT is pathologically defined as paraganglioma. The incidence of paraganglioma is low, with only 1-2 per million in the United States.[1] Some CBTs can produce catecholamine, which may lead to secondary hypertension. Moreover, CBTs have potential invasion capability, adjacent nerve and vessels may be involved, which may cause cerebrovascular accident and neurological symptoms, such as Horner syndrome, hoarseness, and choking. The primary treatment of CBTs is surgical resection,[2] and adjuvant radiotherapy[3] or preoperative embolization[4] may be useful for CBTs.

Although CBTs grow slowly, all of them have the potential for recurrence and metastasis. Their metastasis rate ranges from 5% to 35%.[5-9] However, unlike other types of neoplasms, no test or marker can distinguish malignant from benign tumors.[10] Studies defined malignant paraganglioma as the presence of distant metastasis.[11-13] Thus, a long-term follow-up is recommended. In recent years, studies have shown that approximately 12%-16% CBTs have *SDHx* mutations,[14-16] and *SDHB* mutations are expected to have a correlation with the bad prognosis of CBTs.[14,17,18] Our previous study[19] showed operations for catecholamine-producing CBTs are safe, but the sample size of the prior study was small and the prognosis of these functional tumors has not been investigated before. We determine if the level of plasma catecholamine can be a predictor for the surgical outcomes and prognosis of CBT. This study is designed to assess the surgical outcomes of patients with CBT and if prognosis can be varied significantly in catecholamine-producing CBTs.

2 | PATIENTS AND METHODS

2.1 | Patients

All patients diagnosed with CBT at our department between 2009 and 2018 were included. Patient demographics, laboratory testing results, imaging examination findings, and operative records were reviewed. Patients were evaluated via biochemical test and electron fibrolaryngoscopy, imaging studies (CT with 3D reconstruction, Doppler ultrasound, and MRI) preoperatively and postoperatively. These patients were follow-up at 1, 3, 6, 12 months, and yearly after surgery. Patients were excluded when (a) complicated with other pheochromocytoma or paraganglioma, (b) they had distant metastasis at diagnosis, (c) they had other malignant tumors, and (d) their records or image data were incomplete. A total of 168 patients with 182 CBT lesions were included in this study, 207 patients were excluded because of lacking complete data and 3 patients were excluded due to developing thyroid malignancy. A total of 13 patients who refused to undergo operation were excluded when perioperative and follow-up data were evaluated. All CBTs were classified in accordance with the Shamblin classification.[2] That is, a Shamblin I tumor was small, locally grew between internal and external carotid arteries, and was minimally attached to vessels; Shamblin II tumors were partially encased vessels and had moderate arterial attachment; Shamblin III tumors were completely incarcerated arteries, and vessel replacement was often necessary.

This study was approved by the Ethics Committee of Sichuan University. Informed written consent was obtained from all subjects prior to the study.

2.2 | Surgical procedure and complication assessment

We started the surgical treatment for CBTs from 2002; nine surgeons were included, and each one had more than 8 years of experience. The most difficult part of each operation was accomplished by one surgeon. Thus, there is no technical difference between these operations. Our surgical procedure has been elucidated before.[20] In this study, tumors of 78 patients were simply resected, and the rest needs bypass when tumors were completely resected. Autogenous saphenous veins or artificial grafts were used to revascularize arteries. Injured nerves were repaired using prolene threads if possible. Adjacent lymph node, together with tumor samples, was dissected, and examined via biopsy.

The major perioperative complications analyzed include cerebrovascular infarction (CI), laryngeal obstruction, malignant hypotension, and mortality. Other complications, such as Horner syndrome, dysphagia, hoarseness, and local paralysis, were considered to have resulted from nerve injuries or disturbances. They were defined as minor complications together with wound infection.

2.3 | Statistical analysis

Data were presented as mean ± SD of mean, or median and its range, on the basis of their distributions. The SPSS 24.0 statistical package for windows (IBM, Armonk, NY) and Graphpad Prism 6 (Graphpad software, San Diego, CA) were used to perform analyses. Patients were divided into two groups in accordance with their plasma catecholamine level. Differences between the groups in terms of patient age, tumor size, and intraoperative blood loss were tested using unpaired Student's t test. The relationships between plasma catecholamine level and sex, tumor location, local invasion, tumor classification, and operative complications were evaluated with chi-square and Mann-Whitney U tests. Multiple linear regression was performed to adjust cofounding factors. The variable postoperative neurological complications during same periods of time were evaluated using a Spearman's coefficient of rank correlation.

The association among follow-up variables, including overall survival, distant metastasis, local recurrence, cerebrovascular accident, and plasma catecholamine level, was analyzed through the Kaplan-Meier method. Multiple linear regression was used to investigate the relationship between variables and overall survival. A P value <.05 was regarded as statistically significant, and P values are 2-tailed. R^2 was used to compare the fitness of multiple linear regression models, and an improved model was achieved when R^2 was close to 1.

3 | RESULTS

3.1 | Preoperative characteristics

The normal ranges of plasma norepinephrine and epinephrine were 174-357 and 60-104 ng/L, respectively. A total of 56 patients (33.3%) defined as "high group" had a higher level of plasma catecholamine (either plasma norepinephrine or epinephrine) than normal people, and the other 112 patients (66.6%) with a normal level of plasma catecholamine were defined as the "normal group." The maximum tumor diameters in both groups were 4.2 ± 1.6 and 3.8 ± 1.3 (Figure 1). Women predominated significantly in the normal group (69.6%), but only account for 53.6% of total patients in the high group. The average age at diagnosis was 46 years in the normal group and 45 years in the high group. Most patients were seen as a painless mass, and only a few patients had symptoms caused by compression. However, no significant difference was observed between the groups. A total of 14 patients in the normal group and 9 patients in the high group developed bilateral CBT. Three

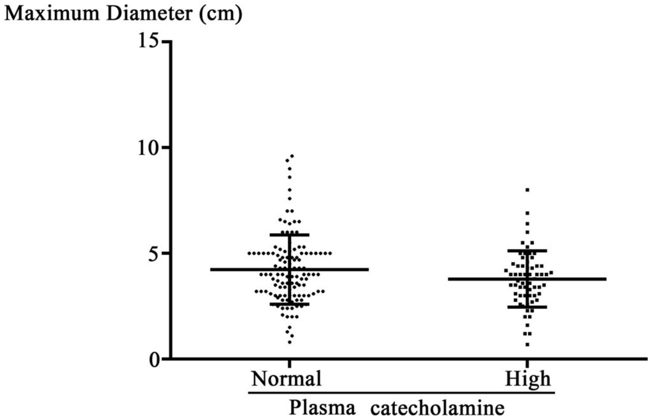

FIGURE 1 Tumor size in two groups was presented as the maximum diameter of tumor. No statistical difference was observed between the groups

TABLE 1 Patient clinical characteristics

Characteristic Plasma catecholamine	Observed data in two groups Normal	High	*P* value
Total patient number	112	56	
Total tumor number	126	65	
Tumor size, cm	4.2 ± 1.6	3.8 ± 1.3	NS
Sex (male/female)	34/78	26/30	.04
Age at diagnosis, y			
Mean ± SD	46.3 ± 12.8	44.8 ± 11.5	NS
Median, range	47, 20-79	47, 15-67	
Symptoms			
Neck mass	82	37	NS
Dysphagia	3	1	NS
Tinnitus	2	0	NS
Hoarseness	8	2	NS
Horner syndrome	5	1	NS
Tongue paralysis	7	5	NS
Tumor location			
Left side	41	31	
Right side	57	16	
Bilateral	14	9	NS

patients in the normal group underwent embolization prior to operation. No significant statistical difference was observed in patient characteristics except sex ($P = .04$) between the groups. Table 1 lists additional details.

3.2 | Intraoperative characteristics and outcomes

Table 2 shows the intraoperative characteristics and operation outcomes. All CBTs were resected successfully. A total

TABLE 2 Operative characteristics and follow-up

Univariate variables Plasma catecholamine	Observed data in two groups Normal	High	*P* value
Patients performed operation	101	52	
Tumors resected	114	58	
Tumor size, cm	4.3 ± 1.5	4.0 ± 1.7	NS
Local invasion	28 (27.7%)	13 (25%)	NS
Hemorrhage, mL	975.0 ± 801.9	558.2 ± 486.4	.03
Shamblin classification			.02
I	11 (10.9%)	5 (8.9%)	
II	38 (37.6%)	30 (53.6%)	
III	57 (56.4%)	21 (37.5%)	
Perioperative complications			
Major			
Cerebral infarction	1 (1.0%)	0	NS
Mortality	1 (1.0%)	0	NS
Malignant hypotension	2 (2.0%)	1 (2.0%)	NS
Laryngeal obstruction	1 (1%)	0	NS
Minor			
Nerve injuries[a]	52 (51.2%)	15 (28.8%)	.008
Facial nerve	7 (6.9%)	3 (6.3%)	
Glossopharyngeal nerve	9 (8.9%)	1 (2.0%)	
Vagus nerve	37 (36.7%)	9 (17.3%)	
Accessory nerve	0	1 (1.9%)	
Hypoglossal nerve	30 (29.7%)	7 (13.5%)	
Superior laryngeal nerve	4 (4.0%)	3 (5.8%)	
Recurrent laryngeal nerve	3 (3.0%)	1 (1.9%)	
Multiple nerves injuries	33 (25.7%)	7 (13.5%)	.01
Wound infection	2 (2.0%)	0	NS
Follow-up			
Withdraw	19 (18.8%)	9 (17.3%)	NS
Recurrence in situ.	9 (11.0%)	4 (9.3%)	NS
Distant metastasis	7 (8.5%)	4 (9.3%)	NS
Neuro-sequela[a]	16 (19.5%)	8 (18.6%)	NS
Cerebrovascular accident[b]	10 (12.2%)	3 (7.0%)	NS
Deceased	7 (8.5%)	3 (7.0%)	NS

[a]Include Horner syndrome, hoarseness, dysphagia, tongue muscle atrophy, and local paralysis.
[b]Include transient ischemic attacks (TIA) and cerebral infarction (CI), six/four patients in normal plasma catecholamine group suffering CI/TIA, whereas three patients in high plasma catecholamine group suffering TIA.

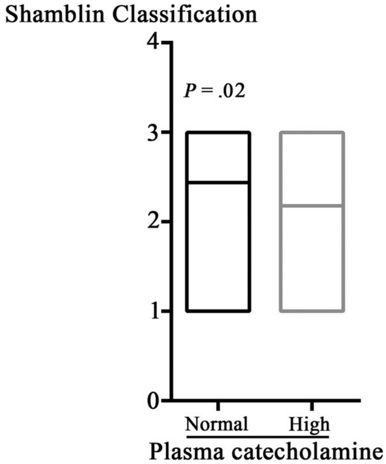

FIGURE 2 Patients in two groups were classified in accordance with the Shamblin classification in operations

of 101 patients in the normal group and 52 patients in the high group underwent operation, 114 and 58 CBTs were removed, respectively. Moreover, 28 patients in the normal group and 13 patients in the high group had adjacent nerves or vessels invaded in operation. More CBTs in the normal group than that in the high group were classified as Shamblin III (Figure 2). The mean volume of blood loss in the normal group was 975 ± 801.9 mL, whereas that in the high group was 558.2 ± 486.4 mL ($P = .03$), as shown in Figure 3. The multiple linear regression formula for adjustment is as follows:

$$
\begin{aligned}
\mathrm{Y(hemorrhage)} = {} & 221.690{*}\mathrm{X}_1(\mathrm{diameter}) \\
& + 344.137{*}\mathrm{X}_2(\mathrm{Shamblin\ classification}) \\
& - 228.174{*}\mathrm{X}_3(\mathrm{plasma\ catecholamine}) \\
& - 927.222, \\
R^2 = 0.458,\ & \mathrm{Adjusted}\ R^2 = 0.432,\ P = .00.
\end{aligned}
$$

All CBTs were resected successfully, and only one patient died in the perioperative period due to cerebral hernia. One patient suffered a severe CI. Three patients required fluid infusion combined with noradrenaline pump to maintain a normal blood pressure. One patient underwent tracheotomy for laryngeal obstruction. No significant difference in major operative complications was observed between the groups. The normal group had a higher incidence of neurological complications associated with nerve injuries or disturbances ($P = .008$) than the high group. Specifically, 52 patients (51.2%) in the normal group and 15 patients (28.8%) in the high group suffered neurological complications (Figure 4). More patients in the normal group had multiple nerve injuries than that in the high group (25.7% vs 13.5%, $P = .04$). Table 2 lists other details. Two patients in the normal group developed an incision infection that was not resolved at discharge.

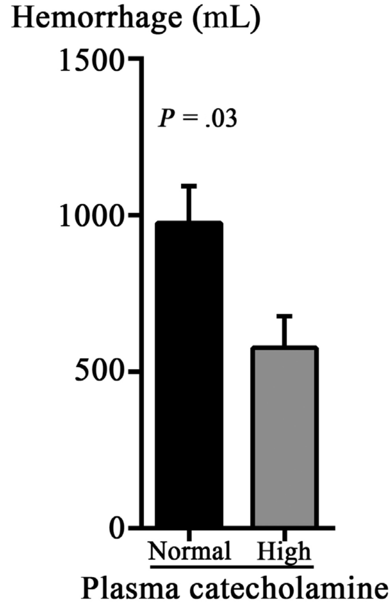

FIGURE 3 Intraoperative blood loss in two groups

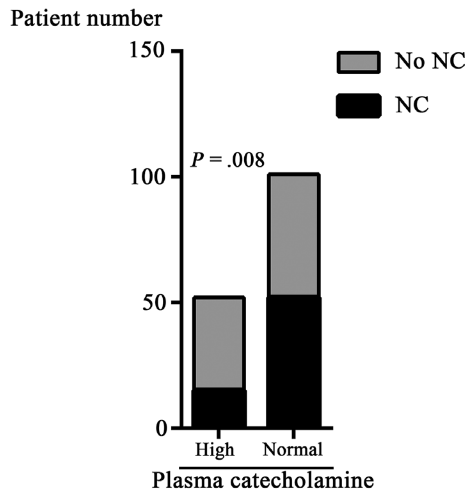

FIGURE 4 Patients in two groups either had operative neurological complications or not. NC, neurological complication

3.3 | Follow-up

The median follow-up time was 44 months (range: 4-155). Nine patients in the normal group and four patients in the high group developed local recurrence. Six patients in the normal group and four patients in the high group grew pulmonary or bone metastasis. Only one patient in the normal group developed mediastinum metastasis. Moreover, 8/3 patients in normal/high group had cerebrovascular accident. Among them, only three patients in the normal group were identified with CI by CT scan. Others were diagnosed with transient ischemic attacks. The incidences of neurological complications remaining at last follow-up interval in normal and high groups were 19.5% and 18.6%, respectively.

Plasma catecholamine would not significantly vary the prognosis of CBTs, and no difference in overall survival, complication incidence, and local recurrence/remote metastasis was observed between the groups.

The relationship among complications, such as cerebrovascular accident, neurological complications, recurrence, metastasis, and overall survival, was assessed through multiple linear regression. Only local recurrence and distant metastasis correlated with overall survival. The model included two variables, that is, recurrence and metastasis, which fit best with $R^2 = 0.430$ and adjusted $R^2 = 0.421$ ($P = .00$).

4 | DISCUSSION

Plasma catecholamine screen is not a routine laboratory testing unless patients have hypertension in most medical centers. However, we found that the blood pressure of some patients increased sharply during operations, which will result in massive bleeding regardless of whether they had hypertension before. This occurrence may be caused by the release of catecholamine secreted by CBTs when the tumors are touched or compressed in operations. As reported in our previous study,[19] the operations for functional CBTs become safe when appropriate preoperative preparation was performed. Routine plasma catecholamine screen can help to reduce operation risks and damage. In this study, the most important finding is that a high plasma catecholamine is a protective factor for patients with CBT, which has not been reported before. Functional CBTs seem to be less aggressive than nonfunctional ones. Neurological complications incidence is relatively low in patients who developed functional CBTs. Although the incidence of permanent or long-term neurological complications was similar in the two groups, the reversible neurological complications were relieved or completely recovered early in the high group (Figure 5). Half of the neurological complications were relieved in the high/normal group after 72/90 months. Hemorrhage volume in operation was also relatively small in the high group. The sensibility of plasma catecholamine testing for evaluating functional CBTs was comparatively limited, which resulted in false-negative results. Blood pressure of these patients may increase during operations, which led to massive bleeding. Combined with plasma metanephrines test, the results can be more reliable.[21-24]

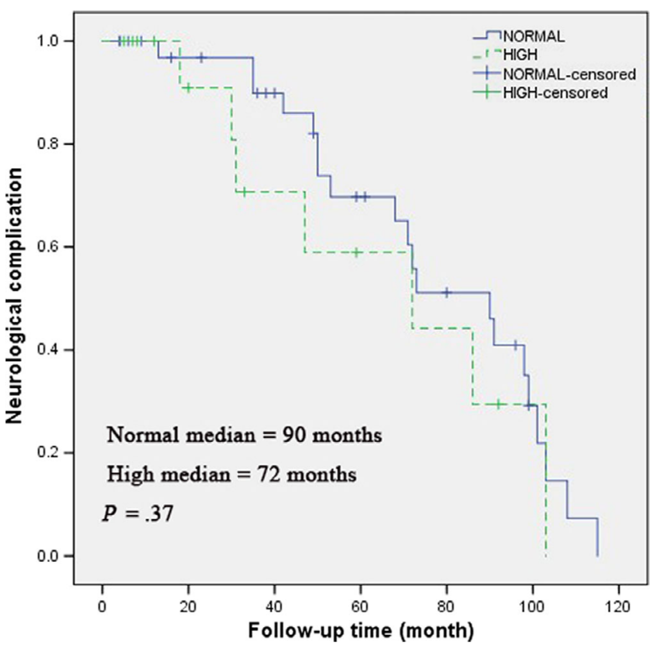

FIGURE 5 Patients whose nerves were injured or disturbed in operations still suffered neurological complications at follow-up in two groups [Color figure can be viewed at wileyonlinelibrary.com]

Although there is no statistical difference in tumor size observed between the groups, we still can see the trend that functional CBTs might grow slower than nonfunctional ones. However, we believe that either the maximum diameter or volume of tumors calculated by the available formula[25] is not accurate for assessing the growth rate of tumor. Tumor volume is calculated on the premise that CBTs are more or less round or oval in shape, they are irregular actually. Their volume cannot be calculated unless encased vessels are excluded. Moreover, most early stage CBTs are asymptomatic, and the onset time of CBTs is difficult to ensure. As described in previous studies,[17,25,26] Shamblin classification and tumor size are correlated with surgical blood loss and cranial nerve injuries. In our study, nonfunctional CBTs were associated with higher grade of Shamblin classification than functional CBTs. When growth rate of CBTs cannot be exactly measured, which can partially reflect the fact that nonfunctional ones grow faster than functional CBTs.

We proposed a hypothesis that functional CBTs were less aggressive than nonfunctional ones probably because functional CBTs differentiated better than nonfunctional ones. For instance, tumors that are obtained from the digestive system and have endocrine function have a well or moderately differentiated histology.[27] Endocrine and proliferation are high-energy-consuming processes. Considering that these two progresses can be maintained simultaneously in the same cell is difficult, especially in a relative energy-deficient tumor tissue. Consistent with that in a normal tissue, “functional cell” is not likely to proliferate in tumor tissue. Therefore, nonfunctional CBTs grew more aggressively as we found, which resulted in more surgical complications.

Till now, surgical excision was still primary treatment for CBTs, but it may result in many surgical complications and massive blood loss. We attempted to reduce risks of cerebral ischemia by using shunt intraoperatively.[28,29] And mean postoperative neurological complications incidence of patients treated by us declined as time went on (Figure 6). However,

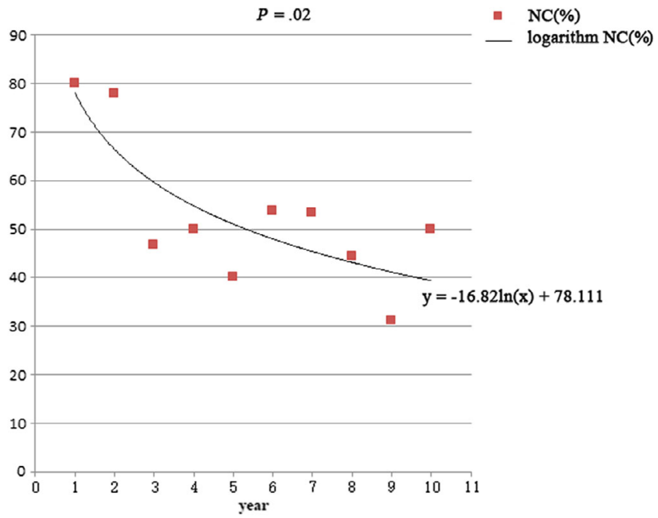

FIGURE 6 Annual neurological complications declined as time went on. NC, neurological complication [Color figure can be viewed at wileyonlinelibrary.com]

nerve injuries were hard to be avoided completely in operations, especially for large CBTs. Some studies reported that preoperative embolization can shorten operative time, reduce blood loss, and neurological complications.[4,30] However, other studies[31,32] believed that patients cannot benefit from this therapy. Larger prospective studies are necessary for proving its effectiveness. Radiotherapy was mainly performed for recurred tumors[3] and tumors which located closely to skull base. But there were only some studies with small sample size or case series presented, the reliability of radiotherapy was questioned.

The limitations of this study are inherent in the retrospective nature of the study. The sample size of this study, especially functional CBTs, is small due to their rarity. Moreover, the accuracy of plasma catecholamine for the endocrine function evaluation of CBTs is limited. Moreover, our hypothesis requires subsequent experiment to sustain.

5 | CONCLUSIONS

Plasma catecholamine predicts the operative complications of CBTs, such as neurological complications and hemorrhage. Catecholamine-producing CBTs have less short-term surgical complications than normal ones. The operations for functional CBTs are safe if appropriate treatments are performed. Long-term survival is associated with tumor recurrence and metastasis, which suggests a lifelong follow-up.

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