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Diagnosis and outcomes of surgical treatment of carotid bifurcation tumors

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Abstract

Objective: To retrospectively review our experience with the diagnosis and treatment of carotid bifurcation tumors (CBFT).

Methods: This was a retrospective study of 60 patients with CBFT who underwent surgical and conservative treatment. The patients' clinicopathological features, imaging examination findings, treatment strategy, and prognosis were analyzed. The surgical grade, blood loss, tumor size, operative time, and postoperative complications were analyzed by Spearman's correlation.

Results: Resection was performed in 52 patients with 53 tumors. The mean tumor volume, operative time, estimated blood loss, and follow-up time was $47.62 \pm 65.28\,cm^3$, 176.1 ± 86.55 minutes, 231.3 ± 354.0 mL, and 44.42 ± 29.30 months, respectively. Pathological examination showed that the number of carotid body tumors (CBT; paraganglioma), neurilemmoma, mesenchymal tissue tumor, and angioleiomyoma was 42, 8, 1, and 1, respectively. Of the CBT group, the rate of Shamblin Type I, II, and III was 11.9%, 59.5%, and 28.6%, and three cases were malignant CBT with lymph node metastasis. Spearman's correlation analysis showed that complication grade was significantly related to surgical difficulty grade and operative time.

Conclusion: CBT is the most frequent lesion in CBFT, and CBT may be treated safely by surgical management. The severity of surgical complications is significantly correlated with surgical difficulty.

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Introduction

Different tumor types may arise at the carotid bifurcation, and most of these tumors require surgical treatment. The most frequent pathology in this location is carotid body tumor (CBT), which receives a rich arterial blood supply originating from branches mainly derived from the external carotid artery (ECA). CBT usually presents as an asymptomatic slow-growing mass with the possibility of pain, and involves cranial nerves with sufficient growth. CBTs are rare and usually benign neoplasms with a slow growth rate, but these tumors also have the potential for malignancy. The reported rate of malignant CBT is 5%, with most malignant tumors diagnosed after the detection of metastases.[1] Therefore, patients benefit if carotid bifurcation tumors (CBFT) can be diagnosed and treated earlier.

It is challenging to resect large tumors surrounding the carotid artery bifurcation or those involving the nearby cranial nerves. For these tumors, the carotid artery may require reconstruction and consequently, complications, such as cranial nerve injury (CNI) and/or stroke, may occur. Many surgeons have only limited experience treating CBTs, which can be associated with a significant risk of approximately 30% to 40% morbidity and mortality,[2] which is especially related to perioperative stroke and CNI. Therefore, experienced surgeons proficient in the anatomy of this region are critical for diagnosing and treating CBTs.

The aim of the current study was to retrospectively review our experience with 60 consecutive patients with CBFT and investigate the diagnosis and treatment of these tumors.

Methods

This was a retrospective study analyzing all consecutive patients with CBTs undergoing surgical and conservative treatment between May 2010 to December 2018. The study was reviewed by the Institutional Review Boards of our institution and received an exemption because of the retrospective design. Written informed consent for treatment was obtained from each patient.

Patients' demographics, preoperative, operative, and postoperative data, and complications data were collected by reviewing each patient's medical records. Tumor size was measured from preoperative ultrasonographic images and preoperative computed tomography angiography (CTA). The treatment methods constituted either conservative treatment or surgical resection of the mass. Surgical data constituted tumor type, complications, tumor size, and pathological results. Every resected tumor was sent to the Clinical Pathology Department for histopathologic diagnosis and immunohistochemical assays.

Surgical procedures included: simple mass resection (MR), external carotid artery ligation (ECL), cranial nerve dissection (CND), internal carotid artery

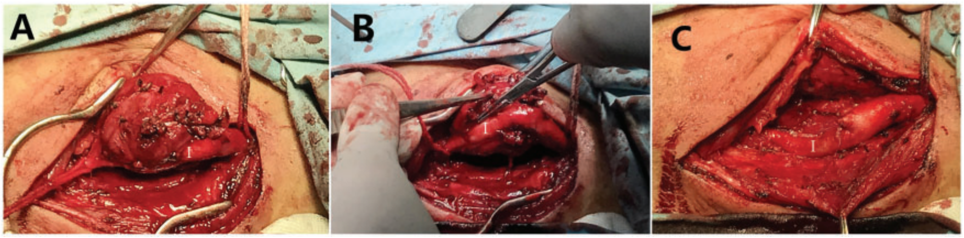

Figure 1. Simple mass resection (MR) and external carotid artery ligation (ECL) surgical procedures (A) Tumor in the carotid artery bifurcation; "I" indicates the internal carotid artery. The external carotid artery is involved in the tumor; (B) dissection of the tumor along the internal carotid artery; (C) the tumor has been removed, the external carotid artery has been ligated, and the bifurcation has been reconstructed.

reconstruction (ICR), and internal carotid artery ligation (ICL), in different combinations. Figure 1 shows representative images of the MR and ECL procedures.

We evaluated and recorded the following data: CNI, estimated blood loss (EBL), perioperative stroke rate (30-day), and procedure-related mortality. We also recorded the 30-day procedure-related reintervention rate and all-cause mortality rate. All preoperative variables, including cohort characteristics and procedure variables, namely characteristics, timing, and procedure type, were studied to assess their impact on the primary and secondary endpoints. We then performed a correlation analysis (Spearman's) between complications and surgical treatment/tumor characteristics. GraphPad Prism 7.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for the statistical analyses. For the correlation analysis, we defined different grades of CNI, surgical management, complication grades, tumor size grades, operative time grades, and EBL grades. All of the patients underwent follow-up physical examination, and survival was assessed using outpatient clinic visits or telephone interviews.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as number and frequencies. Continuous variables were compared using Student's T-test or the Mann–Whitney U test, and categorical variables were compared using the χ^2 or Fisher's exact test. when feasible. Spearman's correlation was performed to analyze the relationship between complication grades and other risk factors.

Results

Table 1 shows the grade definition details. Sixty patients with CBFT were included in this study. The mean age of the patient cohort was 42.9 years, with the majority being female (68%, n = 39). A neck mass was the most common presentation. Of these patients, 57 had painless and asymptomatic neck masses, while 3 were symptomatic (one with neck pain, one with hoarseness, and another with dizziness). The duration from detecting the mass to hospital admission was 37.40 ± 60.43 months. Bilateral tumors were found in 2 patients (3.3%), right-sided tumors were found in 27 (45%), and left-sided tumors were found in 17 (28.3%); Table 2 contains additional descriptive and demographic data. The mean tumor volume was 47.62 ± 65.28 cm^3 (range, 6 to 448 cm^3); 52 patients with 53 tumors underwent surgical resection; 8 patients declined surgery and chose conservative treatment (13.3%).

Table 1. Definitions and grades of the patient, surgical, and tumor characteristics.

Characteristic	Definition or Grade
In-hospital mortality	Death before hospital discharge or after surgery
Reintervention	Repeat procedure related to surgery or postoperative complications
Operative time	Duration from skin incision to completing suturing the skin
Cranial nerve injury (CNI)	Temporary CNI: CNI symptoms less than 1 year after surgery
	Persistent CNI: CNI symptoms more than 1 year after surgery
Surgery difficulty classification	Grade 1: MR
	Grade 2: MR+ECL/MR+CND
	Grade 3: MR+ECL+CND/MR+ECL+ICR
	Grade 4: MR+ICL/MR+ECL+ICR+CND
Complication grade	Grade 1: one complication, excluding stroke and death
	Grade 2: two complications, excluding stroke and death
	Grade 3: stroke or death or more than 3 complications
Tumor size	Grade 1: 0 to 15 cm^3
	Grade 2: 16 to 30 cm^3
	Grade 3: 31 to 45 cm^3
	Grade 4: 46 to 60 cm^3
	Grade 5: >60 cm^3
Operative time	Grade 1: 0 to 60 min
	Grade 2: 61 to 120 min
	Grade 3: 121 to 180 min
	Grade 4: 181 to 240 min
	Grade 5: 241 to 300 min
	Grade 6: >300 min
Estimated blood loss	Grade 1: 0 to 300 mL
	Grade 2: 301 to 600 mL
	Grade 3: 601 to 900 mL
	Grade 4: 901 to 1200 mL
	Grade 5: 1201 to 1500 mL
	Grade 6: >1500 mL

MR, simple mass resection; ECL, external carotid artery ligation; CND, cranial nerve dissection; ICR, internal carotid artery reconstruction; ICL, internal carotid artery ligation.

Results of the surgical procedures

Table 3 shows the details of the 52 patients who underwent surgical resection and the surgical procedure details, namely: (1) MR; (2) MR+ECL; (3) MR+CND; (4) MR+ECL+CND; (5) MR+ECL+ICR; (6) MR+ICL; and (7) MR+ECL+ICR+CND. The surgical success rate was 98.1%. One patient underwent ICL and died of massive cerebral ischemia in the neurological ward. Two patients (3.8%) developed significantly low heart rate (HR) (<40 beats/minute) intraoperatively, and one patient (1.9%) developed cardiac arrest intraoperatively. Fortunately, HR was recovered in the cardiac arrest patient by ceasing surgery and immediately imitating cardiopulmonary resuscitation (CPR) on the operating table. No sequelae developed post-CPR in this patient. In the present study, complications constituted stroke, hoarseness, dysphagia, choking when drinking, headache, slurred speech, deviation of the corner of the mouth, incisional infection, and death. The complications are summarized in Table 4. Lymph nodes were identified in the surgical field

Table 2. Patients' and tumor characteristics (n = 60).

Demographic	n or mean ± standard deviation (range)
Male	21
Age, years	42.92 ± 13.43
Duration, months	37.40 ± 60.43
Clinical presentation	
Neck mass on examination	60
Symptomatic	3
Radiologic studies	
Tumor diameter, cm	4.22 ± 1.37
Left-sided lesion	24
Right-sided lesion	34
Bilateral lesion	2
Histology	
Neurilemmoma	8
Angioleiomyoma	1
Mesenchymal tissue tumor	1
Carotid body tumor	42
Malignant	3
Benign	38
Borderline tumor	1
Shamblin classification	
I	5
II	25
III	12
Intraoperative characteristics (n = 52)	
Operation time, minutes	176.1 ± 86.5
Estimated blood loss (mL)	231.3 ± 354.0
Tumor volume, cm^3	47.6 ± 65.3

Table 3. Details of the surgical procedures and pathological results.

	CBT					
	Shamblin I (n = 5)	Shamblin II (n = 25)	Shamblin III (n = 12)	Neurilemmoma (n = 8)	Angioleiomyoma (n = 1)	MTT (n = 1)
Surgical method						
MR	1	9	–	6	1	1
MR+ECL	4	8	–	–	–	–
MR+ICL	–	–	1	–	–	–
MR+CND	–	2	–	2	–	–
MR+ECL+CND	–	–	1	–	–	–
MR+ECL+ICR	–	6	8	–	–	–
MR+ECL+ICR+CND	–	–	2	–	–	–

MTT, mesenchymal tissue tumor; MR, simple mass resection; ECL, external carotid artery ligation; ICR, internal carotid artery reconstruction; CND, cranial nerve dissection; ICL, internal carotid artery ligation.

in 44 patients (84.6%), with an average number of lymph nodes in this group of 1.98 ± 1.43. Four potential risk factors for complications were identified: mass volume, surgical procedure(s), number of lymph nodes, and operative time. Spearman's correlation analysis showed that complication grade was significantly related to surgical difficulty grade ($r = 0.4345$, $p = 0.0013$; 95% confidence interval (CI) = 0.1753, 0.6374), and operative time ($r = 0.3564$, $p = 0.0095$; 95% CI = 0.08423, 0.5790), without a significant relationship to the other three factors (Table 5).

Pathology results

Each mass from the 52 patients was sent to the pathology department in our hospital for pathological analysis. The pathological results were as follows: CBT, paraganglioma: 42 (80.8%); neurilemmoma: 8 (15.4%); angioleiomyoma: 1 (1.9%); and mesenchymal tissue tumor: 1 (1.9%); representative histopathology images are seen in Figure 2. The number of each type of mass according to Shamblin's classification of CBT was as follows: Type I: 11.9%, n = 5; Type II: 59.5%, n = 25; and Type III: 28.6%, n = 12. For the CBT patients, the rate of patients who developed vascular injury and required arterial reconstruction in the Shamblin Type II and III groups was 24% and 83.3%, respectively. Three patients were diagnosed as having malignant CBT with lymph nodes metastasis. The malignant CBT rate among the CBT patients was 5.8%. Lymph node hyperplastic reactivity was identified in 19 cases (36.5%), and lymph node metastasis was identified in 3 cases (5.8%).

Table 4. Complications following surgical treatment (n = 52).

Complication	n (%)
Stroke	1 (1.9%)
Hoarseness	8 (15.4%)
Dysphagia	2 (3.8%)
Choking	4 (7.7%)
Headache	1 (1.9%)
Slurred speech	1 (1.9%)
Deviation of the corner of the mouth	2 (3.8%)
Incisional infection	1 (1.9%)
Death	1 (1.9%)

Follow-up results

Forty-three patients were followed-up, with a follow-up rate of 71.7%. Of the followed patients, the conservative treatment patients and surgical resection patients constituted 7 and 36 patients, respectively. The follow-up duration was 44.42 ± 29.30 (range: 1 to 104) months. No recurrence was seen during the follow-up, and all of the patients were alive at the time of this report except for one who died of a massive stroke after surgery. Three patients had persistent CNI with complaints of not being

Table 5. Spearman's correlation analysis of the complication grades and operative time compared with other factors.

Correlation	CG vs. TS	CG vs. EBL	CG vs. SG	CG vs. LN	CG vs. OT	OT vs. EBL	OT vs. SG	OT vs. LN	OT vs. TS
Spearman's r	0.1183	0.099	0.4345	0.1515	0.3564	0.4604	0.5777	0.2545	0.3094
95% CI	−0.1678	−0.1867	0.1753	−0.1347	0.08423	0.2065	0.3546	−0.02802	0.03156
	0.3860	0.3693	0.6374	0.4145	0.5790	0.6562	0.7385	0.4994	0.5428
P value	0.4036	0.485	0.0013	0.2835	0.0095	0.0006	<0.0001	0.0686	0.0256

CG, complication grade; TS, tumor size; CI, confidence interval; EBL, estimated blood loss; SG, surgical grade; LN, lymph nodes; OT, operative time.

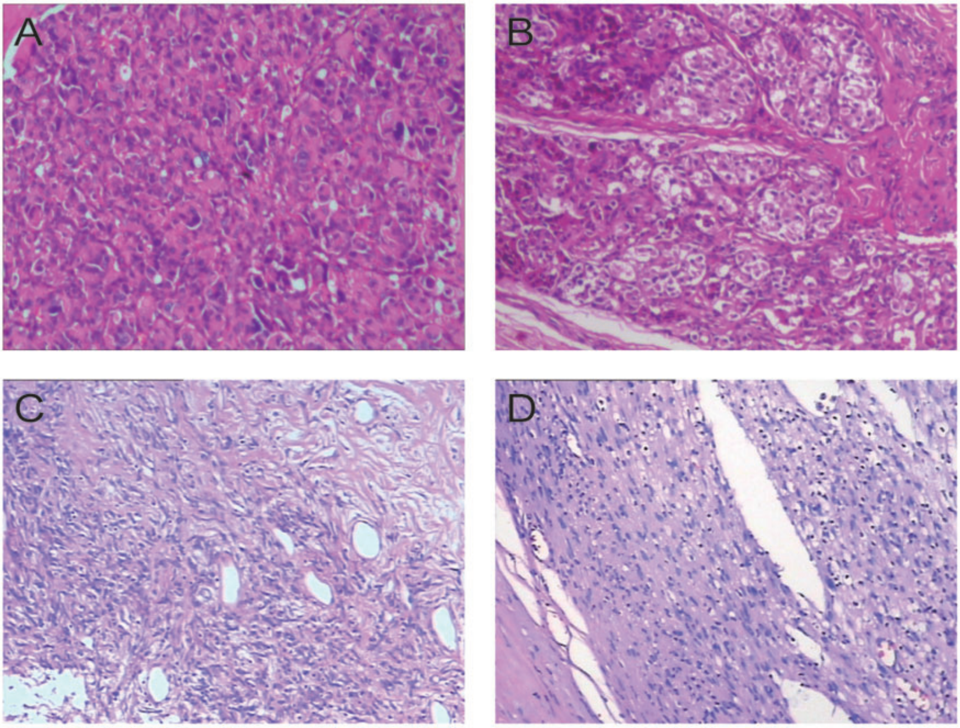

Figure 2. Representative histopathological images (hematoxylin and eosin staining ×100) of a CBFT (A) benign CBT; (B) malignant CBT; (C) mesenchymal tissue tumor; (D) neurilemmoma.
CBFT, carotid bifurcation tumor; CBT, carotid body tumor.

able to speak, or sing loudly; however, these symptoms resolved over time. The remaining patients with complications in the perioperative period experienced a satisfactory life quality without further complications.

Discussion

Outcomes in this series of CBTs confirmed that surgical resection is safe and feasible management, with acceptable morbidity and mortality. The persistent CNI rate, overall stroke rate, and perioperative mortality rate were 5.8%, 3.8%, and 1.9%, respectively. Symptoms related to complications were relieved or resolved, and no recurrence and metastatic disease was identified in the surgery group during the follow-up.

Tumors located at the carotid bifurcation always require relatively complicated surgical management owing to the special and important anatomy. Carotid artery reconstruction is needed when the tumor involves the carotid artery without the opportunity for sufficient dissection.[3] Therefore, preoperative image evaluation and mass consideration at the skull base/in the carotid artery are very important. Some studies indicated that the risk of vascular injury was higher in patients with larger tumors.[4–6] In the current study, patients suffering vascular injury during resection had a significantly larger tumor size than those with no vascular injury. For the CBT patients, the rate of patients who developed vascular injury and required arterial reconstruction in the Shamblin

Type II and III groups was 24% and 83.3%, respectively. Tumor size is considered a risk factor for vascular injury requiring vessel reconstruction. Therefore, early tumor resection is beneficial and useful to reduce the risk of vascular injury if tumor resection is mandatory, regarding the long-term outcomes of this disease.

In the present study, all enrolled patients were admitted as outpatients, and the CBFTs were detected and diagnosed by ultrasonography and CTA. However, the nature of these tumors cannot be demonstrated by ultrasonography and CTA; therefore, tumors must be resected and analyzed pathologically. Torrealba et al.[3] reported 93% CBTs and 7% neurilemmomas in their series of 30 CBFTs undergoing surgical resection, and the rates of Shamblin Type II versus Type III in the CBT group were 63% versus 20%, respectively. In the present study, the results of the pathological analysis in the surgery group were CBT, paraganglioma: 42 (80.8%), neurilemmoma: 8 (15.4%), angioleiomyoma: 1 (1.9%), and mesenchymal tissue tumor: 1 (1.9%). The most frequent CBFT is CBT, and Shamblin type II and III account for 59.5% and 28.6%, respectively. Among our CBT patients, 16 underwent ICR. Pathological results showed that three patients had malignant CBT with lymph nodes metastasis. Malignant CBT accounts for 5% to 7% of patients, and most present at an early age; the longest reported survival time was 15 years.[1,7,8] The mean age of the three patients with malignant tumors in the present study was 28.3 years, which is consistent with previous reports. Fortunately, the postoperative outcomes of these patients were acceptable, without persistent complications. In particular, the youngest case, a 20-year-old woman, had bilateral CBTs and underwent bilateral tumor resection within 6 months (Figure 3). All of the patients with malignant tumors were alive at the time of this report, and have been followed-up well.

Some researchers suggested that the treatment of CBT should consider individual variation. Genetic evaluation prior to surgery is needed to identify whether the tumor has a hereditary component.[9,10] Davila et al.[10] suggested that succinic dehydrogenase (SDH) mutation should be a routine examination in CBT diagnosis.

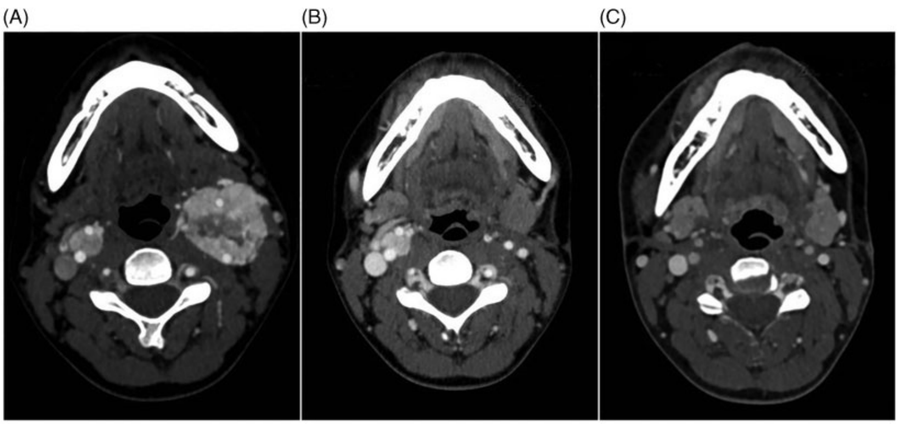

Figure 3. The youngest patient with malignant CBT, who had bilateral CBTs and who underwent bilateral tumor resection within a 6-month interval (a) preoperative CTA image; (b) 6-month CTA image after left CBT resection; (c) 6-month CTA image after right CBT resection.
CTA, computed tomography angiography; CBT, carotid body tumor.

This examination helps exclude familial paragangliomas resulting from the SDH mutation. Furthermore, CBT may have a relationship with hypertension treatment. Fudim et al.[11] observed blood pressure changes in 134 CBT patients, and the authors proposed that removing the carotid artery body may be a method of treating primary hypertension.

Angioleiomyoma may develop in veins, the retinal cavity, intestine, and ureter.[12] Angioleiomyoma rarely occurs at the carotid artery bifurcation. In 2008, Ural et al.[13] reported a patient who was diagnosed as having CBT before surgery and who was confirmed as having angioleiomyoma after surgery. Among the surgery patients in our study, only 34.6% of patients' tumors could be removed simply; in the remaining 65.4% of the patients, tumors required one additional or multiple procedures to fully resect. All the Shamblin Type III CBTs required reconstruction of the internal carotid artery (ICA) (except one case that could not be reconstructed and required ligation). The resection methods constituted simple artery repair, ICA angioplasty, and artificial graft replacement. Luna-Ortiz et al.[14] reported that surgical time and blood loss were related to Shamblin classification. There is a debate regarding whether the ECA be embolized prior to surgery to reduce blood loss. Some specialists believe that there is communication between the external and internal carotid arteries, and if so, ligation during surgery and embolization prior to surgery will not provide satisfactory results regarding decreased bleeding, and might cause cerebral complications.[15–17] Nevertheless, other specialists suggest that ECA embolization prior to surgery can reduce intraoperative blood loss volume.[18–20] Moreover, a recent meta-analysis enrolling 1326 patients suggested that patients who received preoperative embolization had lower intraoperative blood loss volumes and shorter operation duration.[21] However, an interesting study showed that preoperative CBT embolization (0 to 3 days prior to surgery) was associated with an increased unadjusted blood loss rate compared with the non-embolization group, but without statistical significance.[22] Pavlos et al.[21] believed that the reason for this difference could be potentially attributed to the effects of hypoxia-related inflammation caused by embolization, which can induce wall stress in the vasa vasorum of the arteries. Therefore, considering that the blood supply to CBTs arises mainly from the ECA, this artery has been ligated during the surgery to reduce blood loss.[18] In the present study, 18 cases underwent ECA ligation before tumor resection intraoperatively and obtained satisfactory results with less blood loss.

Three patients in our study developed significant bradycardia intraoperatively during management of the carotid bifurcation and vagus nerve. One patient even developed cardiac arrest, and after immediate CPR, he recovered without severe consequences. Therefore, when treating the carotid bifurcation and vagus nerve, surgeons must communicate with anesthesiologists closely; HR and blood pressure should receive careful attention during this period. Unfortunately, one of the three patients died of a stroke that was caused by ICA ligation owing to the huge tumor and no space for distal ICR. There was no choice but to ligate the ICA owing to persistent and massive bleeding during the operation. Therefore, we learned the lesson that the ICA must be reconstructed because not doing so can result in fatal consequences. In addition, pre-operative evaluation of the operation difficulty and determining the appropriate surgical procedures are critical to avoid poor outcomes. One report indicated satisfactory results of superficial temporal artery–middle cerebral artery bypass when ligating the ICA during treatment of huge cavernous sinus aneurysms.[23] Postoperative complication severity had an obvious correlation with surgical grade and operative time but had no obvious correlation with tumor size, EBL, and the number of lymph nodes. These findings may indicate that the correlation with patients' long-term survival rate and complication severity is not significantly related to the quality of the tumor, but more related to the surgical resection procedure. This finding is similar to findings reported by Robertson et al.,[24] who stated that Shamblin Type III tumors are associated with more complicated procedures as well as higher complication rates.

We identified lymph nodes in the surgical field in 84.6% of our patients. Davila et al.[10] also reported high lymph node incidence during CBT resection. However, as with Davila et al.'s study, we found no obvious abnormalities in these lymph nodes by pathological examination.

There was no significant difference between the surgery group and the conservative therapy group during the follow-up, in our study. However, this does not deny the importance of surgery in treating CBFTs. Owing to the possibility of malignancy, even at a rate of only 3% to 5%, metastasis is possible if patients choose not to undergo surgery.[25] Wang et al.[24] reported one case of metastasis to the brain. Survival time with CBFT has no obvious correlation with age, time to occurrence, tumor size, surgery or no surgery, number of lymph nodes, and number of complications. Long-term survival may relate to the lower mortality of this tumor. Surgery to resect the tumor can eliminate the potential for a malignant tumor; however, our surgery group did not show a better survival rate compared with the conservative treatment group. This may be related to the small non-surgery group (only 8 cases), which did not constitute patients with malignant tumors. Longer follow-up of larger samples may reveal different survival results.

The limitations of this study are inherent in the retrospective design. The sample size in this study was comparatively small owing to the rarity of this tumor type. Furthermore, all of the patients were selected from a single center. A randomized trial to compare different surgical methods to prevent complications is required; however, this is difficult currently because CBFTs do not occur at a high frequency, and surgeons have different protocols for surgical technique and postoperative care.

In conclusion, CBT is the most frequent type of CBFT, and this tumor may be treated safely with surgical management. The surgical management of tumors in this location is challenging because the tumors are surrounded by or involve the arteries and cranial nerves. According to the results of the current study, the severity of surgical complications is significantly correlated with surgical difficulty. In addition, early intervention when the tumor is detected and diagnosed may result in fewer complications. Preoperative image assessment may be necessary to decrease the vascular and cranial nerve complications resulting from surgery. However, long-term follow-up is needed to determine the recurrence and survival rate, especially regarding malignancy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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