Original Article

A new potential risk factor for permanent cranial nerve injury following carotid body tumor resection

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Background: To quantify the association between the free distal segment length of the internal carotid artery (FDS-ICA) and permanent cranial nerve injury (p-CNI) following carotid body tumor (CBT) resection.

Methods: This study is a case-control study. We surveyed 109 consecutive patients who underwent CBT resection between June 2015 and June 2020 at our single center. A total of 89 patients met the inclusion criteria and were selected for analysis. The FDS-ICA was measured by image post-processing software for computed tomography angiography (CTA). Postoperative p-CNI complications were evaluated using comprehensive statistical approaches.

Results: The cohort was divided into 2 groups depending on the presence of p-CNI, namely the p-CNI group (n=17) and the non-CNI group (n=79). The average FDS-ICA of patients with p-CNI complications was shorter than that of those without p-CNI complications (P<0.001). For every 1 mm increase in FDS-ICA, there was an associated decrease of 8% in the risk of p-CNI (0.92, 95% CI: 0.85 to 0.98, P<0.05). Threshold effect analysis of the FDS-ICA on p-CNI identified that the FDS-ICA was 28.7 (95% CI: 23.8 to 30.9) mm.

Conclusions: The results of this study revealed a significant independent association between FDS-ICA and permanent postoperative cranial nerve injury complications of CBTs. Further study is warranted to confirm these results in a larger patient cohort.

Keywords: Carotid body tumor (CBT); permanent cranial nerve injury (p-CNI); surgical resection; free distal segment length of internal carotid artery (FDS-ICA)

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Introduction

Carotid body tumors (CBTs) are heterogeneous tumors caused by the abnormal proliferation of paraganglion cells in the carotid body (1). A CBT is a type of paraganglioma which involves uncontrollable and continuous growth that lead to compression of the cranial nerves and vessels and subsequent complications, including the potential for local or distant metastases (2-4). Surgical resection is a generally accepted treatment for CBTs (5). However, it has been reported that the incidence rate of permanent cranial nerve injury (p-CNI), including to the vagus nerve, hypoglossal nerve, sympathetic nerve, and glossopharyngeal nerve injury, after CBT resection is 3–20% (6-8). Hostile neck anatomy and insufficient preoperative preparation are thought to be the main causes of the high incidence of p-CNI (6). Therefore, an accurate preoperative assessment of CBTs is particularly necessary. Preoperative computed tomography angiography (CTA) examination and image postprocessing technology are of great value for CBT identification and surgical risk assessment (9,10). Kim *et al.* (11) found that the vertical growth of CBTs had a substantial impact on cranial nerve preservation during surgery through preoperative CT evaluation. At present, an imaging measurement parameter that can accurately reflect the vertical growth of CBTs is required. The free distal segment length of the internal carotid artery (FDS-ICA), which refers to the length of the internal carotid artery from the upper edge of the CBT to the skull base, reflects the difficulty of intraoperative vascular reconstruction and indirectly reflects the vertical growth of the CBT. However, whether the FDS-ICA is an independent risk factor for p-CNI following CBT resection has not been clarified.

To address this issue, we utilized image post-processing software to reconstruct and analyze the carotid artery, to allow convenient and accurate measurement of FDS-ICA. The first aim of this study was to clarify the importance of CTA and image post-processing in evaluating CBT surgery. The second aim was to identify FDS-ICA as an independent risk factor for p-CNI following CBT resection. Thirdly, by showing that FDS-ICA is associated with a greater risk of p-CNI, we aimed to guide clinicians on optimal surgical planning and posttreatment surveillance. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-464/rc).

Methods

Study design and patients

This study is a case-control study. The sample size was estimated by using the sample size formula for finite population: $N = \left(\frac{z_{1-\alpha/2} \times \sqrt{p \times (1-p)}}{\delta} \right)^2$. Patients who underwent CBT resection between June 2015 and June 2020 at our center and met the inclusion criteria were selected, and their clinical and CTA imaging data were reviewed. The inclusion criteria were as follow: (I) diagnosis of CBT based on preoperative neck painless mass, preoperative typical CBT imaging findings, intraoperative findings and postoperative pathology; (II) had undergone preoperative carotid CTA examination; (III) did not undergo preoperative embolization; and (IV) had no preoperative neurological symptoms. Exclusion criteria included the following: (I) severe organic diseases or other malignant tumors; (II) lost follow-up; and (III) history of previous neck surgery or radiotherapy (*Figure 1*). A large series study of surgically-treated CBTs supported craniocaudal dissection as the surgical technique of choice as it limits blood loss and facilitates safe CBT resection (12,13). The CBT patients at our center were operated on with this technique by the same surgical team. We retrospectively analyzed the imaging features, basic data, and postoperative complications. Permanent nerve injury was defined as intraoperative nerve disconnection or patients whose nerve function had not recovered after 1 year of follow-up (14). We divided all CBTs into two groups based on the occurrence of p-CNI to further explore the risk factors of p-CNI occurrence. Postoperative follow-up mainly included carotid CTA reexamination at 3 months, 6 months, and 1 year after the operation. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for the study was obtained from the institutional review board of the First Affiliated Hospital of Naval Medical University, and informed consent was provided by all cases for the publication of this work.

Imaging analysis

All radiographic images were retrospectively reviewed by 2 investigators (vascular surgeon YL and radiologist ZJ) and a radiologist experienced in head and neck imaging studies (WY). The three reviewers performed the measurements independently and were blinded to intraoperative findings and outcomes. The final value was the average of the 2 investigators. If there was a large deviation between the values of the 2 investigators, the value was determined by the radiologist's measurement. Imaging measurements by such methods can reduce internal bias. We used the vascular analysis of the head and neck tool in the medical image processing software model uWS-CT (version: R005; Shanghai United Imaging Healthcare Co. Ltd., Shanghai, China), which takes into account the tortuosity of the ICA. The system automatically recognizes the upper edge of the ICA CBT and the location of the skull base and displays its length, which is determined on curve-linear reformat reconstruction of the ICA (*Figure 2*). At the same time, the measurer can adjust the ruler according to the actual upper edge of the tumor and the position of the skull base to obtain more accurate results.

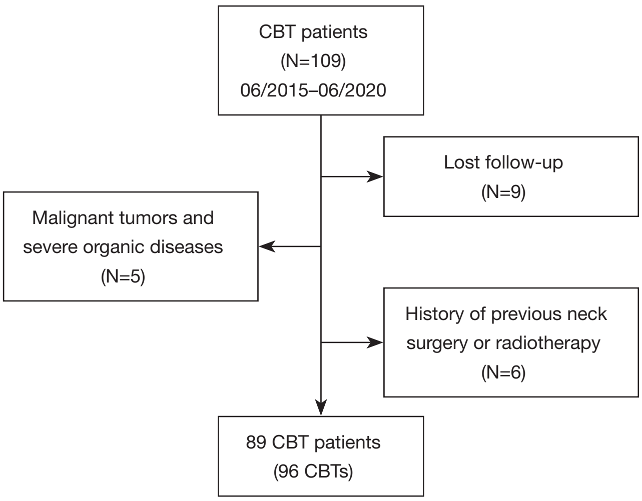

Figure 1 Inclusion and exclusion criteria for this study. CBT, carotid body tumor.

According to intraoperative records and preoperative CTA evaluation, CBTs were graded according to the Shamblin classification (15). The principle of Shamblin classification is based on circumferential involvement and adhesion to the wall of the ICA. Tumor volume was calculated with ellipsoid volume estimation: V = 4/3π* abc, where a, b, and c represent the 3-axis radius.

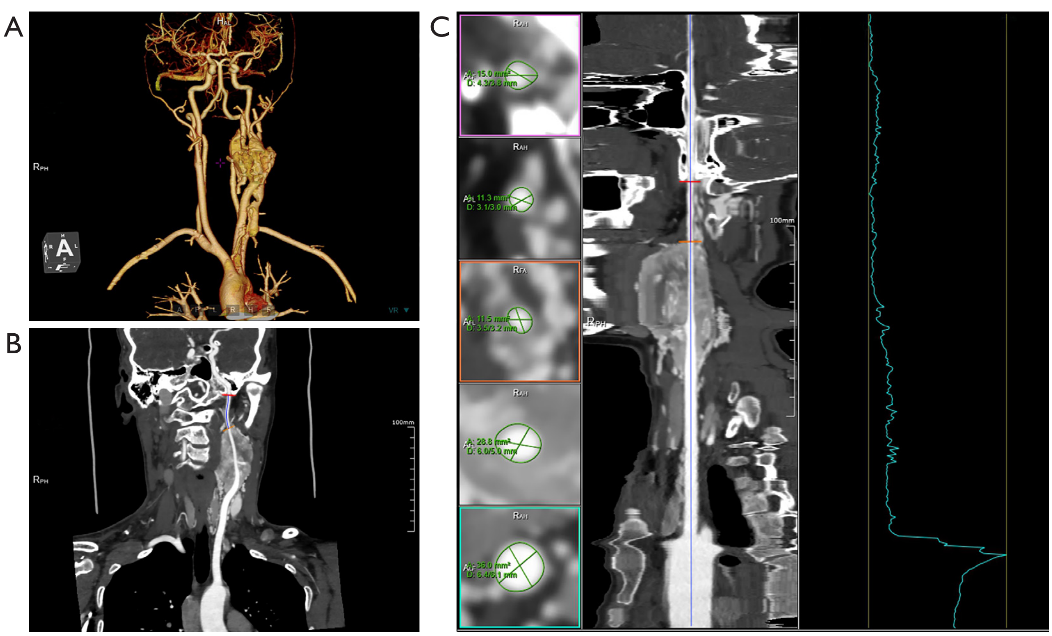

Figure 2 Imaging analysis of the FDS-ICA. (A) Volume rendering. (B) Curved planar reconstruction. (C) Straightened curved planar reconstruction. FDS-ICA length is measured as the distance (blue) from the skull base (red) to the upper edge of the tumor (orange). FDS-ICA, free distal segment length of the internal carotid artery.

Table 1 Patient and tumor characteristics (N=96)

Variables	All CBTs (N=96)	Non-CNI (N=79)	p-CNI (N=17)	P*
Patient characteristics				
Age, years	43±12	44±12	39±10	0.095
BMI, kg/m^2	22.93±3.42	23.03±3.58	22.46±2.56	0.526
SBP, mmHg	122±12	122±13	122±8	0.810
DBP, mmHg	77±8	77±9	78±4	0.502
Gender				0.085
Female	52 (54.17%)	46 (58.23%)	6 (35.29%)	
Male	44 (45.83%)	33 (41.77%)	11 (64.71%)	
Comorbidities				
Hypertension	12 (12.50%)	9 (11.39%)	3 (17.65%)	0.479
Diabetes mellitus	1 (1.04%)	0	1 (5.9%)	0.177
Coronary artery disease	0	0	0	–
Cerebrovascular disease	3 (3.12%)	2 (2.53%)	1 (5.9%)	0.447
Tumor characteristics				
Shamblin grade				0.019
Type I	17 (17.71%)	17 (21.52%)	0 (0.00%)	
Type II	38 (39.58%)	33 (41.77%)	5 (29.41%)	
Type III	41 (42.71%)	29 (36.71%)	12 (70.59%)	
Volume, cm^3	33.80±36.14	26.82±27.52	66.22±52.03	0.003
FDS-ICA, mm	35.66±15.82	38.61±14.08	21.94±16.60	<0.001

Data are presented as n (%) or mean ± SD unless stated otherwise. *, P value of difference between non-CNI group and p-CNI group. CBT, carotid body tumor; Non-CNI, non-cranial nerve injury; p-CNI, permanent cranial nerve injury; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FDS-ICA, free distal segment length of the internal carotid artery; SD, standard deviation.

Statistical analysis

Data were analyzed with statistical software packages R (http://www.R-project.org; The R Foundation for Statistical Computing, Vienna, Austria) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). Categorical data and proportions were used for the description of demographics. Continuous variables were compared using a Student's *t*-test or Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Kruskal-Wallis H test. A 95% confidence interval (CI) was used for the effect size. Statistical significance was defined as P<0.05.

Results

Baseline characteristics

A total of 96 CBTs from 89 patients between June 2015 and June 2020 were included in the final data analysis based on the inclusion and exclusion criteria. All 89 cases had completed the 1-year follow-up, and no metastases were found in any case during follow-up. Demographic information, comorbidities, and tumor characteristics are shown in *Table 1*. The average age of the cases was 43±12 years old, and 45.83% of them were male. The mean body mass index (BMI) was 22.93±3.42 kg/m^2. The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 122±12 and 77±8 mmHg, respectively. Some 12.50% (n=12) of cases had hypertension, 1.04% (n=1) had diabetes, and 3.12% (n=3) had a history of cerebral infarction. Approximately 7.29% (n=7) of cases had bilateral resection of their CBTs. Tumors were classified as Shamblin I (17.71%, n=17), Shamblin II (39.58%, n=38), and Shamblin III (42.71%, n=41). The average tumor volume was 33.80±36.14 cm^3, and the interquartile range was from 11.46 to 39.51 cm^3. The mean FDS-ICA was

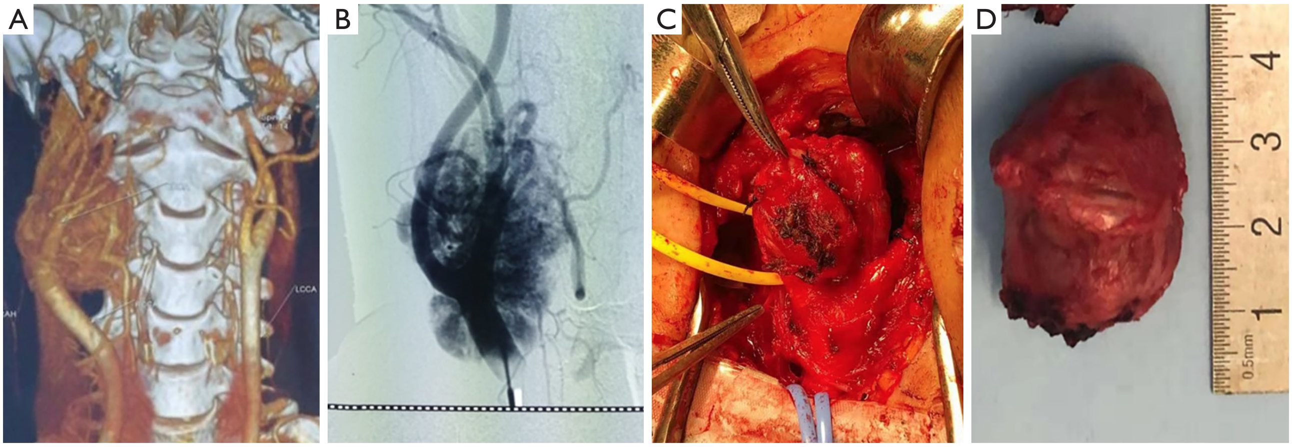

Figure 3 CBT preoperative examination and intraoperative pictures. (A) 3D reconstruction of preoperative carotid artery CTA. (B) Preoperative digital subtraction angiography of carotid artery. (C) Exposure of tumor, blood vessels, and nerves during CBT resection. (D) CBT specimen. CBT, carotid body tumor; CTA, computed tomography angiography.

Table 2 Intraoperative and postoperative event

Complication	n (%)
p-CNI	17 (17.71)
Recrudescence	5 (5.21)
Hematoma	2 (2.08)
Wound infection	3 (3.12)
Vascular reconstruction	13 (13.54)

p-CNI, permanent cranial nerve injury.

Table 3 Binary logistic regression analysis

FDS-ICA, mm	Odds ratio	95% CI	P value
Non-adjusted	0.91	0.86–0.96	0.0003
Adjust I	0.91	0.86–0.96	0.0006
Adjust II	0.92	0.85–0.98	0.0129

Adjust I model adjust for: gender, age, BMI. Adjust II model adjust for: gender, age, BMI, Shamblin grade, volume. FDS-ICA, the free distal segment length of the internal carotid artery; CI, confidence interval; BMI, body mass index.

35.66±15.82 mm. The cohort was divided into 2 groups depending on the presence of p-CNI, namely the p-CNI group (17 patients, 17.71%) and the non-CNI group (79 patients, 82.29%). There were no differences between the 2 groups in age, gender, blood pressure, and BMI. The p-CNI group had a significantly higher rate of Shamblin III CBTs compared with the non-CNI group. Moreover, the CBTs in the p-CNI group had a larger volume and a shorter FDS-ICA than the non-CNI group (P<0.05).

Surgical outcomes

All CBTs were successfully removed during surgery (*Figure 3*). The stroke and mortality rates were both 0%. There were 17 (17.71%) cases of p-CNI recorded during the surgery or nerve injury symptoms that did not recover within 1 year after surgery. Among these patients, 8 had multiple p-CNIs. The p-CNIs included the hypoglossal nerve (12 cases, 70.59%), vagus nerve (11 cases, 64.71%), facial nerve (1 case, 5.88%), sympathetic nerve (1 case, 5.88%). Other intraoperative and postoperative events are listed in *Table 2*.

Correlation of FDS-ICA and p-CNI

In this study, we constructed 3 models to analyze the independent effects of FDS-ICA on p-CNI (univariate and multivariate logistic regression). The effect sizes [odds ratio (OR)] and 95% CI are listed in *Table 3*. In the unadjusted model (model 1), the model-based effect size could be explained as the difference in length of FDS-ICA associated with the risk of p-CNI. For every 1 mm increase in FDS-ICA, there was an associated decrease of 9% difference in the risk of p-CNI (0.91, 95% CI: 0.86 to 0.96, P<0.05). In the gender, age, and BMI-adjusted model (model 2), for every 1 mm increase in FDS-ICA, there was an associated decrease of 9% in the risk of p-CNI (0.91, 95% CI: 0.86

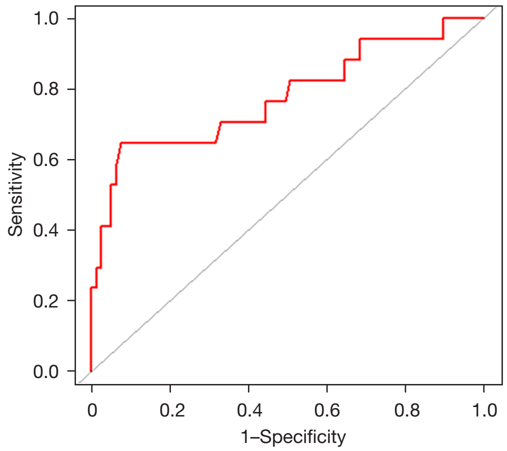

Figure 4 Diagnostic performance of FDS-ICA in the population with p-CNI. AUC =0.777. FDS-ICA, free distal segment length of the internal carotid artery; p-CNI, permanent cranial nerve injury; AUC, area under the curve.

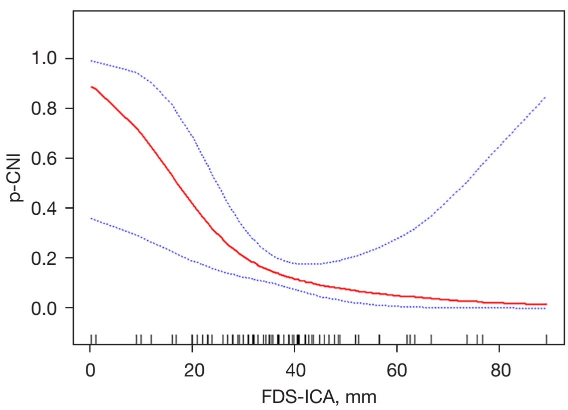

Figure 5 Association between FDS-ICA and p-CNI. The smooth curve fitting presented a threshold, nonlinear association. Adjustment factors included gender, age, BMI, Shamblin grade, and volume. The red curve is the fitted smooth curve, and the blue curve is the 95% confidence interval. FDS-ICA, free distal segment length of the internal carotid artery; p-CNI, permanent cranial nerve injury; BMI, body mass index.

to 0.96, P<0.05). In the gender, age, BMI, Shamblin grade, and CBT volume-adjusted model (model 3), for every 1 mm increase in FDS-ICA, there was an associated decrease of 8% in the risk of p-CNI (0.92, 95% CI: 0.85 to 0.98, P<0.05). Additionally, receiver operating characteristic (ROC) curve analysis was calculated for FDS-ICA with respect to p-CNI, which showed an area under the curve (AUC) of 0.78 (*Figure 4*).

To demonstrate whether there was a linear relationship between FDS-ICA and p-CNI, we performed smooth curve fitting (penalized spline method) and adjusted the gender, age, BMI, Shamblin grade, and CBT volume variables (*Figure 5*). The results showed that the risk of p-CNI predicted by FDS-ICA was not a simple straight line, and there may be a threshold effect between them. Therefore, we further performed threshold effect analysis of FDS-ICA on p-CNI to calculate the turning point using the standard binary logistic regression model and the two-piecewise binary logistic regression model. The threshold level was determined by choosing the turning point which provided the maximum model likelihood using the trial-and-error method, along with a log-likelihood ratio test comparing the one-line logistic regression model with a two-piecewise logistic model to examine the statistical significance. The 95% CI for the turning point was obtained by bootstrapping. As shown in *Table 4*, the P value for the log-likelihood ratio test was less than 0.05, indicating that the two-piecewise binary logistic regression was more suitable for fitting the association between FDS-ICA and p-CNI. The turning point that we identified for FDS-ICA on p-CNI was 28.7 mm. The ORs (95% CIs) for p-CNI were 0.83 (0.72 to 0.96) and 0.99 (0.91 to 1.07) to the left and right of the turning point, respectively. This indicated that when FDS-ICA was less than 28.7 mm, for every 1 mm decrease in FDS-ICA, there was an associated increase of 17% in the risk of p-CNI (0.83, 95% CI: 0.72 to 0.96, P<0.05).

Discussion

Surgical resection is the generally accepted treatment for CBTs. The goal of surgery is to completely remove the tumor and preserve important nerves and blood vessels (8,16,17). The main complications of CBT resection include intraoperative hemorrhage, stroke, and CNI, which affects patient quality of life. Bilateral CNI can even lead to death. Patients can experience symptoms such as hoarseness, choking when drinking, and deviated tongue (8,18,19). Some nerve injuries are temporary and the patient will self-heal, while others are permanent and the patient will never fully recover. According to the literature, p-CNI is defined when the nerve is cut off during the operation or symptoms do not resolve after 1-year of follow-up (14). It has been reported that the incidence of permanent nerve damage is about 3–20% (3,19,20). At present, intraoperative neuroelectrophysiological monitoring technology combined with multidisciplinary cooperation

Table 4 Threshold effect analysis of FDS-ICA on p-CNI using piecewise binary logistic regression models

Outcome	Crude model		Adjusted model	
	OR (95% CI)	P value	OR (95% CI)	P value
Standard logistic regression model	0.91 (0.86–0.96)	0.0003	0.92 (0.85–0.98)	0.0129
Two-piecewise logistic regression models				
Turning point (mm)	28.8 (25.8–31.8)		28.7 (23.8–30.9)	
≤ Turning point	0.84 (0.75–0.93)	0.0015	0.83 (0.72–0.96)	0.0098
> Turning point	0.98 (0.91–1.05)	0.5903	0.99 (0.91–1.07)	0.7753
P for log likelihood ratio test	0.041		0.036	

Adjusted for gender, age, BMI, Shamblin grade, and Volume. 95% CI for the turning point was obtained by bootstrapping. FDS-ICA, free distal segment length of the internal carotid artery; p-CNI, permanent cranial nerve injury; OR, odds ratio; CI, confidence interval.

can facilitate a reduction in the incidence of intraoperative injury. Preoperative identification of patients at high risk of nerve injury can guide preoperative preparation and reduce resource waste. Therefore, accurate risk factors for nerve injury are needed. Previous studies have reported that a high incidence of nerve injury after CBT resection is consistently associated with higher Shamblin grade (18,19). However, Mohebali *et al.* showed that postoperative nerve damage is not directly related to Shamblin classification (7). The main reason for this contradiction is that the Shamblin classification is mainly based on the relationship between the CBT and vascular envelope and does not reflect the adjacent relationships between the CBT and nerves. With advancements in imaging technology, especially the improvement of carotid CTA detection layer thickness and image processing technology, more specific imaging features are available to assess morphological characteristics which might have predictive value for postoperative complications of CBT resection. On this basis, Kim *et al.* (11) found that the distance between the upper edge of the tumor and the skull base could predict postoperative p-CNI. Zhou *et al.* (21) devised a new CBT classification system, improving on the Shamblin classification, which is based on the 2 horizontal lines of the mandibular angle and the mastoid tip, by dividing it into 5 types. Among them, type 4 and type 5 CBTs, which are closer to the base of the skull, have a higher risk of nerve damage. However, accurate measurement of the distance from the skull base relies on the radiologist's skill.

Both CTA post-processing technology and new algorithms are widely used in carotid artery research (21). The FDS-ICA measurement method proposed in this study has several advantages. First, due to the crowded anatomical location of the cranial nerves, the FDS-ICA draws on the advantages of the above research regarding the distance from the upper edge of the CBT to the skull base in predicting p-CNI. Second, in terms of measurement, the upper edge of the tumor and the skull base can be automatically identified by the post-processing software to measure FDS-ICA, which can then be fine-tuned with the ruler. As a result, even clinicians who are not experts in imaging can obtain more accurate results, and the measurement is very simple. Reconstruction of the blood vessels alone can reduce other artifacts and further improve the accuracy of the measurement. Third, FDS-ICA reflects the difficulty of intraoperative vascular reconstruction directly.

This study analyzed 96 CBTs retrospectively and found that FDS-ICA was an independent risk factor for p-CNI. The results of univariate analysis showed that for every 1mm increase in FDS-ICA, the incidence of nerve injury was 9% lower. After adjusting the age, gender, BMI, Shamblin classification, and volume, the results of multivariable analysis were still significantly different. This finding indicated that FDA-ICA could be used to identify patients at high risk of neurological injury.

Furthermore, we performed threshold effect analysis of FDS-ICA on p-CNI to calculate the turning point using the standard binary logistic regression model and the two-piecewise binary logistic regression model. The turning point that we identified for FDS-ICA on p-CNI was 28.7 mm. When FDS-ICA is shorter than 28.7 mm, the surgeon would be required inform patients of the high risk of p-CNI prior to surgery and collaborate with other specialists in areas such as neurosurgery and otolaryngology to prevent severe complications. Meanwhile, careful intraoperative handling and familiarity with neural anatomy and the utility of nerve stimulation might help to reduce the risk of p-CNI.

Intraoperative vascular reconstruction is a common procedure in complex CBTs, especially in the Shamblin III group. Therefore, it is important to identify the FDS-ICA needed for anastomosis of the graft if the continuity of the ICA is to be maintained whether it is artificial blood vessel replacement or great saphenous vein transplantation (22). This study showed that the length of the vascular stump must be longer than 1 cm to ensure the success rate of vascular reconstruction (23). Since the arteries are tortuous and exhibit individual variability, the measurement of the linear distance from the upper edge of the tumor to the skull base does not reflect the length of the distal stump of the blood vessel before surgery, which may cause preoperative evaluation errors, resulting in some patients losing the opportunity for surgery. The determination of FDS-ICA is meaningful in identifying patients at high risk for permanent nerve damage and can also better guide clinicians to formulate an appropriate pre-emptive surgical strategy.

According to our results, we defined CBTs with FDS-ICA less than 28.7 mm as high-position CBTs to guide the operation. We took FDS-ICA =10 mm as the cut-off point. When FDS-ICA <10 mm, vascular reconstruction is difficult, and the risk of CNI is high. Multidisciplinary cooperation should be formulated for mandibular subluxation, mandibular cutting, and removal of the mastoid and part of the external auditory canal by infratemporal fossa approach, or preparation for Viabahn stent – graft-assisted CBT resection. When 10 mm < FDS-ICA <28.7 mm, the risk of nerve injury is high, but the conditions for vascular reconstruction are sufficient. Intraoperative neuroelectrophysiological monitoring should be performed to carefully protect the nerves and blood vessels to reduce damage. The combination of FDS-ICA with traditional Shamblin classification may better identify high-risk groups for surgical complications and better guide surgeons to formulate an appropriate surgical strategy than possible with the traditional Shamblin classification alone. At the same time, our study yielded new evidence to inform patients of the incidence of surgical complications before the operation and emphasize the key points of patient follow-up. In terms of surgical decision-making for patients with bilateral CBTs, preoperative CTA assessment can identify the risk of nerve damage and help the surgeon choose the low-risk side to operate on first. It is particularly important to assess the risk of neurological injury in bilateral CBT patients who have experienced postoperative nerve injury on the contralateral side in the past to avoid the risk of death incurred by bilateral nerve injury.

Limitation

First, this study was a retrospective study with limited data. Second, this study was mainly aimed at exploring the value of preoperative CTA imaging techniques and is therefore not applicable to patients who have not undergone carotid CTA before surgery or who have contraindications to CTA examination (such as contrast medium allergy). In the future, a multi-center prospective study is needed to evaluate the validity and reliability of FDS-ICA in predicting intraoperative and postoperative complications.

Conclusions

This study demonstrated that CTA image analysis for evaluation of p-CNI after CBT resection is feasible and effective. The FDS-ICA is a novel preoperative imaging predictive index that is accurate and simple to obtain. Our study verified that FDS-ICA is an independent risk factor of p-CNI. The risk of p-CNI complications is relatively high in patients with a low FDS-ICA, (especially less than 28.7 mm). This new predictive index supports the implementation of imaging of CBTs for improved risk stratification and management of patients with CBTs. We have provided a new strategy for preoperative evaluation and suggest that CBTs located close to the base of the skull may benefit from preoperative collaboration. Further study is warranted to confirm these results in a larger cohort of patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for the study was obtained from the institutional review board of the First Affiliated Hospital of Naval Medical University, and informed consent was obtained from all patients for the publication of this work.

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