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Review

Challenges of Surgical Resection of Carotid Body Tumors - Multiple Feeding Arteries and Preoperative Embolization

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Abstract. *Background: Carotid body tumor is a hypervascular tumor with multiple feeding arteries and unique orientation at the carotid bifurcation. Although resection is a radical therapy for this tumor, complete resection is challenging. Materials and Methods: Articles reporting carotid body tumor treatment and surgical resection were reviewed including case–control series and review articles. Results: Selected reports were reviewed and discussed focusing on choice of treatment, surgical difficulties and preoperative embolization of feeding arteries. Conclusion: Multiple feeding arteries and adhesion of the tumor to the carotid arterial wall are causes of difficulties in carotid body tumor resection. The effectiveness of preoperative embolization remains controversial due to the varied situations in performing surgical resection among the institutions. However, perfect embolization and resection immediately after embolization reduce blood loss and operative time of surgery for carotid body tumor.*

Carotid body tumor (CBT) is a rare disease that originates from the paraganglion cells (paraganglioma) of the carotid body at the carotid bifurcation. The World Health Organization classification designated this tumor as malignant because it has a malignant potency and there is no requirement to distinguish benign from malignant features in the pathological findings of specimens (1). It is well-known that malignant tumors cannot always be identified by their morphological features in histopathological examinations; clinical findings such as metastatic activity can distinguish malignant tumors from their benign counterparts. Only clinical findings, such as lung, liver, or bone metastasis, indicate that a tumor is malignant. The slow-growing feature of CBT represents an almost benign character and embryonic origin plus germline mutation of this tumor. Its potential for metastatic activity highlights the need for surgical resection. Surgical resection of CBT by head and neck surgeons must be considered once a patient is referred to a hospital. However, in contrast to the slow-growing feature of this tumor, characteristic features, such as a rich vascular network of its capsule supplied by many feeding arteries, complicate resection (2).

In recent years, it has been revealed by molecular biological studies that various types of gene alterations exist in the succinate dehydrogenase (*SDH*) gene family such as point mutations (3-5). Most patients with CBT were shown to have variants with germline mutations, such as *SDHB* and *SDHD*. Conversely, the idea of "hereditary paraganglioma-pheochromocytoma syndrome" has been frequently used to explain patients with familial paraganglioma, and it extends to patients with CBT who have a family history of the disease and gene alterations (6-8). Therefore, analyses of gene alterations are needed for patients with CBT. In addition, systemic diagnosis is needed to identify other types of paraganglioma, such as pheochromocytoma, since patients with *SDH* variants tend to have multiple paragangliomas (9).

The Shamblin classification has been used to evaluate the difficulties of surgical resection of CBTs (2). Although there are several negative opinions about the Shamblin classification, most reports have assigned this classification as a positive predictor of surgical difficulties and postoperative complications in clinical use (10).

The aim of this study was to review the literature concerning the surgical resection of CBTs and survey the

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difficulties of surgery, suggesting the better treatment strategy for patients with CBT.

Materials and Methods

A review of reports discussing the surgical resection of CBTs was performed. A systemic search was performed including case–control series and review articles. A total of 1,025 studies were retrieved between January 1988 and November 2021 from PubMed: 202 were excluded because they were not in English. Case reports describing only one case (251 reports) were excluded. An additional, 178 articles not including CBT surgery were also excluded. This resulted in 394 articles relevant for review.

Results and Discussion

Choice of treatment – Surgery or radiotherapy? Because the World Health Organization classifies paraganglioma with a malignant ICD-O code, namely 8692/3 (1), surgeons must consider surgical resection as first-line treatment once patients are diagnosed with CBT. However, other treatment options such as radiotherapy should be considered for tumors that are large enough to invade surrounding tissues and organs or in patients not healthy enough to undergo surgical resection under general anesthesia. As far as we are aware, no randomized prospective study has compared the effectiveness of treatment results between surgery and radiotherapy due to the rarity of CBT. There is a tendency for surgery being applicable for smaller tumors, and radiotherapy for larger tumors. However, because of the curability and unclear results of radiotherapy for CBT, surgical resection seems to be the first standard treatment for CBTs (11-13). Reports describing radiotherapy for CBTs were fewer compared to those of surgery for CBTs. Although the response rates were low, they described low rates of complications, including cranial nerve palsies (14). Moreover, tumor control rates and deaths caused by the tumor did not differ significantly between radiotherapy and surgery (14). Since CBTs are malignant tumors, the evaluation of radiotherapy must be defined by Response Evaluation Criteria in Solid Tumors. Concerning the response rate, radiotherapy for CBTs is insufficient as a radical therapy (15, 16). Although there have been applications of new modalities of radiation therapy, such as proton beams (17), carbon-ion beams, and robotic stereotactic radiotherapy (CyberKnife) (18, 19), we cannot comment on the efficacy of these treatments because of the rarity of cases. Since these new modalities of treatment have shown effectiveness for various tumor types, except for squamous cell carcinoma of the head and neck (20-27), they would be expected to demonstrate the power of curability against paragangliomas such as CBT.

Another problem is the presence of bilateral CBTs (Figure 1) which frequently occur in patients with SDH variants. If the two tumors are resectable, which tumor should be considered to be resected first, the larger or smaller? Although it depends on the tumor location and size, the smaller tumor should be resected first. The reason for this is that if a larger tumor is resected first and postoperative complications such as paralysis of the cranial nerves occur, the next surgery would be difficult to perform. Another problem with bilateral CBTs is baroreflex dysfunction after their resection (28), *i.e.*, hypertension, tachycardia, headache, anxiety, emotional lability, *etc.*

Difficulties of surgical resection – Various feeding arteries and easy bleeding. The challenges of surgical dissection, prolonged operative time, and significant blood loss in surgery associated with resection of CBTs have been a controversial topic (29-31).

However, the feeding arteries of CBT have not been focused on by researchers. The development of angiographic techniques and imaging revealed that the multi-angle view of the results of angiography make finding multiple feeders of CBTs easier, especially by digital subtraction angiography and construction of the three-dimensional view of the image (32, 33) (Figure 2A). Multiple feeding arteries of a CBT can be recognized using these angiographic imaging techniques, and there have been surprising results obtained by these techniques (34-36) such as that shown in Figure 2. Most CBTs have multiple feeding arteries arising from the branches of the external carotid artery (ECA), such as the superior thyroid, ascending pharyngeal, facial, and occipital arteries. Moreover, CBTs can have feeding arteries that originate directly from the ECA. What is the origin of these aberrant arteries? As most CBTs are the result of familial diseases with SDH variants, it is supposed that most CBTs originate from paraganglion cells of the carotid body in the carotid bifurcation during the embryonic phase of the patient's life. Therefore, their feeding arteries might also be freely introduced from the ECA during the embryonic phase. We propose this idea from our own study data (34-36). Shibao *et al.* also focused on the embryonic origin of the feeding arteries of CBTs (37). They reported that the main feeder of the CBTs was the descending musculospinal branch of the ascending pharyngeal artery and discussed the embryonic origin of the feeding arteries. Katagiri *et al.* reported that direct feeding arteries from the ECA were found in five of 16 tumors in their series of patients, and one tumor had an aberrant accessory superior thyroid artery (35, 36). The cause of easy bleeding and significant blood loss during the surgical CBT resection were thought to be due to multiple feeding arteries with aberrant ones originating directly from the ECA in most tumors. In addition, a few CBTs have a feeding artery from the branch of the contralateral ECA, such as the superior thyroid artery (36), and in rare cases, CBT from the branch of the vertebral artery (36).

Preoperative embolization – Effective or non-effective? Preoperative embolization of the feeding arteries of CBTs has

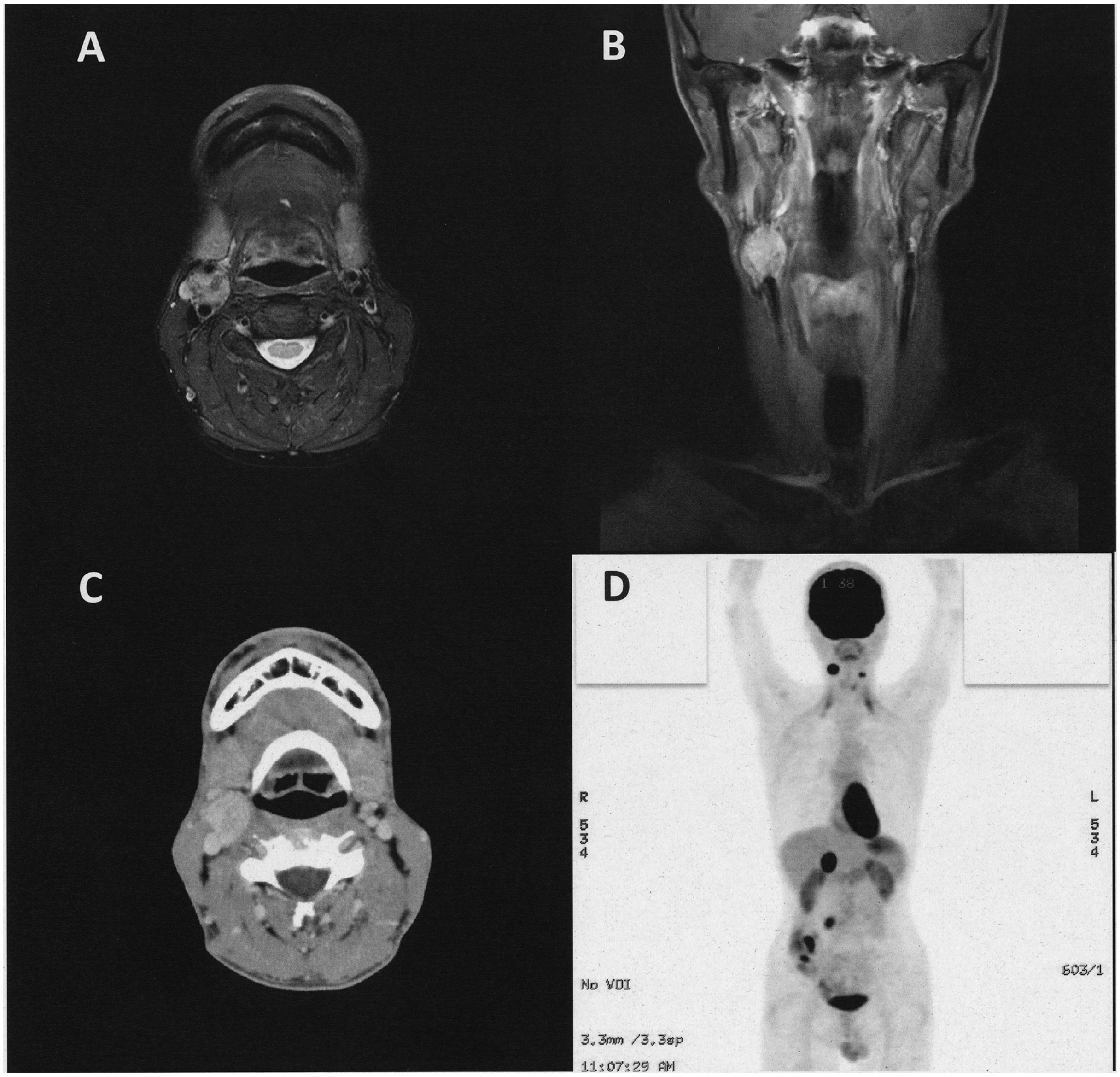

Figure 1. *Imaging modalities for diagnosis of the patients with carotid body tumor. Axial (A) and anterior coronal (B) views of the T2-weighted magnetic resonance images of a carotid body tumor (CBT) of a 47-year-old male with succinate dehydrogenase SDHD variant. The tumor is located at the right carotid bifurcation, with an estimated size of 26×22×21 mm on the image. The tumor is located at the right carotid bifurcation and within the external and internal carotid arteries, suggesting a categorization as Shamblin type II. A small CBT was also observed at the left carotid bifurcation. Axial view (C) of the contrast-enhanced computed tomographic image of the same patient. A mixed pattern of enhancement was observed in the right CBT. The coronal image (D) in 18F-fluorodeoxyglucose positron-emission tomography of the same patient. Bilateral CBTs and a pheochromocytoma in his right adrenal gland were detected.*

been developed and is widely used to prevent significant blood loss and surgical difficulties in dissecting CBTs from the carotid artery wall. The procedure is conducted as an endovascular intervention or by direct percutaneous embolization. The procedure of direct percutaneous embolization of CBTs has been developed as an alternative method to endovascular embolization, and n-butyl cyanoacrylate (38) and ethylene vinyl alcohol copolymer (39-41) have mainly been used as an embolization material.

Is preoperative embolization of feeding arteries of CBTs effective for surgical resection of CBTs? Efficacy evaluation was conducted by analyzing the operative time and blood

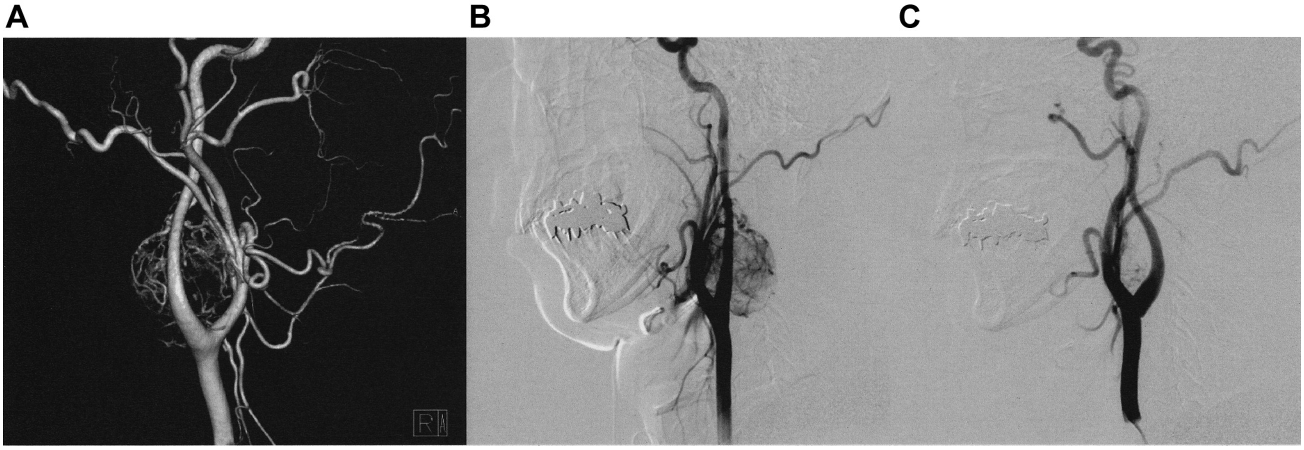

Figure 2. *Angiography findings. A 3D image of the feeding arteries of the right carotid body tumor constructed by the digital subtraction angiography of 53-year-old male with succinate dehydrogenase SDHD variant. His carotid body tumor (CBT) was 44 mm in diameter and fed by the ascending pharyngeal, occipital, accessory superior thyroid arteries, and direct branch of the external carotid artery. The left-sided lateral view of the digital subtraction angiography showing right carotid bifurcation of the same patient before (B) and after (C) preoperative embolization. Almost all the blood supply from the feeding arteries was shut down and same-day surgery was performed to resect the CBT. The blood loss of surgical resection was 5 ml and the operative time was 161 min. Transient cranial nerve X paralysis was observed after surgery but recovered completely 6 months after surgery.*

loss in CBT surgery. Although three meta-analyses have been published concerning preoperative embolization in CBT surgery, these reports showed different and controversial results (42-44). Two stated that preoperative embolization before surgical resection of CBT appeared to reduce the operative time and blood loss than surgery without preoperative embolization (42, 44), while another found no advantages for patients with CBT (43). In detail, in a meta-analysis of 22 studies (39, 40, 45-64) with a total of 578 patients, Jackson *et al.* demonstrated that surgical excision of CBTs with preoperative embolization appeared to reduce estimated blood loss and operative time in comparison to that without preoperative embolization (42). In contrast, Abu-Ghanem *et al.* (42) demonstrated by meta-analysis of 15 studies (45-47, 49, 51, 57-59, 61, 63, 65-69) with a total of 470 patients that preoperative embolization did not show any operative or postoperative advantage in patients scheduled for CBT surgery. Although these two reports were published within a year and included the same 10 reports in their studies, their results were controversial.

Since these meta-analyses, several reports have been published, and at some institutions, surgical resection was performed without preoperative embolization, and the authors maintained that their cases were safely managed by surgery alone (70). However, their reports described a significant amount of blood loss. Perhaps the most prominent effect of the preoperative embolization in CBT surgery was a reduction in blood loss during the surgery followed by a reduction in operative time due to the easy dissection procedure from the carotid arterial wall. Thus far, several reports have described the effectiveness of preoperative embolization (71-73). However, several reports have reported no efficacy of preoperative embolization (74-77).

Because of the rarity of CBTs, a prospective study to directly compare blood loss or operation time, nerve injury, *etc.*, is very difficult to perform. Therefore, selection bias of patients who underwent or did not undergo preoperative embolization was present in several studies. In practice, larger tumors or Shamblin II/III tumors tend to be the target of preoperative embolization (78).

We are in agreement with the preoperative embolization of feeding arteries of CBTs because if we choose the "same-day procedure" for the patients with CBT who undergo surgical resection, blood loss may be most effectively minimized (35) (Figure 2B and C). However, to perform the procedure precisely, it is necessary to have resources such as expert interventional radiologists, a back-up system for vascular surgery, an operative room, and the respective staff.

Why did the evaluation of preoperative embolization differ among several reports? It seems that the timing of preoperative embolization is a key factor for effective results. Katagiri *et al.* reported that a "same-day procedure" markedly reduced the blood loss and operative time of CBT surgery (35). In their report, resection of the CBT was performed routinely within 3 hours after the preoperative embolization procedure had been done. The splendid advantage of this procedure was remarkable shrinkage of the tumor after preoperative embolization, resulting in easy resection by surgeons as well as reduction of blood loss. Rich vascular networks supplied by many feeding arteries are naturally the characteristic feature of within CBTs and around their capsules. Once preoperative embolization has been performed, recanalization of the blood vessels from the collateral feeding arteries was observed soon after the embolization procedure. Since surgeons should consider this phenomenon, they must perform surgical resection of CBTs as soon as possible after preoperative embolization. In addition, during the procedure of preoperative embolization, new collateral feeding arteries appeared occasionally after the main feeding artery was blocked by the embolization procedure. Although an intentional delay of 1 or 2 days between preoperative embolization and surgery is recommended for resolving edema, reconstitution or recruitment of feeding arteries and inflammation may occur during this interval (43). No edema was observed in the specimen resected by surgery in the report by Katagiri *et al*. (35), indicating that we do not need this intentional delay for CBT surgery.

Although several reports described preoperative embolization followed by surgical resection, the time from preoperative embolization to successive surgery varies from hours to several days. Most studies reported that the duration from embolization to surgery ranged from 24 to 72 h (46, 51, 58, 59, 61, 63, 67-69). However, differences in evaluation concerning the effectiveness of preoperative embolization of the feeding arteries of CBTs derived from these various intervals from preoperative embolization and surgical resection.

Cranial nerve palsy is a crucial complication of surgical resection for CBTs (43, 44, 72). No complications were observed in some patients, and several nerve palsies were observed simultaneously in a single patient (35, 36). Symptoms of nerve paralysis are expressed to various degrees in patients. It is a puzzling matter why patients have postoperative nerve paralysis, such as recurrent nerve (vagal nerve) paralysis or hypoglossal nerve paralysis, even though their paralysis is reversible and disappears several months after surgery. Head and neck surgeons perform neck dissection routinely for patients with neck metastases who have oral, pharyngeal, and laryngeal cancer. In the process of neck dissection, the vagal and hypoglossal nerves are more clearly visible and separated from surrounding tissues in routine procedures. However, after neck dissection surgery, few patients have recurrent nerve or hypoglossal nerve paralysis. Although there is no clear answer based on clinical or basic evidence for this question, we speculate that these nerve paralyses were caused by ischemic changes in the nerve. When the rich vascular supply of the tumor and its capsule are observed in surgery, simultaneously, we have frequently observed that cranial nerves, such as vagal and hypoglossal nerves, are covered by rich capillary vessels. These nerves are suddenly separated from the tumor and the vascular supply is reduced to almost zero after tumor resection. This change in vascular supply may likely influence nerve function (35, 36).

Conclusion

Multiple feeding arteries and adhesion of the tumor to the carotid arterial wall are causes of difficulties in surgical resection of CBT. The effectiveness of preoperative embolization remains controversial due to the varied situations in performing surgical resection among the institutions. However, perfect embolization and resection immediately after embolization can reduce blood loss and operative time of CBT surgery.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Conceptualization, K.S; methodology, K.S.; investigation, K.S.; resources, K.K., A.I., D.S., S.O., K.T., J.M., T.K., and A.T.; writing—original draft preparation, K.S.; funding acquisition, K.K., K.S., and D.S. All Authors have read and agreed to the published version of the article.

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