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Management of Vagal Paragangliomas Including Application of Internal Carotid Artery Stenting

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Key Words
Chemodectoma · Vagal paraganglioma · Tumors, associated · Internal carotid artery · Stenting

Abstract
Background: The primary treatment of vagal paraganglioma (VP) includes 'wait and scan', surgery and radiotherapy. ***Objectives:*** To present the clinical findings, surgical treatment including application of internal carotid artery (ICA) stenting to facilitate surgery, and complications, as well as to review the literature and to discuss the decision-making process in the management of VP cases based on our experience and the literature. ***Design:*** A retrospective case review of 22 cases with VP. ***Setting:*** Quaternary neurotologic and skull base referral center. ***Material and Methods:*** The retrospective chart review identified 22 patients presenting with VP. Our indication for surgery was VP in younger patients, irrespective of the existence of vocal cord paralysis. Preoperative endovascular management of the ICA included permanent balloon occlusion (PBO) and stenting. The transcervical approach and the infratemporal fossa approach type A (ITFA) were used. ***Results:*** Fifteen cases had multicentric paragangliomas, 5 cases bilateral tumors, 3 cases a genetic mutation, and 2 cases a positive family history. The most common symptoms were hoarseness, tinnitus and hearing loss. The surgical approaches commonly employed for excision were the transcervical approach (9 cases) and the ITFA (12 cases), whereas 1 case did not have surgery. Three cases had PBO and 7 had intracarotid stent insertion. Gross total removal was achieved in 19 cases, and 1 case had a recurrence. Eighteen cases had no dysphagia or were well compensated after surgery. There were no significant complications noted in our series. ***Conclusions:*** In younger patients with VP, surgery should be recommended. The proper preoperative endovascular intervention and surgical approach facilitates gross total tumor removal. In the management of bilateral or familial paragangliomas, careful and appropriate decision making is essential.

Introduction

Vagal paragangliomas (VP) are rare neuroendocrine neoplasms that may arise from paraganglia along the course of the vagus nerve and account for approximately 5% of all head and neck paragangliomas, with an annual incidence of 1 per 100000 population [Eriksen et al., 1991; Lawson, 1980; Netterville et al., 1998; Persky et al., 2004; Zanoletti and Mazzoni, 2006]. VP generally present as a slow-growing neck mass which may protrude medially

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with deviation of the oropharyngeal structures. VP can displace the palatine tonsil and the carotid arteries, infiltrate local tissues at the base of skull, and extend intracranially [Browne et al., 1993]. Infrequently, VP can undergo malignant transformation and then metastasize and invade the internal carotid artery (ICA) [Biller et al., 1989; Eriksen et al., 1991].

Because the tumor arises from the paraganglionic tissue within the perineurium of the vagus nerve, surgical resection invariably results in complete vagal paralysis [Arts and Fagan, 1991; Biller et al., 1989; Bradshaw and Jansen, 2005; Eriksen et al., 1991; Hirsch et al., 1982; Moore et al., 1986; Urquhart et al., 1994; van der Mey et al., 1992; Zanoletti and Mazzoni, 2006]. The morbidity associated with resection, especially of the remaining cranial nerves, is dependent on the tumor's size and superior extent. The relationship of the lower cranial nerves (LCN) to the tumor differs in VP as opposed to tympanojugular paraganglioma (TJP). The hypoglossal nerve is involved more commonly in VP and is at great risk during removal of medium- to large-sized tumors. The rates of additional LCN injuries which may interfere with restoration of effective swallowing range from 30 to 60% in VP [Borba and Al-Mefty, 1996; Bradshaw and Jansen, 2005; Browne et al., 1993; Eriksen et al., 1991; Miller et al., 2000; Netterville et al., 1998]. There are therefore controversies regarding the management of VP. Some authors insist that 'wait-and-scan' policies (which may prolong the period of a patient's normal vocal cord mobility and swallowing) should be considered in VP cases with normal function of the vagus nerve [Bradshaw and Jansen, 2005; van der Mey et al., 1992]. This policy is difficult to adopt in cases with a large VP which erodes the skull base or extends intracranially. Surgical resection of the tumor in contrast to a wait-and-scan policy can avoid additional damage to the LCN (except the vagus nerve) as well as vascular complications, and can liberate the patient from the disease [Bradshaw and Jansen, 2005]. Decision making on the ideal candidate for surgery and its timing is an important and difficult issue. We present the clinical findings, endovascular intervention, surgical treatment and complications of VP with a literature review and discuss the decision making in the management of VP patients.

Patients and Methods

A retrospective chart review identified 22 patients presenting with VP who were diagnosed and treated at the Gruppo Otologico from 1989 to 2009. All the patients treated surgically were operated on by the senior author (M.S.). In general, our indication for surgery is VP in younger patients, irrespective of the existence of vocal cord paralysis. A wait-and-scan policy is adopted for VP in elderly patients with no serious complications. For bilateral lesions, if the patient has an abnormal vagus nerve function on one side, surgical removal is considered on that side, and conservative management is applied to the contralateral side.

According to the Fisch classification [Browne et al., 1993], VP were classified into three stages. In stage I, the tumor is located in the parapharyngeal space without invasion of the jugular foramen. In stage II, the tumor invades the jugular foramen without bone destruction, and in stage III, the tumor deeply invades the jugular foramen and middle ear with bone destruction and variable involvement of the carotid canal. In this study, we included patients with multiple paragangliomas combined with VP. We collected pre-, intra- and postoperative data from all patients. A minimum follow-up of 6 months was required for inclusion in the study. All cases underwent preoperative computed tomography (CT) scanning, magnetic resonance imaging (MRI) and diagnostic angiography.

Preoperative endovascular management of the ICA included permanent balloon occlusion (PBO) and stenting. Indications for preoperative endovascular management of the ICA were according to MRI and angiographic data and included:

(1) encasement of the distal cervical and vertical segments of the ICA between 270 and 360°, as shown by CT and MRI in the axial plane;
(2) evidence of stenosis and irregularities of the arterial lumen of the distal cervical and vertical segments of the ICA, as determined by angiography;
(3) extensive blood supply from ICA branches, as seen on angiography;
(4) previous surgery with ICA manipulation and/or previous radiotherapy.

In addition, the functional integrity of the circle of Willis was checked using Matas' and Alcock's tests. A PBO was made if the patient tolerated these tests and good angiographic data demonstrated cross-flow. The PBO procedure was performed under local anesthesia with mild sedation and systemic heparinization. A bilateral femoral approach was employed, in which an 8-Fr guiding catheter was inserted into one femoral artery and positioned in the ICA to be occluded. The contralateral femoral artery puncture was used for the angiographic evaluation. Reinforcement with stents was performed under general anesthesia as a separate procedure sometime after diagnostic angiography. Three different types of self-expanding nitinol stents have been employed: Xpert Stent (Abbott Laboratories Vascular Enterprises, Dublin, Ireland), Neuroform (Boston Scientific, Fremont, Calif., USA) and Carotid Wallstent (Boston Scientific, Natick, Mass., USA). To reduce the risk of thromboembolic complications, antiplatelet therapy was commenced 1 week before stent insertion, using a combination of clopidogrel (75 mg/day) and aspirin (100 mg/day). This therapeutic regimen was administered for a minimum of 30 days after stenting and then reduced to single-drug treatment with aspirin only. The interval between insertion of a stent and surgery varied between 1 and 3 months. Antiplatelet therapy was suspended 1 week before surgery and resumed 1 week afterward. Low-molecular-weight heparin was given during the intervening period [Sanna et al., 2009].

The embolization of tumor-feeding vessels depended on tumor size and angiographic findings. It was performed under general anesthesia 2–3 days before surgery. Embolization in medium- and large-sized tumors was performed with polyvinyl alcohol particles of 150–300 μm (Contour Emboli), injected through a microcatheter after superselective catheterization of the feeding vessels coming from the external carotid artery. In very selected cases, embolization of muscular branches of the vertebral artery arising from the distal portion of the V2 segment was performed.

In cases of big arteriovenous shunts or anastomotic branches between the external carotid and the ipsilateral vertebral arteries, coils were used to occlude the anastomotic pathway or to slow the flow in the arterial pedicles in order to facilitate the efficacy of the polyvinyl alcohol particles. The interval of time between insertion of the stent and surgical removal varied between 2 and 4 months in order to allow incorporation of the stent in the carotid wall by neointimal growth.

Surgical Approaches

(1) Transcervical approach: this approach is suitable for lesions within the parapharyngeal space but not invading the skull base, and with minimal ICA involvement (mainly stage I cases or certain stage II cases) [Browne et al., 1993]. The key points to ensure superior exposure are resection of the posterior belly of the digastric muscle, identification of the extratemporal facial nerve, and transection of the styloid process. Retraction of the angle of the mandible can marginally improve access.
(2) Transcervical-transmastoid approach: this approach is used in addition to the above when a tumor has minimal extension to the skull base (mainly stage II cases) [Browne et al., 1993]. It involves removal of the mastoid tip and infralabyrinthine dissection, allowing exposure of the sigmoid sinus down to the jugular bulb.
(3) Infratemporal fossa approach type A (ITFA): an ITFA is required in most stage III cases [Browne et al., 1993]. This allows continuous exposure from the neck to jugular fossa, and allows the concurrent removal of any small intradural tumor extension. The technique is identical to that described for the treatment of TJP [Sanna et al., 2008]. The initial step is to expose the great vessels, the facial, vagus, spinal accessory and hypoglossal nerves in the neck, freeing them from tumor when possible. Division of the digastric muscle, the styloid process and associated musculature greatly aids in the superior exposure. Progression to an ITFA with facial nerve rerouting, extraluminal closure of the sigmoid sinus and ligation of the internal jugular vein [Bhansali et al., 1991] provides optimum exposure of the tumor and distal ICA. For TJP concurrent with VP, this approach is used.

The patients were reviewed every 6 months for the first year after surgery, then once a year, and studied by MRI and/or CT at 1, 3 and 5 years after surgery. The review process involved a literature search using the PubMed database to identify papers in the English literature addressing VP treatment. The following key words were used: vagal paraganglioma, glomus vagale, chemodectoma intravagale or juxtavagale. Among articles complying with the aims of the study, those reporting the largest number of patients were reviewed. The data collected from each article included in the review were analyzed for number of patients treated, associated tumors, preoperative endovascular management, surgical approaches, ICA management, complications, recurrences and length of follow-up.

Results

The study group consisted of 22 patients, 17 females and 5 males (table 1). Ages ranged from 27 to 62 years, with an average of 44.7 years. Follow-up ranged from 0.5 to 8 years. Ten of the VP occurred on the left side, and 10 were on the right. Two cases had bilateral VP. Two cases had a positive family history of paragangliomas. Three cases had a genetic mutation, which is the germline mutation of succinate dehydrogenase subunits B, C and D (SDHB/C/D) in each case. None of the cases had undergone previous surgery for VP. Five cases had undergone surgery for carotid body tumor (CBT) or TJP. One case had had radiotherapy for TJP and VP. Metastatic VP was not present. Presenting symptoms (table 2) included hoarseness in 10 cases, tinnitus in 10, hearing loss in 10, neck mass in 5, and dysphagia in 5. In 9 cases with solitary VP, the most common presenting symptom was a neck mass. Multicentric paragangliomas of the head and neck were present in 15 cases (68%), and 5 cases had bilateral paragangliomas (table 3).

On preoperative LCN status, the most common cranial nerve deficit was of the vagus nerve, followed by the glossopharyngeal nerve (tables 1, 4). Cases No. 9 and 19 (table 1) showed contralateral LCN palsies. Tumor involvement of the ICA, as shown by MRI and angiography, was detected in 10 cases. In our early experience before the introduction of arterial stenting, a bypass graft between the ICA and middle cerebral artery bifurcation using the radial artery was attempted in 1 case (case No. 6) to allow safe PBO of the ICA due to poor compensation through the circle of Willis. However, 2 months later, on the day of the PBO, angiography unfortunately showed an occlusion of the bypass. The possible reason for the occlusion of the bypass was the long 2-month interval between the bypass and the day of the scheduled PBO procedure. As a result, we proceeded to stenting in this case. Three cases had PBO of the ICA according to a protocol previously published [Sanna et al., 2004b]; in 1 case (case No. 4), this was due to a huge VP occluding the ICA, while in the other 2 cases, the reason for PBO was a huge TJP associated with a VP (cases No. 1 and 15).

Carotid artery stenting was performed globally in 7 patients, in 5 of which this was due to the presence of a VP (cases No. 6, 9, 10, 11 and 13) and in the remaining 2 in order to protect the ICA during removal of a huge TJP (cases No. 14 and 16). In case No. 9, both external carotid arteries and ICA were encased on axial T_1-weighted MRI, and on angiography there was left ICA compression by

Table 1. Patient characteristics according to surgical data (n = 22)

Case No.	Sex	Age years	Side	Prior treatment/genetic study/family history	Stage[1]	Surgical approach	Associated tumor	ICA treatment	Emb
1	M	28	R	radiotherapy	Im	ITFA (1989)	TJPi	PBO for TJP	Y
2	F	49	R	–	IIm	ITFA (1992)	TJPi	–	Y
3	M	61	R	–	IIIi	ITFA (1997)	–	–	Y
4	F	40	L	–	IIIi	ITFA (1999)	–	PBO for VP	Y
5	F	60	L	–	IIi	TC (2000)	–	–	Y
6	M	46	R	–	Ii	TC (2000)	–	bypass for VP (fail) → stent for VP	Y
7	F	41	L	ITFA for TJP (L), thyroplasty type I, SDHC+	Im	TC (2002)	TJPi (operated)	–	N
8	F	32	R	–	Im	ITFA (2003)	TJPi	–	Y
9	M	51	B	–	IIb	TC (2003)	VPb	stent for VP primary repair	Y
10	F	39	L	ITFA for TJP (L), family history	Im	TC (2004)	TJPi (operated)	stent for VP	Y
11	F	37	R	–	Ii	TC (2004)	–	stent for VP	Y
12	F	42	L	–	IIIm	ITFA (2005)	TJPi	–	Y
13	F	56	L	–	Ii	TC (2005)	–	stent for VP	N
14	M	42	R	–	Im	ITFA (2005)	TJPi	stent for TJP	Y
15	F	56	L	–	IIm	ITFA (2006)	TJPi	PBO for VP and TJP	Y
16	F	61	R	hemipetrosectomy for TJP (R)	IIm	TC (2006)	TJPi (operated)	stent for TJP	Y
17	F	27	R	SDHB+	IIIi	ITFA (2006)	–	–	Y
18	F	62	L	–	IIIm	ITFA (2006)	CBTi	–	Y
19	F	41	R	TC for CBT (L)	Ib	– (2007)	CBTc (operated), TJPb	–	–
20	F	34	B	SDHD+	Ib	TC (2008)	VPb	–	Y
21	F	51	L	–	Ib	ITFA (2008)	TJPi, CBTc	–	Y
22	F	27	L	TC for CBT (R), family history	Ib	ITFA (2009)	CBTb, TJPi	–	Y

R = Right; L = left; B = bilateral; Emb = embolization; LCND = LCN deficits; TC = transcervical approach; CBT = carotid body tumor; stent = preoperative stent insertion into the ICA; bypass = ICA bypass surgery; IX = glossopharyngeal nerve; X = vagus nerve; XI = spinal accessory nerve; XII = hypoglossal nerve; total = gross total removal; subtotal = subtotal removal; Rev. = revision; mo = month(s); i = ipsilateral; b = bilateral; c = contralateral; m = multiple; SDHB, SDHC, SDHD = succinate dehydrogenase subunits B, C and D. [1] According to the staging system by Browne et al. [1993].

the tumor, which was resolved after stenting (fig. 1). In case No. 13, due to the kink in the distal cervical segment of the ICA, the stent insertion was difficult but successful (fig 2). Various types of stents (table 5) have been used according to a technique previously described [Sanna et al., 2009].

Superselective embolization of the tumor vasculature, mainly branches of the external carotid artery, was preoperatively performed in 20 cases without complications. In 2 cases, muscular branches of the V2 segment of the vertebral artery were embolized. In 1 case, embolization was not performed (case No. 7). Twelve cases were classified as Fisch stage I. Of these 12 cases, 6 underwent a transcervical approach, 5 had an ITFA due to concurrent TJP, and 1 (case No. 19) was followed up due to her contralateral LCN palsies, insufficient cerebral collateral circulation and a contralateral anomaly of the venous drainage system. Of the 5 Fisch stage II cases, 3 underwent a transcervical approach, and 2 had an ITFA. All 5 Fisch stage III cases were operated via an ITFA.

Postoperatively, all cases had complete vagal palsy secondary to resection. Table 4 shows the comparison between the pre- and postoperative deficit rates for LCN in combination-plus-solitary VP cases and in cases with solitary VP. The postoperative deficit rate (66.7%) for the hypoglossal nerve was higher in solitary VP cases than in

Preoperative LCND	Postoperative LCND	Surgical outcomes	Degree of dysphagia	Additional treatment	Follow-up (period, recurrence, complications)
X	X	total	mild dysphagia good compensation	–	22 mo, no recurrence
IX, X, XII	IX, X, XI, XII	total	dysphagia good compensation	–	91 mo, no recurrence
IX, X, XI	IX, X, XI, XII	total	dysphagia good compensation	–	48 mo, no recurrence
IX, X, XII	IX, X, XI, XII	total	dysphagia good compensation	–	35 mo, no recurrence
–	X, XII	total	dysphagia good compensation	–	14 mo, no recurrence
X, XI	IX, X, XI	subtotal	dysphagia good compensation	–	60 mo, recurrence → Rev. TC after cervical stent insertion 72 mo, recurrence → Rev. ITFA, after petrous stent insertion 90 mo, residual tumor at the cavernous sinus → radiotherapy
IX, X, XI, XII	IX, X, XI, XII	total	dysphagia good compensation	–	56 mo, no recurrence L CBT 19 mm (size check)
–	IX, X	total	dysphagia good compensation	–	87 mo, no recurrence
X, XIIc	X, XIIb	subtotal	dysphagia not compensated	gastrostomy	26 mo, intraoperative rupture of ICA with subsequent ICA occlusion, 1.5-cm residual tumor (L)
–	X	total	no dysphagia	–	70 mo, no recurrence CBT (contralateral → wait-and-scan policy)
IX	IX, X	total	dysphagia good compensation	–	25 mo, no recurrence
IX, X, XI, XII	IX, X, XI, XII	total	dysphagia good compensation	–	46 mo, no recurrence
–	IX, X	total	no dysphagia	–	29 mo, no recurrence
IX, X	IX, X, XI, XII	total	dysphagia good compensation	–	22 mo, no recurrence
X, XII	X, XII	total	dysphagia good compensation	–	36 mo, no recurrence
IX, X, XI, X	IX, X, XI, X	total	dysphagia not compensated	–	6 mo, follow-up loss
IX, X, XI, XII	IX, X, XI, XII	total	dysphagia good compensation	–	24 mo, no recurrence
IX, X	IX, X, XI	total	dysphagia not compensated	–	25 mo, no recurrence
IXc, Xc, XIIc	–	–	mild dysphagia	–	36 mo, no recurrence
–	X, XII	total	no dysphagia	radiotherapy for VPc	31 mo, no recurrence
XI	X, XI	subtotal	no dysphagia	–	3 mo TC, 22 mo, no recurrence
–	X	total	no dysphagia	–	12 mo, no recurrence

combination-plus-solitary VP cases. Table 6 shows the comparison between the postoperative functional preservation rate for the LCN in VP and TJP [Sanna et al., 2004a]. The functional preservation rate was 72.7% for the glossopharyngeal nerve, 73.3% for the spinal accessory nerve and 66.7% for the hypoglossal nerve. The glossopharyngeal nerves were better preserved and the hypoglossal nerves were less well preserved in VP cases.

Gross total removal was achieved in 19 cases. In 1 case (case No. 9), some tumor surrounding the hypoglossal nerve was retained in order to preserve it due to the contralateral hypoglossal nerve palsy. In another case (case No. 21), the VP was not completely resected due to contralateral CBT, but postoperatively, vagus nerve palsy was noted and the residual VP was removed 3 months later.

One case (case No. 6) had tumor recurrence. His diagnosis was an atypical VP showing the extremely rare sustentacular tissues (type II glomus cells), which may show aggressive biological behavior [Bhansali et al., 1991]. After 2 revision surgeries, radiotherapy was performed to control the residual lesion at the cavernous sinus.

Eighteen cases had no dysphagia or were well compensated after surgery. Of these 18, 1 (case No. 7) had had a TJP surgery with type I thyroplasty at another institute. Two cases did not adequately compensate for the postoperative loss of LCN function, probably secondary to ad-

Table 2. Presenting symptoms in total cases and sole vagal paragangliomas (n)

	Patients affected/total	
	total cases (n = 22)	solitary VP (n = 9)
Hoarseness	10/22	3/9
Tinnitus	10/22	1/9
Hearing loss	10/22	2/9
Neck mass	5/22	4/9
Dysphagia	5/22	2/9
Instability	2/22	–
Odynophagia	1/22	–
Otorrhea	1/22	–
Vertigo	1/22	–
Pulsatile tinnitus	1/22	1/9
Shoulder weakness	1/22	–

Table 3. Multiple paragangliomas (n = 15)

	Patients, n
VP + TJPi	9
VPb	2
VP + TJPi + CBTc	1
VP + TJPi + CBTb	1
VP + TJPb	1
VP + CBTi	1

i = Ipsilateral; c = contralateral; b = bilateral.

vanced age. One case with postoperative bilateral hypoglossal palsies showed severe dysphagia and underwent percutaneous endoscopic gastrostomy.

Concerning vascular complications, we had 1 case of intraoperative rupture of the distal cervical portion of the ICA before entry into the carotid foramen beyond the distal extremity of the stent (case No. 9); the artery was repaired, but a few days later, angio-CT showed an asymptomatic carotid occlusion.

Literature Review

There were 8 series in the English research literature that met our inclusion criteria, with a total of 211 cases (table 7). Including our own series of 22 cases, the total number of cases is 233.

The presence of second paragangliomas was about 45%. Most authors [Biller et al., 1989; Browne et al., 1993; Miller et al., 2000; Netterville et al., 1998; Urquhart et al., 1994; Zanoletti and Mazzoni, 2006] except for van der Mey et al. [1992] and Bradshaw and Jansen [2005] advocated surgical resection as the mainstay of treatment for VP. In a small number of cases, radiotherapy was performed. Regarding the surgical approach, the transcervical approach was most commonly used, followed by the ITFA. Some authors used median mandibulotomy to enlarge the surgical field [Biller et al., 1989; Miller et al., 2000; Urquhart et al., 1994]. Four series including our present series presented a variety of carotid artery treatments including preoperative PBO and sacrifice, primary repair, intraoperative balloon occlusion and bypass (tables 1, 8). Among these series, stenting was utilized only in our institute. Netterville et al. [1998] and Zanoletti and Mazzoni [2006] reported a combined total of 3 cases of cerebral vascular accidents (table 6). Table 8 shows a summary of the management of ICA and its complications, comparing reported cases from 8 published series and our present series. Table 9 summarizes the deficit rates for vagal and hypoglossal nerves in 6 of the 8 series and our series; Netterville et al. [1998] and van der Mey et al. [1992] did not specify their surgical results for vagal and hypoglossal nerve deficits. There were only 3 cases of vagus nerve preservation in the literature reviewed [Browne et al., 1993; Miller et al., 2000]. The vagus nerve was sacrificed in most cases (97.3%). The cumulative rate of hypoglossal nerve palsy was 45.5%. The cumulative incidence of recurrence was about 4%. There were 3 cases of mortality due to airway obstruction, but these were not directly related to the surgery.

Discussion

VP are less common than CBT and TJP, occurring in the 4th and 5th decades of life, and are more common in females [Borba and Al-Mefty, 1996; McNicol, 2010]. Familial VP may have a more aggressive growth pattern than a nonfamilial one [Bradshaw and Jansen, 2005]. Due to the high probability of a familial form of the disease [Spector et al., 1976; Zanoletti and Mazzoni, 2006], a detailed family history has to be obtained. If positive, genetic testing including VHL, RET, NF1, SDHD, SDHB and SDHC genes [Klein et al., 1993] is suggested for the patient and first-degree relatives. More than 50% of paragangliomas associated with SDHB mutations are malignant [Timmers et al., 2007]. There appears to be an increased risk of malignancy in patients with genetically detected mutation in the SDHD genes [Havekes et al., 2007]. In our series, 3 cases showed the mutation of SDH subunits, which needs lifelong follow-up.

Table 4. Pre- and postoperative deficit rates of LCN in all cases and cases with solitary VP (%)

Cranial nerve	Preoperative deficit rates		Postoperative deficit rates	
	VP + solitary VP (n = 22)	solitary VP (n = 9)	VP + solitary VP (n = 21)	solitary VP (n = 9)
IX	45.5	55.6	61.9	66.7
X	59.1	55.6	100.0	100.0
XI	27.3	22.2	52.6	44.4
XII	27.3	22.2	52.4	66.7

IX = Glossopharyngeal nerve; X = vagus nerve; XI = spinal accessory nerve; XII = hypoglossal nerve.

Table 5. Endovascular management of the ICA in VP (n = 6)

Case No.	Stage[1]	MRI	Finding by angiography	ICA endovascular treatment	Intraoperative complication
4	III	Global encasement of cervical ICA	Stenosis of cervical ICA; patent circle of Willis	PBO of ICA	None
6	I	Global encasement of cervical ICA	Stenosis of cervical ICA; incompetent circle of Willis	Bypass failure; Xpert Stent insertion in cervical ICA in 2004; Xpert Stent insertion in petrous ICA in 2007	None
9	II	Global encasement of left cervical ICA	Stenosis of left cervical ICA; patent circle of Willis	Carotid Wallstent insertion in cervical ICA	ICA rupture at distal end of stent with subsequent asymptomatic occlusion
10	I	Partial encasement of left cervical ICA	Stenosis of left cervical ICA; incompetent circle of Willis	Xpert Stent insertion in cervical ICA	None
11	I	Partial encasement of right cervical ICA	Incompetent circle of Willis	Xpert Stent insertion in cervical ICA (2 stents in series)	None
13	I	Global encasement of cervical ICA	Stenosis of distal cervical ICA; incompetent circle of Willis	Xpert Stent insertion in cervical ICA; Neuroform stent insertion in petrous ICA	None

[1] According to the staging system by Browne et al. [1993].

Depending on the extension of the tumor, 3 stages were suggested by Browne et al. [1993]. Coronal and sagittal CT imaging or MRI is essential to differentiate stage II from stage III, and VP from other paragangliomas. Angiography is essential (1) to confirm the diagnosis, (2) to check ICA involvement shown as stenoses of the arterial lumen, (3) to check the adequacy of arterial collateral circulation through the circle of Willis, (4) to check the adequacy of venous drainage of the brain, and (5) to detect hidden paragangliomas.

VP are contiguous with the vagus nerve, lie 1–2 cm below the jugular foramen and frequently displace the lateral pharyngeal wall medially and the ICA anteromedially, whereas CBT centered in the carotid bifurcation may compress the vagus nerve and splay the external

Table 6. Function preservation rates for LCN in 21 VP cases compared with TJP cases

Cranial nerve	Nerves preserved[1]/clinically uninvolved nerves[2]	
	VP	TJP[3]
IX	8/11 (72.7%)	66.7%
X	0/8 (0.0%)	69.7%
XI	11/15 (73.3%)	74.3%
XII	10/15 (66.7%)	87.5%
Overall	27/49 (59.2%)	75.1%

IX = Glossopharyngeal nerve; X = vagus nerve; XI = spinal accessory nerve; XII = hypoglossal nerve.

[1] At least 6 months after surgery. [2] Preoperative status. [3] Sanna et al. [2004a].

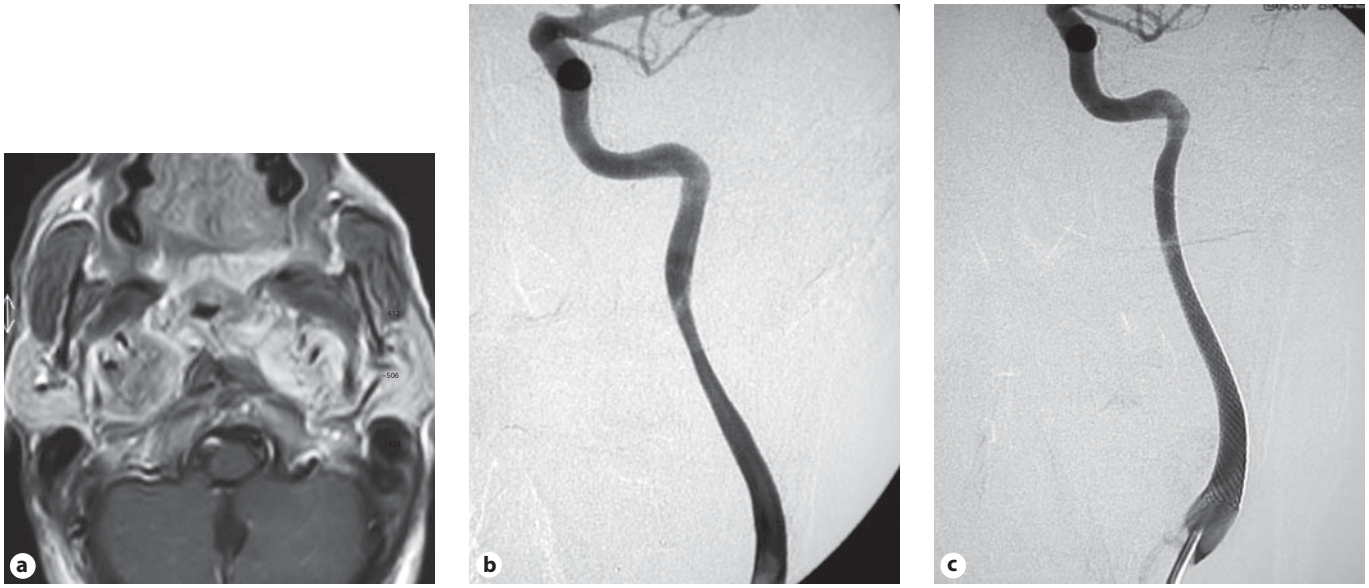

Fig. 1. Case No. 9. **a** Axial T_1-weighted MR image showing bilateral encasement of the ICA by VP. **b** Selective injection of the left ICA in anteroposterior projection showing stenosis. **c** Selective injection of ICA after stent deployment, showing absence of stenosis.

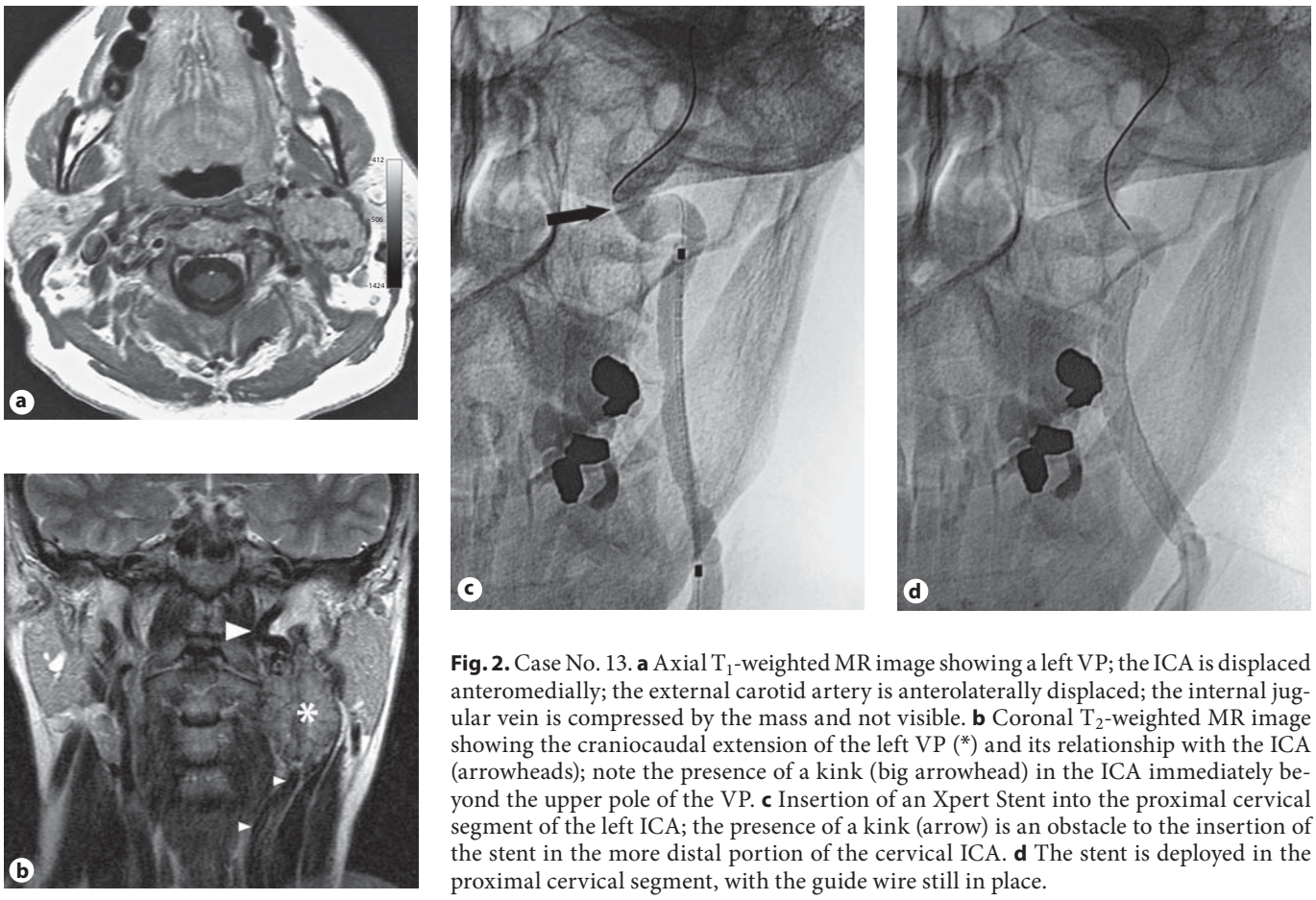

Fig. 2. Case No. 13. **a** Axial T_1-weighted MR image showing a left VP; the ICA is displaced anteromedially; the external carotid artery is anterolaterally displaced; the internal jugular vein is compressed by the mass and not visible. **b** Coronal T_2-weighted MR image showing the craniocaudal extension of the left VP (*) and its relationship with the ICA (arrowheads); note the presence of a kink (big arrowhead) in the ICA immediately beyond the upper pole of the VP. **c** Insertion of an Xpert Stent into the proximal cervical segment of the left ICA; the presence of a kink (arrow) is an obstacle to the insertion of the stent in the more distal portion of the cervical ICA. **d** The stent is deployed in the proximal cervical segment, with the guide wire still in place.

carotid artery and ICA [Arts and Fagan, 1991; Borba and Al-Mefty, 1996; Endicott and Maniglia, 1980; Noujaim et al., 2000]. Large VP may extend caudally towards the carotid bifurcation or cephalad into the jugular foramen [Harnsberger, 2004]. TJP are located in the jugular foramen and usually show permeative-destructive bony margins on CT scans. However, it may be difficult to differentiate a Fisch stage III VP from large TJP [Browne et al., 1993], and this can lead to preoperative misdiagnosis, especially with multiple paragangliomas.

This situation can arise with superior extension of a VP into the jugular foramen, or when a TJP extends caudally into the parapharyngeal space via the jugular foramen, and even in situations where the two distinct tumors coexist. The patient's symptoms are often the best indicator for the site of the tumor, as a VP will present with hoarseness and neck mass earlier as its epicenter is in the parapharynx. Conversely, a TJP would present with otologic symptoms first as its epicenter is the jugular foramen [Biller et al., 1989; Leonetti and Brackmann, 1989].

In the decision-making process, many factors should be considered, such as: the patient's age; preoperative medical fitness; tumor factors such as size, bilaterality and multiplicity; preoperative LCN function; the patient's preference; genetic results; family history; an inevitable loss of vagal nerve function, and the risk of carotid artery injury [Biller et al., 1989; Netterville et al., 1998; Zanoletti and Mazzoni, 2006].

In elderly patients, we have different options: observation; near total resection with LCN preservation; total resection with vocal cord medialization, and radiotherapy. If a patient has normal LCN function and a small tumor, observation is the best option. However, VP are usually large before they produce symptoms and are therefore seldom treated at an early stage. If the tumor is large and the patient's health permits surgery, we can consider near total resection with LCN preservation, or total resection with vocal cord medicalization [Netterville et al., 1998]. If a patient is unfit for surgery, a wait-and-scan policy or radiotherapy may be performed.

Bradshaw and Jansen [2005] reported that a wait-and-scan policy preceding surgery may lead to prolonged preservation of vocal and swallowing functions. If this strategy is adopted, intervention prior to the development of skull base invasion is recommended. If we follow a wait-and-scan policy, the tumor may have enlarged, requiring more extensive surgery with associated greater postsurgical morbidity. We believe that in young patients, total tumor removal is the mainstay of treatment. Most younger patients usually tolerate the loss of LCN function after surgery. Given their potential local mass effect on the ICA and the LCN and their unpredictable malignant behavior, VP are usually surgically removed [Bradshaw and Jansen, 2005]. The presence of bilateral disease, where there is a risk of bilateral LCN paralysis, modifies this approach. Surgery is indicated for the side of LCN defect, and the contralateral lesion is followed up by MRI if it is small, or irradiated if large. However, if the patient has no deficit in LCN function, we observe the tendency of tumor growth. If the tumor exhibits growth, the patient is given the options of either radiotherapy or functional LCN preservation surgery. Should the chosen option be unsuccessful in treating the patient, the remaining treatment option is offered to the patient.

We had 5 cases with bilateral tumors. Of these, 1 (case No. 9) had a preoperative vagal palsy on the right side and contralateral hypoglossal palsy. During a transcervical approach, the ipsilateral hypoglossal nerve was also involved by the tumor, which was incompletely removed to preserve nerve function. In spite of this, he showed postoperative bilateral hypoglossal palsies and severe dysphagia, which led to percutaneous endoscopic gastrostomy. Another case (case No. 22) had had previous resection of the right CBT without loss of LCN function, and the combined left CBT, VP and TJP were simultaneously removed via an ITFA. Postoperatively, she presented with only vagal palsy and had no dysphagia. As in this case, we prefer simultaneous resection of ipsilateral multiple tumors including CBT and TJP.

Some authors [Browne et al., 1993; Davidson and Gullane, 1988; Eriksen et al., 1991; Miller et al., 2000; Ogura et al., 1978; Wong et al., 1987] advocate preoperative embolization, but others [Biller et al., 1989; Black et al., 1977; Forbes et al., 1986; Urquhart et al., 1994] do not. In our practical experience, the decision for embolization depends on tumor size and angiographic findings. If the tumor is small and has a minimal blood supply, embolization is not performed; if a tumor is large and has an extensive blood supply, embolization is performed to facilitate gross total tumor removal, to minimize intraoperative bleeding, to reduce the operative time, and to decrease the incidence of postoperative hypoglossal nerve paralysis [Miller et al., 2000]. In medium-sized tumors between 3 and 5 cm in diameter, embolization of the external carotid artery branches – namely the ascending pharyngeal and occipital artery – is performed. In larger tumors more than 5 cm in diameter, embolization of the branches of the external carotid artery is performed, but in addition there may be an extensive supply from muscular branches of the ipsilateral vertebral artery. Micro-

Table 7. Literature review on surgical treatment of VP

Source	Cases treated/total, n			Associated tumor	Carotid artery treatment
	surgery	wait and scan	definitive RT		
Biller et al. [1989]	18/18	–	–	CBT: 2 TJP: 1 CBT + TJP: 3 VPb + CBTb + SCBT: 1	sacrifice: 2 bypass: 2
van der Mey et al. [1992]	19/30	11/30	–	not specified	–
Browne et al. [1993]	15/15	–	–	CBT: 4 TJP: 3	PBO: 8 IBO: 2
Urquhart et al. [1994]	16/19	–	3/19	CBT: 4 CBTb: 1 VPb: 1 VPb + TJP: 1 CBT + TP: 1 TP: 2	–
Netterville et al. [1998]	40/46	2/40	4/40	17/46 mostly CBT + VP	sacrifice: 1 postop. radiation: 1 bypass: 1 primary repair: 2
Miller et al. [2000]	16/19	–	3/19	2/19	–
Bradshaw and Jansen [2005]	10/48	38/48	–	92%	–
Zanoletti and Mazzoni [2006]	16/16	–	–	TJP: 4	–
Present series	21/22	1/22	–	TJPi: 9 VPb: 2 TJPi + CBTc: 1 TJPi + CBTb: 1 TJPb: 1 CBTi: 1	stent insertion: 7 PBO: 3 bypass: 1 primary repair: 1

TP = Tympanic paraganglioma; SCBT = subclavian body tumor; RT = radiotherapy; TC = transcervical approach; TCMM = transcervical with midline mandibulotomy; TCTM = transcervical transmastoid approach; TCo = transcochlear approach; IBO = intraoperative balloon occlusion; CSF = cerebrospinal fluid; CVA = cerebrovascular accident; i = ipsilateral; c = contralateral; b = bilateral tumor; NA = not available; XII = hypoglossal nerve; postop. = postoperative.

Surgical approach	Recurrence	Postoperative rate of X deficit	Postoperative rate of XII deficit	Complications
TC: 8 TCMM: 8 TCTM: 2	2/18	100%	66.7%	mortality: 1 (tracheotomy related) follow-up mortality: 1 (bilateral vocal cord palsy)
not specified	NA	90%	not specified	not specified
ITFA: 11 TCo: 4	0/15	87%	33.3%	hypertensive tachycardia: 1 CSF leak: 1 meningitis: 1 sepsis: 1
TC: 14 TCMM: 2	0/16	100%	31.2%	airway obstruction: 1 XII palsy: 5 hematoma: 1 Horner's syndrome: 1
TC: 12 TCTM: 10 ITFA: 18	0/39	100%	not specified	death: 1 CVA: 2 CSF leak: 3 wound: 6 hematoma: 3 necrosis: 2 infection: 1 pneumothorax: 2 endocarditis: 1 airway obstruction: 3 major depression syndrome: 2
TC: 15 TCMM: 1	3/16	87.5%	56.3%	aspiration: 9
not specified	NA	100%	50%	aspiration pneumonia: 1 wound infection: 1
TC: 12 ITFA: 4	0/16	100%	25.0%	CVA: 1
TC: 9 TCTM: 1 ITFA: 11	1/19	100%	52.4%	bypass failure: 1

Table 8. Management of ICA in VP and its complications in the literature compared with this series (n)

	Cases in the literature (n = 73)[1]	Cases in this series (n = 21)
Preoperative balloon occlusion	8	3
Bypass graft	3	1
Sacrifice	3	–
Primary repair	2	1
Intraoperative balloon occlusion	2	–
Stent insertion	–	7
Cerebral vascular accidents	3	–

[1] Biller et al. [1989]; Browne et al. [1993]; Netterville et al. [1998].

Table 9. Review of the literature for vagal and hypoglossal nerve deficits in cases with VP

Source	Cases	Cases of preop. X deficit	Cases of postop. X deficit	Postop. rate of X deficit	Cases of preop. XII deficit	Cases of postop. XII deficit	Postop. rate of XII deficit
Biller et al. [1989]	18	6	18	100%	4	12	66.7%
Browne et al. [1993]	15	8	14	87%	3	5	33.3%
Urquhart et al. [1994]	16	9	16	100%	0	5	31.2%
Miller et al. [2000]	16	7	14	87.5%	4	9	56.3%
Bradshaw and Jansen [2005]	10	2	10	100%	NA	5	50%
Zanoletti and Mazzoni [2006]	16	5	16	100%	2	4	25.0%
Present series	21	13	21	100%	6	11	52.4%
Total	112	50	109	97.3%	19+?	51	45.5%

Values denote numbers unless specified otherwise.
Preop. = Preoperative; Postop. = postoperative; X = vagus nerve; XII = hypoglossal nerve; NA = not available.

catheterization of these branches is a very difficult task because they are very small and tortuous; moreover, once the microcatheter is in place, the flow inside these muscular branches becomes slow, and the risk of reflux of embolizing material towards the vertebral artery is very high even with careful injection. Thus, embolization of branches of the vertebral artery should be undertaken in very selected cases: branches of considerable size and without tortuosity in order to allow superselective catheterization distal to their origin from the vertebral artery, as well as a sufficient flow towards the tumoral mass once the microcatheter is in place.

Due to its close anatomical relationship with the vagus nerve, the ICA is often affected by tumor and tends to be anteromedially displaced by VP. In cases of large VP usually more than 5 cm in diameter, the functional integrity of the circle of Willis and wall of the ICA is carefully scrutinized by MRI and intra-arterial angiography [Sanna et al., 2004b, 2009]. While displacement and partial encasement of the ICA seen on MRI associated with a normal angiographic study can be safely managed by microsurgical techniques, global encasement of the ICA as shown in axial MR sections is a finding that may predict a tedious surgical dissection of the wall of the ICA. Moreover, the angiographic sign of stenosis of the arterial lumen should heighten the suspicion of invasion of the adventitia of the ICA by VP.

Though Borba and Al-Mefty [1996] advocate that supra-adventitial dissection is adequate for ICA treatment in every case [tumor involvement of the ICA wall often leads to multimodal ICA treatment including PBO and stent insertion. Biller et al. [1989] presented 2 cases with ICA sacrifice and another 2 cases with bypass graft due to invasion of the carotid artery. Browne et al. [1993] reported 10 cases with preoperative or intraoperative balloon occlusion. Netterville et al. [1998] had 1 case with

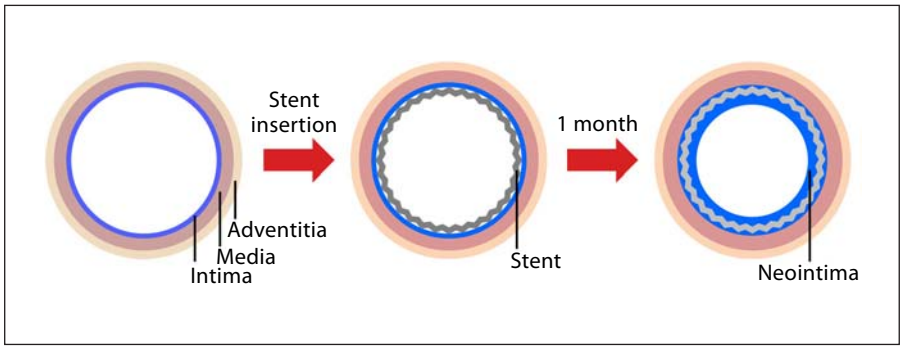

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Fig. 3. Changes in anatomy of the ICA after stent insertion. One month after the stent insertion, the neointimal layer is developed and subsequent subadventitial dissection can be safely performed.

sacrifice and 1 case with postoperative radiation for residual tumor around the ICA. Eriksen et al. [1991] proposed that a vascular surgeon must be available during the removal of VP should carotid injury occur or carotid sacrifice be necessary. Our recent experience with stenting of the ICA in TJP has led us to try this technique on VP [Piazza et al., 2007; Sanna et al., 2009]. The introduction of intraluminal stent insertion in patients with VP and TJP [Sanna and Flanagan, 2007; Sanna et al., 2006] has changed the concept of ICA treatment, which in the early period of our experience was based on PBO of the ICA. In cases of TJP, balloon occlusion of the ICA still maintains its role in the presence of extensive blood supply from branches of the ICA. This is not the case with VP, where the blood supply usually does not come from petrous and/or cavernous branches of the ICA, with the exception of huge stage III VP.

With the introduction of stents in surgical practice, tumor dissection from the ICA has become easier and safer than before, and total removal can be safely achieved without risk of carotid blowout. One month after stent insertion, a stabilized neointimal layer develops on the luminal surface of the stent (fig. 3). When the plane lateral to the stent is dissected, the stent together with the neointimal layer act as a barrier against surgical trauma so that the surgeon can easily establish a cleavage plane on the external surface of the stent and aggressively remove the tumor without the risk of blowout. In our series, 5 cases have safely undergone stent insertion for VP (tables 1, 5).

Early in our series, with cases No. 9, 10 and 11, we believed that stenting of the cervical portion of the ICA would be enough to allow safe surgical dissection of the carotid wall, but in case No. 9, we experienced a carotid blowout immediately beyond the distal end of the stent, near the entrance of the ICA to the carotid foramen. The wall of the ICA was successfully repaired, but angio-CT performed a few days later demonstrated occlusion of the artery. Fortunately, the occlusion happened without clinical consequences because this patient had a competent circle of Willis.

Thus, after this unpleasant experience and the knowledge accumulated with stenting of the petrous portion of ICA in TJP, we decided that in selected cases when the upper extremity of the VP reaches the skull base, contiguous stenting of the cervical and petrous segments of the ICA should be performed in order to allow safer surgical manipulation of the ICA. Stenting of petrous ICA is a more demanding procedure and carries a higher risk of vasospasm and ischemic complications. Moreover, the risk of failure is quite high because of the difficulty in advancing the device into the bony petrous carotid canal and the large amount of time spent on identifying a stent suitable for that difficult task. The ideal stent should possess a mixture of qualities that are technically difficult to combine in one device: it should possess a good tractability in order to pass beyond the knee between the vertical and horizontal portions of the petrous ICA canal, but it must also offer enough intraoperative support for surgical manipulation. The Carotid Wallstent is good for cervical stenting but is very difficult to pass through the carotid foramen into the petrous carotid canal. Softer stents such as the Neuroform and Leo (Boston Scientific, Natick) can be easily navigated in the petrous portion of ICA, but they do not give enough surgical support. The Xpert Stent has been shown to give very good intraoperative support for surgical manipulation, associated with good tractability in the petrous carotid canal, and has been employed successfully in 1 case of VP (case No. 6) and in a few cases of TJP. However, with the Xpert Stent, we also experienced a few failures, so we recently moved our attention to another kind of stent (Biotronik) which offers the same

save intraoperative support as the Xpert Stent, associated with very good tractability. This stent has been successfully utilized in a few cases of skull base tumors other than VP, but it will be our first choice in the next VP case needing stenting of a petrous ICA.

Each stent is carefully selected and tailored to the individual patient. With very tortuous ICA, a PBO still represents the safest option. The timing of reinforcement with stents also plays an important role; an interval of at least 4–6 weeks has been advocated between stenting and surgery to allow the formation of a stabilized neointimal lining on the luminal surface of the stent. One very special situation is worth mention: the presence of an important blood supply from the ICA. In these circumstances, a bare stent is unable to reduce the vascular supply to the tumor. Use of PBO, preoperative embolization with particles during temporary balloon occlusion of the ICA, or insertion of covered stents could represent an alternative solution.

In this series, the two surgical approaches used were the transcervical approach and the ITFA. Some authors assert that a median mandibulotomy might be required to control the ICA [Biller et al., 1989; Borba and Al-Mefty, 1996; Miller et al., 2000; Urquhart et al., 1994]. However, it can cause related complications including bony nonunion, palatal exposure and inadequate soft tissue coverage [Dai et al., 2003]. For a stage III VP or concurrent VP and TJP, the ITFA is preferred.

The deficit rate for the vagus nerve was 100% in this series. Netterville et al. [1998] and Miller et al. [2000] reported they could preserve the vagus nerve in only a few cases. Browne et al. [1993] tried segmental grafting of LCN and experienced disappointing results. Recently, Lamarre et al. [2010] reported promising results with laryngeal reinnervation after the resection of VP.

We compared the functional preservation rates for LCN in VP and TJP in table 6, which shows a far higher postoperative deficit rate for hypoglossal cranial nerves in VP compared with TJP. The hypoglossal nerve usually passes over the lateral aspect of the tumor in the parapharynx, and this makes it vulnerable to VP surgery. With tumor extension up to the jugular foramen, it is often involved by the tumor [Netterville et al., 1998]. Hypoglossal dysfunction usually results from surgical traction rather than sacrifice [Eriksen et al., 1991].

Dysphagia commonly occurs after VP surgery. Some authors advocate type I thyroplasty at the time of LCN injury to avoid postoperative aspiration [Netterville et al., 1998]. In our practice, 3 weeks of postoperative rehabilitation usually allows the patient to compensate for dysphagia. If the dysphagia still remains unchanged, a type I thyroplasty is performed. Eighteen cases had mild dysphagia or no dysphagia after surgery, most of whom had 1 or 2 LCN deficits. Therefore, it is unnecessary to perform type I thyroplasty during tumor removal. The other 3 cases with dysphagia did not compensate in spite of intensive rehabilitation. Of these cases, 1 did not overcome dysphagia due to bilateral hypoglossal palsies, and the other 2 possibly due to poor compensation secondary to advanced age.

One case (case No. 6) had a recurrence, which probably resulted from aggressive tumor characteristics and imprecise staging. To prevent recurrence, precise staging – particularly concerning skull base erosion or jugular foramen involvement – is essential, and lifelong follow-up is necessary for detection of recurrent tumors [Biller et al., 1989; Browne et al., 1993; Leonetti and Brackmann, 1989].

Conclusion

Surgical management of VP is currently considered the treatment of choice. Accurate diagnostic imaging and preoperative surgical planning are extremely important for successful VP surgery. In younger patients with VP, surgery should be encouraged due to excellent compensation for any postoperative dysphagia. The proper preoperative endovascular intervention (balloon occlusion or stenting) and selection of approach facilitate gross total removal and avoid all the possible complications associated with ICA management. In the management of bilateral or familial paragangliomas, precise and appropriate decision making is essential, and lifelong follow-up is necessary in patients with genetic mutation of SDHB or D.

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Disclosure Statement

None.

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