Contemporary Management of Jugular Paraganglioma

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Preface

Despite being the most common tumor of the jugular foramen, Jugular Paragangliomas are rare tumors. The nature of these tumors and their close proximity to neurovascular structures such as the lower cranial nerves and the internal carotid artery render optimal management challenging. To date there is no clear consensus regarding treatment—some centers advocate for operative treatment in most cases, while others frequently utilize upfront radiosurgery. With refinements in neuroimaging and radiation delivery techniques as well as a better understanding of the pathology, there has been a paradigm shift toward conservatism, prioritizing maintenance of function and quality of life over disease eradication. In this book *Contemporary Management of Jugular Paraganglioma*, a cadre of international experts has contributed to create a comprehensive publication that details the evaluation and management of jugular paraganglioma. We wish to thank all our contributors for their outstanding chapters and hard work which was essential to complete this task.

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Chapter 1
History of Jugular Paraganglioma

Sunshine Dwojak, James L. Netterville, and Alexander Langerman

The first description of paraganglia of the temporal bone was by Stacy R. Guild, an anatomist from Johns Hopkins School of Medicine (Fig. 1.1). In a brief presentation at the American Association of Anatomists at the University of Chicago in April of 1941 entitled "A hitherto unrecognized structure, the Glomus Jugularis, in man," Guild wrote: "Human temporal bone sections reveal structures in several respects like the carotid body, for which the name glomus jugularis is proposed. Usually they are in the adventitia of the dome of the jugular bulb, immediately below the bony floor of the middle ear and near the ramus tympanicus of the glossopharyngeal nerve…. Each glomus, wherever located, consists of blood vessels of capillary or precapillary caliber with numerous epithelioid cells between vessels. Usually, but not always, the vessels are the more prominent feature. Innervation and blood come from the same trunks that supply the carotid body; namely, glossopharyngeal nerve and ascending pharyngeal artery (through its inferior tympanic branch). Presumably it has functions like the carotid body, perhaps limited to a smaller circulatory region. Suggestion: similar structures may be present along other parts of the peripheral circulatory system" [1].

In 1945, Harry Rosenwasser reported a case of a 36-year-old male presenting to Mount Sinai Hospital with a growth of the left ear and a 10-year history of hearing loss (Fig. 1.2). "He had a facial paralysis and a large, red mass in the ear." Standard roentgen exams showed "good pneumatization, but clouding of the periantral region

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Fig. 1.1 Stacey Rufus Guild, Ph.D. (1890–1966) (From: Ruben RJ. The history of glomus tumors—nonchromaffin chemodectoma: a glimpse of biomedical Camelot. Acta Oto–Laryngologica. 2007;127:411–416)

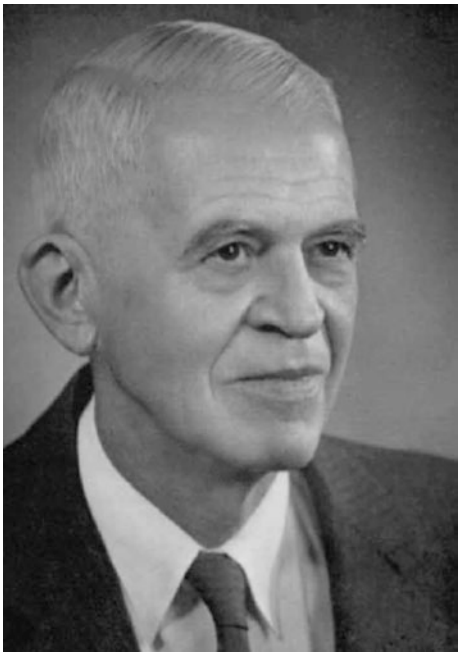

Fig. 1.2 Harry Rosenwasser, MD (1902–1987) (From: Ruben RJ. The history of glomus tumors—nonchromaffin chemodectoma: a glimpse of biomedical Camelot. Acta Oto–Laryngologica 2007;127:411–416)

and decalcification of the septums in the perisinal region." On April 18, 1942, Rosenwasser performed an exploratory radical mastoidectomy and encountered "excessive bleeding" of the bone; the facial nerve was embedded in "vascular granulation tissue." When the canal wall was taken down, the middle ear was filled with "a large purple mass, which appeared continuous with the mastoid tip." He felt no bone on the floor of the middle ear and believed that the tumor could be involved

with the jugular dome. Only the middle ear portion of the tumor was excised, leaving the hypotympanic disease behind [2].

Based on his operative findings, Rosenwasser felt that this must be some sort of aggressive malignant tumor. So while waiting for final pathology, the patient received radiation therapy. The pathology report returned showing "large tumor cells in groups, separated by dense fibrous tissue septums, which contain dilated veins. The groups of tumor cells are bordered by capillaries and form small alveolar structures. The general histologic picture, however, is that of a carotid body tumor." Referring to Guild's report in 1941, Rosenwasser states "The possibility of the tumor herein reported may have developed from the glomus jugularis, first named by Guild, is tentatively proposed" [2]. Dr. Rosenwasser sent printed reports of this paper to Stacey R. Guild. The two men then began a correspondence, and Guild agreed that the tumor indeed may have grown from the glomus jugularis [3].

Over the next several years, multiple case reports of glomus jugularis tumors were reported in the literature in an attempt to further elucidate their character and behavior. In 1949, Lattes and Waltner reported eight cases in New York in addition to the ten cases found in the literature. They propose a correction to the naming of the tumor. "The correct Latin diction should be "glomus jugulare," not "glomus jugularis," because the Latin noun "glomus" is neuter." Within this report, we get the first clinical characteristics of glomus jugulare tumors; the tumors are slow growing, present with pulsatile tinnitus, and bleed easily. Two of the reported tumors metastasized, one to a lymph node and one to the liver. In these early reports, tumors were generally treated with a combination of radical mastoidectomy and radiation therapy (Fig. 1.3). Pathologically, they describe the tumors similar to Guild as "highly vascular, and the walls of most of the blood vessels are limited to an endothelial lining. In the vascular network, are ribbons and round nests of cells that are usually referred to as epithelioid" (Fig. 1.4) [4]. Until this point, the anatomic origin of these tumors remained unclear, and there was still speculation that glomus jugulare tumors may represent metastasis from carotid body tumors. Lattes and Waltner report that serial sections show glomus bodies in the dome of the jugular bulb, reported by Guild, but also "along the course of the tympanic nerve, in its bony canal, and in the bone of the promontorium, very near the mucosal lining of the middle ear." They postulate that some of these tumors originate in the middle ear and argue for recognizing the entity of "paraganglia tympanicum" (Fig. 1.5) [4].

In 1951, Weille and Lane published their experience from the Massachusetts Eye and Ear Infirmary detailing the operative difficulties of glomus tumors, including the risk of bleeding, facial paralysis, and the difficulty of identifying anatomic landmarks during the operation. They assumed that the tumor originated from the dome of the jugular bulb, "from which the most violent bleeding is expected to occur." In order to account for this, they report leaving a "small bit of neoplasm in the floor of the hypotympanum until the tumor is widely exposed." Then they proceed with rapid dissection and removal of all gross tumor except disease in the floor of the hypotympanum. Weille and Lane felt that compressing the lateral sinus and tying off the internal jugular vein would not control the blood flow from the inferior petrosal veins, or the arterial supply from the ascending pharyngeal artery; "therefore, we feel that the bulb must be spared" [5].

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TABLE I — NONCHROMAFFIN PARAGANGLIOMA OF MIDDLE EAR

Author	*Age*	*Sex*	*Chief complaint*	*Dura. of sympt. when first seen*	*Side*	*Ext. auditory canal*	*Middle ear*
Capps 1944	49	F	Deafness and pain, left ear	12 Yrs.	Left	Polypoid swelling	Highly vascular polypoid mass (oper. finding)
Capps 1944	51	F	Long history, chronic suppurative otitis media (rt.); discharge, deafness, earache, slight facial weakness	20 Yrs. (about)	Right	Polyp filling right meatus	Filled with polypoid, highly vascular mass
Rosenwasser 1945	36	M	Deafness; weakness of left facial nerve	10 Yrs.	Left	Filled with reddish mass	Filled with tumor (oper. finding)
Kipkie 1947	39	F	Discharge from ear	10 Yrs.	Left	Filled with "polyps"	Filled with tumor extending into mastoid cells (oper. finding)
LeCompte, Sommers, and Lathrop 1947	43	F	Recurrent "polyps" in external ear canal	10 Yrs.	Left	Filled with "polypoid mass"	Contained "polypoid tumor" (oper. finding)
Winship 1948	54	F	Nausea, dizziness, discharge, then deafness (left), paralysis of 7, 8, 10, 11, 12 nerves	5 Yrs.	Left	Hemorrhagic "granulations"	Involved (x-ray finding)
Winship 1948	81	M	Left facial paralysis, deafness, tinnitus, dizziness, discharge	4 Yrs.	Left	Red mass apparently coming from middle ear	Filled with red tumor (oper. finding)
Köhlmeier & Czurda 1948	48	M	Left facial paralysis treated with faradic current; deafness	6 Yrs.	Left	Pulsating polypoid mass	Filled with soft tumor masses (oper. finding)
Köhlmeier & Czurda 1948	67	M	Discharge, buzzing, bleeding from right ear. "Blood tumor" removed 5 yrs. prev.	5 Yrs.	Right	Grayish-red polypoid hemorrhagic tumor masses	Not known
Poppen & Rienmenschneider (private communication by LeCompte)	26	F	Tinnitus, diplopia, nystagmus, weakness rt. palate and facial nerve. "Brain abscess" drained	Not known	Right	Polypoid mass	Filled with tumor involving mastoid and petrous bone (autop. finding)
Columbia Univ. (S.P. 43544) R.M.	60	F	Mass rt. ear canal, loss of hearing. Nine prev. removals of "polyps"; deafness	20 Yrs.	Right	Filled with firm pedunculated tumor	Apparently uninvolved (?)
Columbia Univ. (S.P. 62030) H.K.	23	F	Discharge left ear, dizziness, loss of hearing. "Stuffed ear"	4 Yrs.	Left	Filled with polypoid growth; foul discharge	Probably involved (oper. finding)
Columbia Univ. (P.&S. 15415) M.E.	71	F	Facial paralysis, difficulty in swallowing, hoarseness, trigeminal neuralgia, left side (chr. otitis media since childhood)	9 Mos.	Left	"Papillomatous growth" protruding from canal. Drum destroyed	Involved (autop. finding)
Columbia Univ. (S.P. 82404) E.R.	77	F	Discharge rt. ear, rt. facial paralysis, deafness, difficulty in swallowing, dizziness, nystagmus	5 Yrs.	Right	Completely filled with a polypoid mass; fetid discharge	Involved (oper. findings)
Columbia Univ. (P.&S. 21102) M.P.	38	F	Biopsy submitted from outside doctor—no history	Not known	Left	Filled with "Papillomatous mass"	Not known
Columbia Univ. (S.P. 98018) E.F.	30	F	Pain, buzzing in ear synchronous with pulse, impaired hearing, headache	2 Yrs.	Left	Circumscribed bulging of ear drum; no masses	Filled with vascular tumor mass (oper. finding)
Columbia Univ. (S.P. A-8955) M.H.	47	F	Earache, buzzing in ear synchronous with pulse	2 Yrs.	Right	Circumscribed bulging of ear drum; no masses	Filled by vascular tumor (oper. finding)
Columbia Univ. (P.&S. 29084) A.C.	40	M	Discharge left ear since childhood. One yr. ago, pain and dizziness. More recently dysphagia and hoarseness	1 Yr.	Left	Filled with hemorrhagic granulation tissue	Filled with tumor tissue (oper. finding)

Fig. 1.3 Eighteen reported cases as of 1949 (From: Lattes R, Waltner JG. Nonchromaffin paraganglioma of the middle ear; carotid–body–like tumor; glomus–jugulare tumor. Cancer 1949;2: 447–68)

TABLE 1 (*Continued*)

Preoperative clinical diagnosis	*Path. diagnosis on biopsy*	*Surgical treatment*	*Operative findings*	*X-ray therapy*	*Follow-up, complications*
Chronic infection, cholesteatoma	No biopsy	Radical mastoidectomy	Polypoid, highly vascular tumor arising from region of eustachian tube; profuse bleeding	Radium	Followed 3 yrs. No recurrence. Published under diagnosis of hemangioendothelioma.
Chronic infection, acute mastoiditis	No biopsy	Radical mastoidectomy	Highly vascular polypoid tumor arising from inner tympanic wall; profuse bleeding	No	Followed 11 mos. No recurrence. Published under diagnosis of hemangioendothelioma
Chronic mastoiditis	Granulation tissue	Radical mastoidectomy	Middle ear filled with tumor and facial nerve involved; destruction of bony floor of middle ear	Yes	Followed 2 yrs. No recurrence of tumor
Polyps of external canal	Angiomatous polyp	2-Stage radical mastoidectomy	Middle ear and mastoid cells involved by tumor	No	Recurrence. Death after 10 yrs. following attempt at removal of assoc. tumor of rt. carotid body. Autopsy showed extensive destruction of left temporal bone
Chronic mastoiditis	Not known	Radical mastoidectomy	Polypoid tumor region eustachian tube, anterior to promontory, eroding bone; profuse bleeding	No	Postop. facial paralysis, followed 1 yr. No recurrence
Cholesteatoma, then tumor	Biopsy cervical lymph node: glomus-jugularis tumor	Fulguration, radium needles, x-rays	No ear operation	Yes; also radium	12-yr. follow-up. Paralysis 7, 8, 10, 11, 12 nerves. Extensive destruction left temporal bone. Ataxia. Metastasis to cervical lymph node
Not known	Not known	Radical mastoidectomy	Tumor arising from region of jugular bulb	Radium	Followed 17 yrs. No recurrence. Deafness and facial paralysis still present
Polyps of external ear	"Highly vascular" tumor	Radical mastoidectomy	Middle ear, antrum and neighboring mastoid cells filled with soft tumor masses; profuse bleeding	No	Died 10 days after oper. with signs of meningitis. Autopsy: neoplastic destruction of petrous bone and extension into extradural space. Published as probable glomus tumor
Angiomatous tumor	Carotid-body-like tumor	Not known	Not known		No follow-up in published report. Published under tentative diagnosis of carotid-body-like tumor
Brain abscess or tumor	Not known	(1) Drainage "brain abscess"; (2) removal vascular tumor compressing cerebellum	Large vascular tumor mass compressing cerebellum and medulla on right side	No	Died 4 yrs. after operation. Autopsy showed invasion of petrous bone and mastoid by tumor tissue.
Tumor (?) ext. ear canal	Not known	Excis. tumor ext. canal, fol. by cauterization	Pedunculated tumor; profuse bleeding	No	Followed 2 yrs. At last visit a red mass seen in ext. canal protruding from middle ear. Total loss of hearing. (Prev. classified as granular-cell myoblastoma)
Tumor (?) ext. ear canal	Granuloma	Excis. tumor ext. canal (2-stage oper. because of bleeding)	Highly vascular tumor probably involving middle ear	Yes	Followed 5 yrs. No tumor seen on last visit. No improvement in hearing. (Prev. classified as capillary hemangioma)
Tumor ext. ear canal	(1) Basal cell epithelioma; (2) undiagnosed tumor	Excis. polypoid masses, ext. ear	Pedunculated tumor external ear	Yes; also radon seeds	After x-ray treatment, 5th- and 9th-nerve symptoms subsided, but facial paralysis persisted. Died about 2 yrs. after onset of symptoms. Autopsy: extensive involvement middle and ext. ear and extens. into cranial cavity. Metastasis in liver
Chronic mastoiditis	(1) Polyp; (2) granuloma	Radical mastoidectomy (2-stage oper. because of bleeding)	Tumor arising in middle ear; severe bleeding	No	Died 2½ yrs. after operation, in another hospital, with symptoms of paralysis of 7, 9, 12 nerves on right side. No autopsy performed. (Prev. classified as granular-cell myoblastoma)
(?) Growth ear canal	(1) Granuloma; (2) adenoma of ceruminous glands	Local excision	Large "papilloma"; severe bleeding	Not known	Followed 3 yrs. When last seen, presented no recurrence in ear, but a bilat. cervical swelling interpreted clinically as carotid-body tumors. (Prev. classified as adenoma of probable ceruminous-gland type)
Tumor middle ear	Granuloma	Radical mastoidectomy	Vascular tumor filling middle ear; profuse bleeding	Yes	Followed 3 yrs. No recurrence
Paraganglioma middle ear	Paraganglioma, middle ear	Radical mastoidectomy	Vascular tumor filling tympanic cavity apparently arising from hypotympanum	No	A partial facial-nerve weakness developed immediately after operation
Chronic mastoiditis (?)	Angiomatous granulation tissue	(1) Radical mastoidectomy; (2) revision of mastoidectomy cavity	Destruction of bone ant. wall of extern. canal; reddish tumor mass filling cavity of previous oper.	Yes	Before operation there was paralysis of 9, 10, 11 nerves. Following oper. there occurred a facial paralysis. Patient died 1 mo. postop. with symptoms of left cerebellar abscess. Autopsy: destruction of whole petrous portion of temporal bone and an abscess of left lobe of cerebellum

Fig. 1.3 (continued)

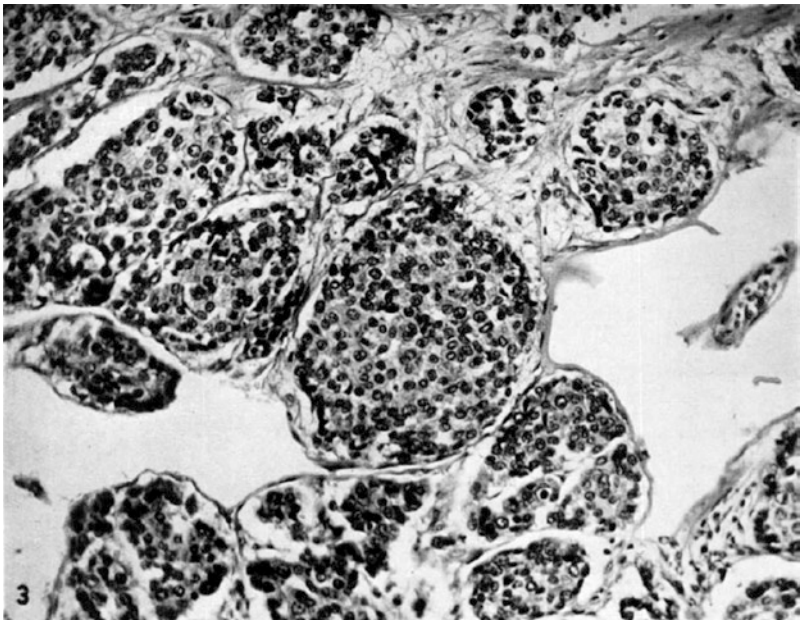

Fig. 1.4 Pathology from early reports of glomus jugulare. Solid tumor nests adjacent to endothelial-lined spaces (From: Lattes R, Waltner JG. Nonchromaffin paraganglioma of the middle ear; carotid–body–like tumor; glomus–jugulare tumor. Cancer 1949;2:447–68)

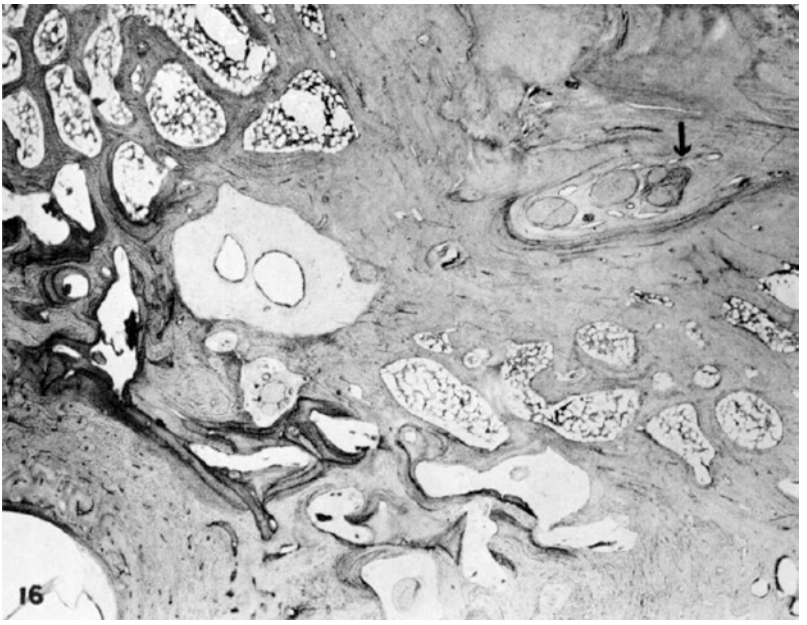

Fig. 1.5 Paraganglionic tissue associated with the tympanic nerve (From: Lattes R, Waltner JG. Nonchromaffin paraganglioma of the middle ear; carotid–body–like tumor; glomus–jugulare tumor. Cancer 1949;2:447–68)

In their report, Weille and Lane relay a conversation held between the surgeons and radiation oncologists when discussing the merits of adjuvant radiation following subtotal tumor removal: "The specialist from the X-ray department there made the following answer 'The histology of glomus tumor arising in the ear is essentially that of glomus tumors elsewhere in the body. They are notoriously radioresistant, and there is no reason to presume that those in this location should be more responsive. The literature is quite wanting in any enthusiastic statement regarding the value of X-ray treatments, although a number have been recorded. Treatment is not without hazard to the normal tissues in which the tumor lies, and I would not recommend this procedure.'"

In 1952, Winship performed a comprehensive review of the literature up to that point, including 65 cases of histologically proven glomus jugulare tumors. Clinically, most patients presented with a long history of hearing loss and a mass in the external auditory canal. In advanced cases, further symptoms of tinnitus, dizziness, pain, and paralysis of the cranial nerves occur. The average age of the patients in his review was 44 years, with a range from 17 to 80 years, and 85% were women. By this time, the pathology was classically described as "cuboidal cells with eosinophilic, finely granular cytoplasm and prominent vesicular nuclei. The nests of cells are separated by thin, vascular strands of fibrous tissue. Mitosis is rare even in the obviously malignant cast" (Fig. 1.6) [6]. In this publication, Winship reports on early treatment and outcomes. Radiation following biopsy was used to treat only six cases. Of these six, one patient died soon after treatment, but others were still living and one had even been followed for 20 years. The remaining 59 patents were treated

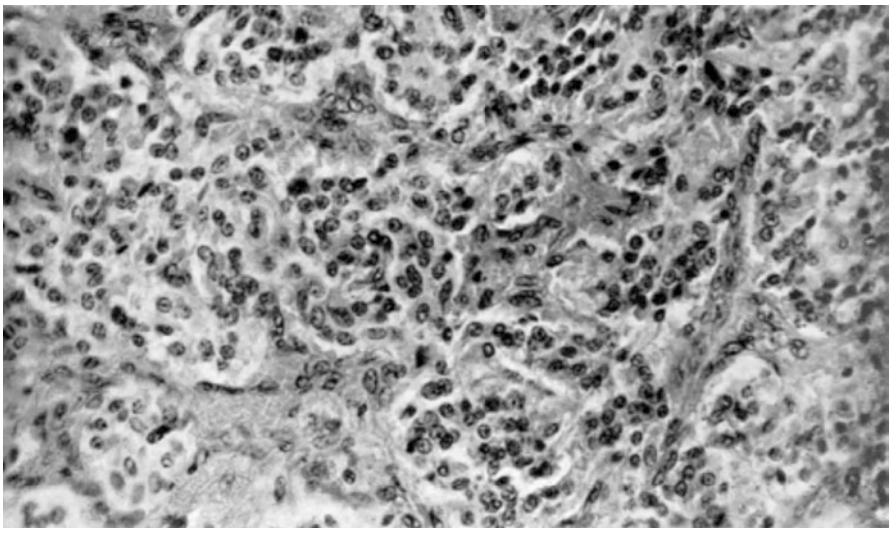

Fig. 1.6 Characteristic nests of epithelioid cells, separated by a vascular, fibrous network (From: Winship, T., B. Godwin, and E. V. Creveld. "Glomus Jugulare Tumours." Archivum Chirurgicum Neerlandicum 4, no. 4 (1952): 249–54)

with surgery, and most were followed for at least 4 years with an overall mortality rate of 21.5%. Based on these findings, Winship concluded that glomus jugulare tumors might be controlled for long periods of time with radiation and that early recognition was needed in order to facilitate prompt treatment and reduce patient mortality [6].

Brown's seminal report published in 1953 provides us with the first description of the "pulsation sign" with tumor blanching to aid in diagnosis, early descriptions of X-ray findings, as well as the first description of angiography in a glomus jugulare tumor. The "pulsation sign" is meant to diagnose a glomus tumor on otoscopy: "The patient is placed in the sitting position. By fitting the external auditory canal with an aural speculum large enough to seal off the canal, and while looking through the magnifying otoscope, if the air pressure is increased in the external auditory canal, through the otoscope, by means of compressing the attached rubber bulb, the tumor will be seen to pulsate, sometimes almost violently. As the air pressure is increased by more compression of the rubber bulb, the tumor will blanch, and the pulsation will decrease. Then, as the air pressure is reduced by less compression of the rubber bulb, the pulsation of the tumor will return, until the normal room pressure has been reached, at which time the pulsation will again subside, or return to the pretest spontaneous pulsation" [7].

In Brown's original description of early imaging characteristics of glomus tumors, he admits that an X-ray may not be helpful in the diagnosis, as "in the earliest stages of the disease, no changes are seen in the films." However, "as the disease progresses, the mastoid cellular structure becomes Roentgenographically cloudy… If there is any characteristic X-ray evidence of the glomus jugulare tumor, it is the picture of the mastoid and petrous cells being 'rubbed into coalescence.' There is not so much demineralization as is seen in acute surgical infection; there is not sclerosis that appears in long-standing chronic infection of the mastoid bone; there is not the complete obliteration of the bone as is seen in cancer of the temporal bone."

Brown pioneered the arteriogram by injecting X-ray opaque solution into the carotid system. Unfortunately, in his experiments, diagnostic imaging studies did not demonstrate any radiologic abnormalities. In an effort to reduce operative blood loss, Brown injected sclerosing solution into the tumor in two cases; however, no changes were noted in the tumors after the injection. He also tried to ligate the external carotid artery, distal to the superior thyroid, but proximal to the ascending pharyngeal artery in one patient; however "bleeding seemed to be as severe as it was in each case where the artery was not ligated" [7]. In his surgically treated cases, Brown describes preparing the radical mastoid cavity first, then teasing the tumor from the periphery of the middle ear with an elevator, and then finally lifting the tumor out of the middle ear. Following rapid tumor extirpation, Brown controlled bleeding with Gelfoam packing. Each of his five cases required 500 cc of transfusion. Seven to 10 days after surgery, adjuvant radiation was routinely given in doses of 2500–4800 rads [7].

In 1953, Guild reports again on the anatomy of the normal jugular body in 88 ears. In this report, Guild confirms that glomus bodies are associated with the

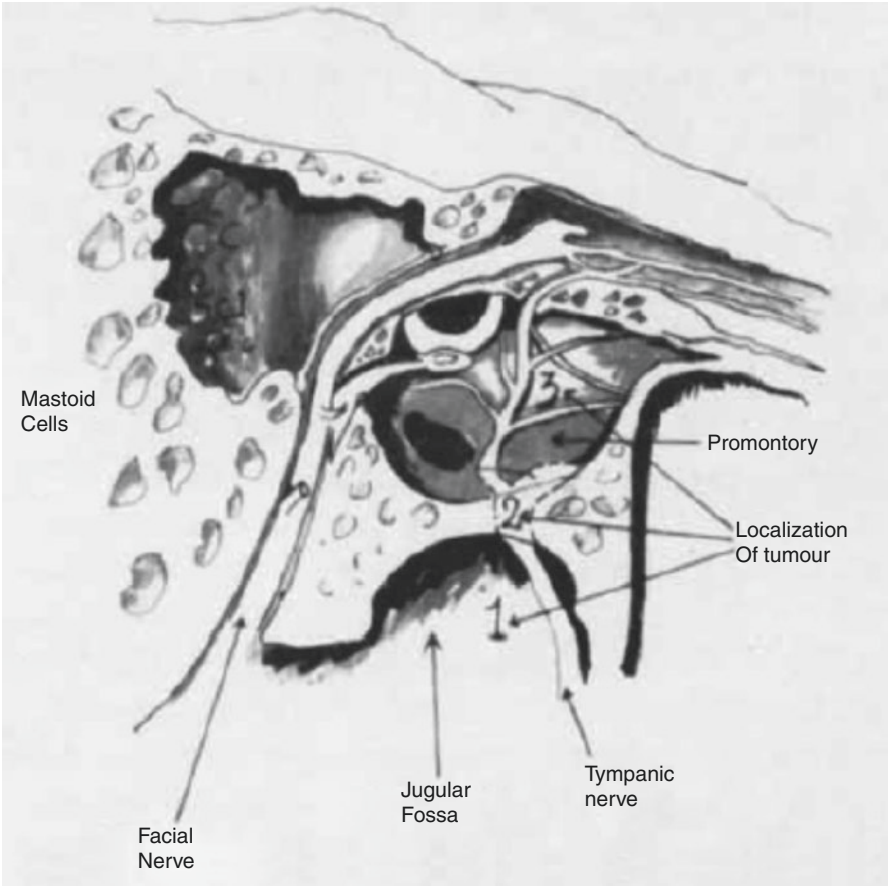

Fig. 1.7 Predilection of the glomus bodies: (1) The adventitia over the jugular dome, (2) along the tympanic nerve, and (3) along the auricular branch of the vagus nerve (From: Gejrot, T. "Surgical treatment of glomus jugulare tumours with special reference to the diagnostic value of retrograde jugulariography." *Acta Oto-Laryngologica* 60 (August 1965): 150–68)

tympanic branch of the glossopharyngeal nerve and with the auricular branch of the vagus nerve and are found in the adventitia over the jugular bulb and the mucosa of the cochlear promontory (Fig. 1.7). He further confirms that the blood supply is from the ascending pharyngeal artery from the tympanic branch (Fig. 1.8). He notes that the tympanic branch "accompanies the nerve of Jacobson and in the jugular fossa often gives off a branch that accompanies the nerve of Arnold. Given these anastomoses it may not be the sole source of blood" [8].

In 1955, Shambaugh, from the University of Chicago, presented the new endaural "hypotympanotomy" surgical approach to glomus tumors that would preserve hearing. Up until this point, radical mastoidectomy was the treatment of choice. The first two patients had significant bleeding when they encountered the tumor at the jugular bulb, so they then began ligating the internal jugular vein and tying off

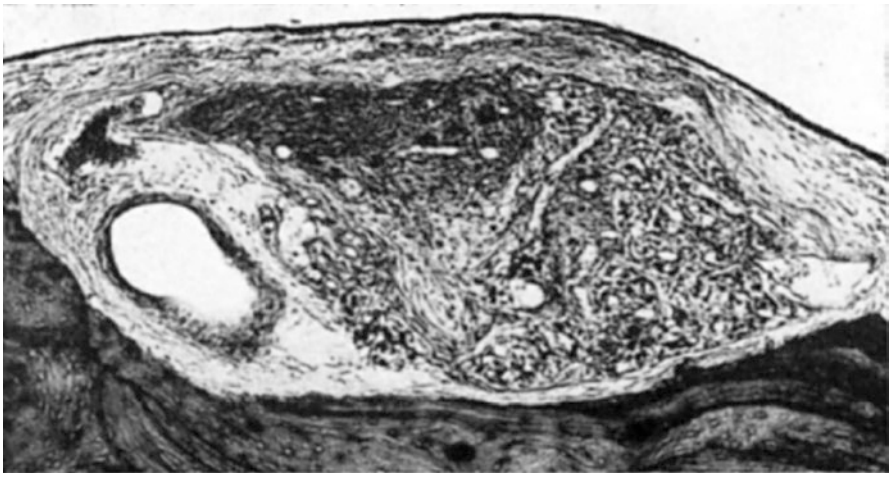

Fig. 1.8 Photomicrograph of glomus with rich vascularity. The artery is the tympanic branch of the ascending pharyngeal artery (Guild, S. R. "The glomus jugulare, a nonchromaffin paraganglion, in man." *The Annals of Otology, Rhinology, and Laryngology* 62, no. 4 (December 1953): 1045–71; concld)

the external carotid artery. They then exposed the tumor via an endaural hypotympanotomy. "The hypotympanum and jugular bulb were then exposed by resecting the entire tympanic bone forming the anterior, inferior, and posterior osseous meatal wall until the ascending portion of the carotid artery in its bony canal, the facial nerve emerging from the stylomastoid foramen and the jugular bulb with the attached tumor protruding into the tympanic cavity lay fully exposed. This was done without any attempt to remove or mobilize the tumor. Only when the tumor lay fully exposed was it rapidly dissected away from the dome of the jugular bulb, using a small periosteal elevator, with constant suction for the profuse bleeding. After this the point of origin at the jugular bulb is cauterized using a topical sclerosing solution" (Fig. 1.9). Both patients have no evidence of recurrence 2 and 5 years from surgery.

In 1955, Williams reported a series of patients who received external beam radiation therapy from the Mayo Clinic [9]. The patients all had extensive jugular tumors presenting with cranial nerve deficits and received between 1080 and 4000 roentgens over 1–2 weeks. Five cases were treated with radiation alone and eight received adjuvant radiation following subtotal resection. Among those patients receiving primary radiation therapy, they reported "little evidence of regression of the tumor"; however, there was growth of the lesion in only one case. This patient initially received 1230 roentgens and was given an additional 1500 roentgens establishing tumor arrest. In the eight cases receiving radiation therapy following incomplete resection, the authors reported: "In all cases when operation alone was used, the advance of the tumor seemed to continue unabated until irradiation was used…We believe that it is fair to conclude that radiation therapy has a definite therapeutic effect on chemodectomas of the glomus jugulare. The results seem to indicate that

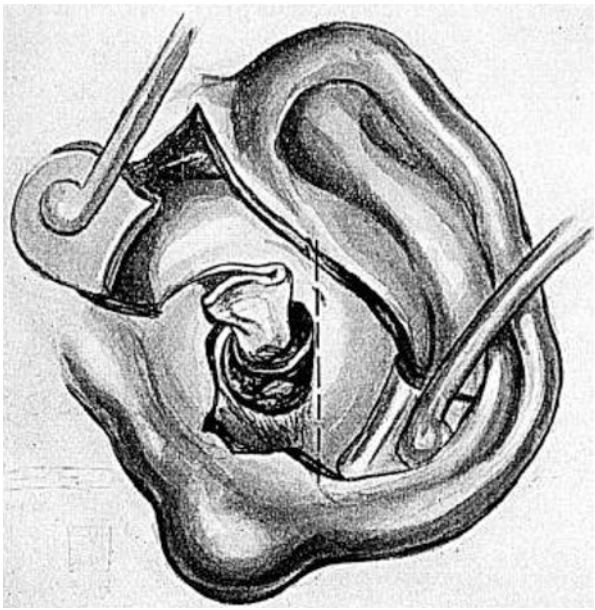

Fig. 1.9 Endaural exposure for the hypotympanotomy approach described by Shambaugh. The bone is removed anterior to the vertical line through the posterior meatal wall to preserve the facial nerve (From: Shambaugh, G. E. "Surgical approach for so-called glomus jugulare tumors of the middle ear." *The Laryngoscope* 65, no. 4 (April 1955): 185–98)

Fig. 1.10 Presenting symptoms in 316 glomus jugulare tumors (From: Alford, B. R., and F. R. Guilford. "A comprehensive study of tumors of the glomus jugulare." *The Laryngoscope* 72 (June 1962): 765–805)

Tumors of the Glomus Jugulare

	Presenting Symptoms. (277 suitable cases.)	
Hearing Loss	249 cases	91%
Tinnitus	145 cases	52%
Facial Paralysis	91 cases	33%
Discharge	90 cases	33%
Pain	77 cases	28%
Vertigo	67 cases	25%
Hemorrhage	45 cases	16%
Palsy IX	57 cases	21%
X	71 cases	26%
XI	51 cases	19%
XII	62 cases	22%

if surgical procedures are used, they should always be combined with radiation therapy….It seems probable in the future that cases of chemodectomas may be best treated with radiation therapy alone" [9].

In 1962, Alford published a literature review of all 316 published cases in the literature, including 11 from their own experience at Baylor University in Houston. They note the "slow, incipient growth of the tumor." In their report, the average interval of symptoms prior to diagnosis was 6 years. Again, a female preponderance is reported with 66% of cases occurring in women. Presenting symptoms were similar to those previously reported, with the most common being hearing loss and tinnitus (Fig. 1.10) [10].

Of the 316 cases, 183 included results of various imaging studies. Seventy-eight percent had abnormal findings including 36% with clouding, 37% had erosion of the petrous bone, 33% with erosion of the mastoid, 10% with erosion of the jugular foramen, and two patients had erosion of the foramen lacerum or foramen magnum. Angiography was performed in nine cases and showed the tumor in five of those cases. Seven patients also had concomitant carotid body tumors. Metastatic lesions were reported in six patients: two to the liver, two to the neck, and two to the ribs. Based on his review, Alford devised a classification scheme in an attempt to correlate the results of treatment with location and size of the tumor. He identified five stages based on symptoms, physical exam findings, and imaging results (Fig. 1.11). Based on this staging schema, Alford was able to show that there was a significant difference in outcome based on stage (Fig. 1.12) and proposed the following treatment algorithm: "For stage 0 tumors, surgical removal by tympanotomy or

	Symptoms	Ear Findings	X-rays	Cranlal Nerves and Other
Stage 0:	Hearing loss and/or Pulsating tinnitus	Normal hearing or Conductive loss Intact but dis-colored tympanic membrane	Normal	Normal
Stage I:	Hearing loss Pulsating tinnitus Discharge	Conductive loss Bulging tympanic membrane or polypoid mass external canal	Clouding but no bone erosion	Normal
Stage II:	Hearing loss Pulsating tinnitus Facial paralysis Discharge	Perceptive loss Bulging tympanic membrane or polypoid mass external canal	Clouding but no bone erosion May have slight enlarged jugular foramen	Paralysis Facial
Stage III:	Hearing loss Pulsating tinnitus Facial paralysis Discharge Maybe vertigo Hoarseness	Perceptive loss Bulging tympanic membrane or polypoid mass external canal	Erosion of petrous and / or enlarged jugular foramen	Paralysis IX, X, XI, XII and/or Facial Palsy
Stage IV:	All above and Intracranial Symptoms	As above	Erosion Petrous and other parts skull	Papilledema Palsy IX, X, XI, XII, and III, IV, V or VI, Metastasis

Fig. 1.11 First classification/staging scheme for glomus jugulare (Alford 1962)

Stage	Total Cases	No Recurrence	Persistent Tumor No Progression	Progressed	Died	No Treatment
Stage 0	27	25 (94%)	1 (3%)	0	0	1
Stage I	57	44 (77%)	4 (7%)	8 (14%)	1 (2%)	0
Stage II	37	20 (54%)	9 (24%)	5 (12%)	1 (3%)	2
Stage III	62	10 (16%)	24 (39%)	11 (17%)	14 (22%)	3
Stage IV	21	0	3 (14%)	2 (10%)	16 (76%)	

Fig. 1.12 Outcome based on stage (From: Alford, B. R., and F. R. Guilford. "A comprehensive study of tumors of the glomus jugulare." *The Laryngoscope* 72 (June 1962): 765–805)

hypotympanotomy technique of Shambaugh can usually result in complete removal. If surgical exploration reveals a true glomus jugulare tumor, radiotherapy followed by surgery is indicated. For stage 1 and 2 lesions radical mastoidectomy followed by radiotherapy is recommended. Stage 3 lesions appear to be controlled by therapeutic doses of radiation, and we believe this to be the preferred treatment as it would be unusual for all the tumor to be removed by present surgical techniques. For stage 4 lesions, it appears that palliation by radiotherapy and neurosurgical decompression when applicable is all that is indicated" [10].

Before the early 1960s, determining tumor extent preoperatively based on imaging was difficult. It was during this time that new imaging modalities were developed to allow for more precise preoperative planning. In 1964, Gejrot and Lauren described the process of retrograde jugulariography: "The tip of the catheter is placed in or just below the superior jugular bulb. Twenty milliliters of 45% urografin is injected with the highest possible manual pressure; two or three films are then exposed while the vein is compressed distally. Two routine projections are used, namely, the usual occipital projection angled 30 degrees in the caudal direction, and a lateral projection, slightly oblique to avoid over-projection from the other side" (Fig. 1.13).

Normal jugulariograms were able to show both jugular veins with the sigmoid sinus filled with contrast, while an abnormal jugulariogram showed constriction at the site of the tumor (Figs. 1.14 and 1.15). They used this technique in 12 cases of possible glomus tumors, and 11 of these were positive. The one patient with a negative exam died of a pulmonary embolism in the hospital, and at autopsy a "rice grain"-sized tumor was found in the jugular bulb, likely too small to correspond to a filling defect. They performed angiography in ten cases at the same time and only four were positive, clearly demonstrating the increased sensitivity over angiography. With this new technique, clinicians were able to accurately assess the extent of the tumor before surgery [11].

In 1964, Shapiro reported on a new surgical technique permitting complete surgical removal. He described the use of hypothermic-hypotensive anesthesia and the

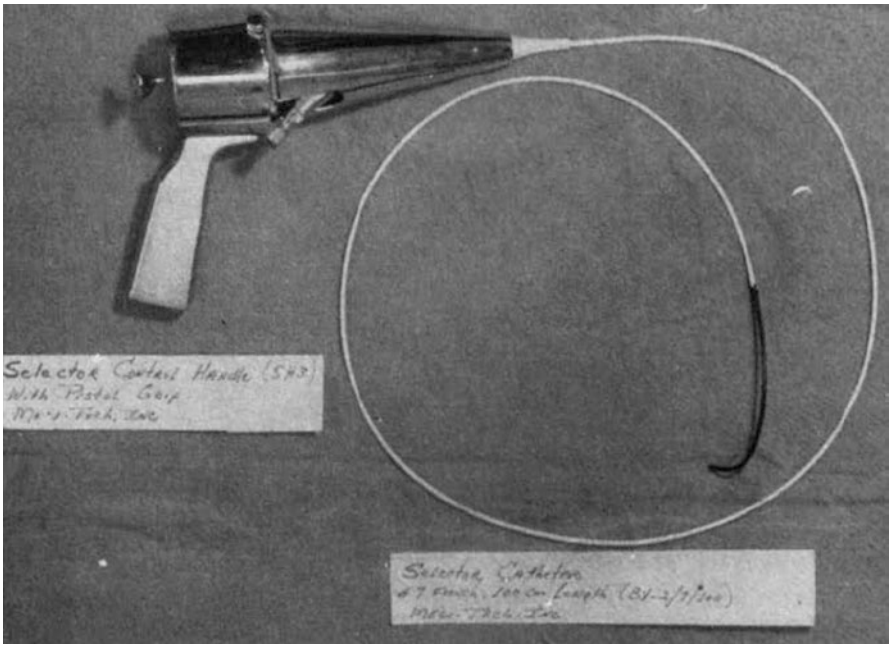

Fig. 1.13 Catheter used to perform retrograde venograms (From: Glasscock, M. E., P. F. Harris, and G. Newsome. "Glomus Tumors: Diagnosis and Treatment." *The Laryngoscope* 84, no. 11 (November 1974): 2006–32)

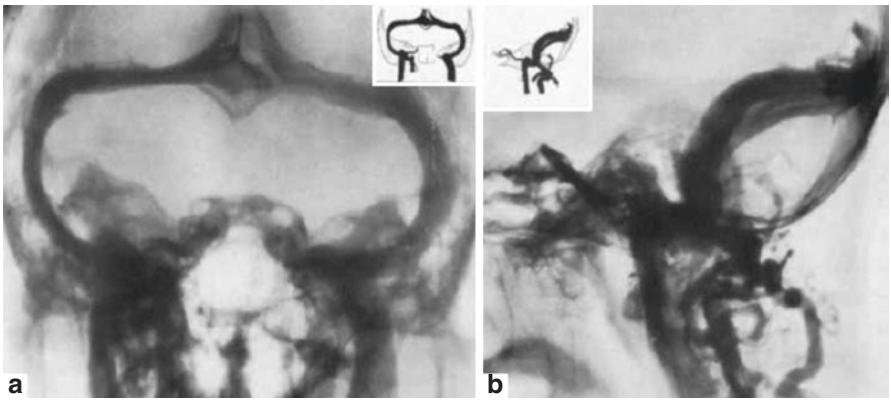

Fig. 1.14 (**a**) Normal jugulargram, anterior–posterior view. (**b**) Normal jugulargram, lateral view (From: Gejrot, T. "Surgical treatment of glomus jugulare tumours with special reference to the diagnostic value of retrograde jugulargraphy." *Acta Oto-Laryngologica* 60 (August 1965): 150–68 Fig. 3)

use of a surgical microscope: "The incision is post-auricular and goes above the auricle and down to the anterior border of the sternocleidomastoid muscle to the level of the larynx. Anterior and posterior flaps were made, and the auricle was

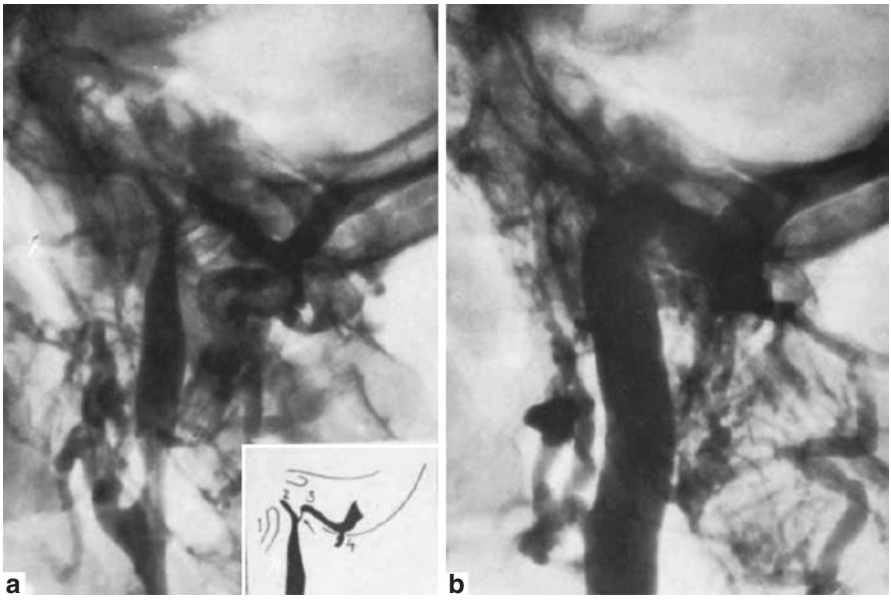

Fig. 1.15 (**a**) Constriction of the jugular bulb (arrow). (1) Head of the mandible, (2) inferior petrous sinus, (3) dome of the jugular bulb, and (4) mastoid emissary vein. (**b**) Normal side (Gejrot, T., and T. Lauren. "Retrograde jugularography in diagnosis of glomus tumours in the jugular region." *Acta Oto-Laryngologica* 58 (September 1964): 191–207)

included in the anterior flap. The external ear canal was cut across the bony portion. The sternomastoid muscle was separated from the mastoid tip and reflected backward. The mastoid cavity was exenterated completely, and the sigmoid sinus was widely exposed; the upper part was packed off tightly with oxidized cellulose (Oxycel) gauze. The mastoid tip was then removed to expose the digastric muscle and the beginning of the stylomastoid foramen. The posterior belly of the digastric was divided, and the posterior auricular and occipital arteries were identified, cut, and tied. The external carotid artery was ligated above the facial artery branch. Tapes were passed around the internal carotid artery and the internal jugular vein after identifying the vagus and accessory nerves…The facial nerve was then traced forward into the parotid gland and upward into the middle ear. At the same time the bony posterior and inferior canal walls were removed with an electric drill. The facial nerve was carefully displaced from the canal and reflected forward and upward out of the way. At this time the internal jugular vein was ligated high in the neck. Bony removal with the drill was completed including the base of the styloid process. This exposed the entire hypotympanum and jugular bulb where the tumor was seen … and was completely removed with almost no blood loss and preservation of the 9th, 10th, and 11th cranial nerves." Shapiro felt that this was not suitable for cases with intracranial extension but was a new technique that would allow complete removal of tumor from the mastoid, middle ear, and jugular foramen with minimal blood loss [12].

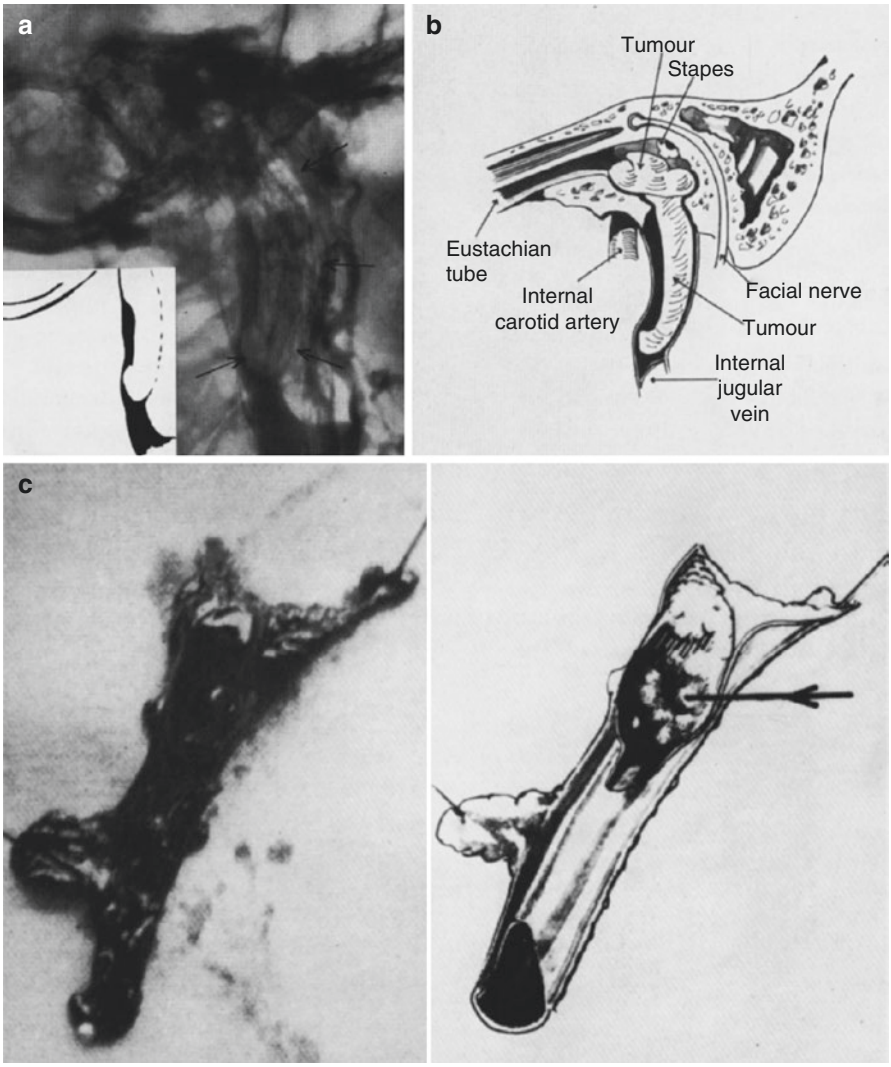

Fig. 1.16 (**a**) Constriction of the jugular bulb (*arrow*) (1, Head of the mandible; 2, Inferior petrous sinus; 3, dome of the jugular bulb; 4, mastoid emissary vein.) B. Normal side. (**b**) Jugular Paraganglioma tumor extending from the internal jugular vein to the middle ear. (**c**) Specimen showing the jugular vein filled with tumor. (Gejrot T, Lauren T. "Retrograde jugularography in diagnosis of glomus tumours in the jugular region." Acta Oto-Laryngologica 58. (September 1964): 191–207)

The following year, Gejrot published his technique of using retrograde jugularography to clearly identify tumors with extension into the jugular venous system (Fig. 1.16). He then elaborates on the technique of Shapiro, using hypotensive anesthesia and a similar post-auricular incision, exposure of cranial nerves, and ligation of the carotid and internal jugular vein (Fig. 1.17). The addition of Gejrot's technique

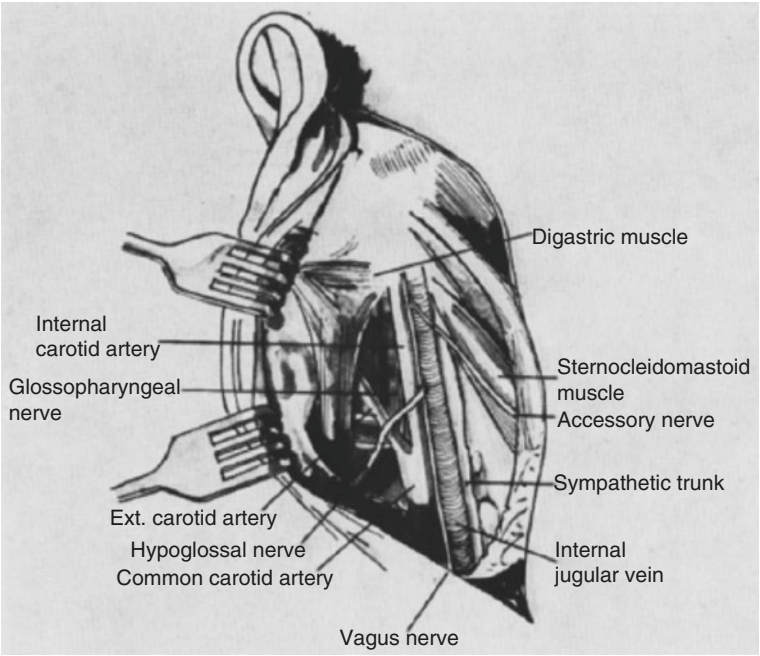

Fig. 1.17 Description of surgical exposure (From: Gejrot, T. "Surgical treatment of glomus jugulare tumours with special reference to the diagnostic value of retrograde jugulary ography." *Acta Oto-Laryngologica* 60 (August 1965): 150–68)

was to expose the sigmoid sinus and pack it. The internal jugular vein was then opened, and the intraluminal component of the tumor was removed (Fig. 1.18). In five cases, one patient had significant bleeding postoperatively, due to insufficient packing of the inferior petrosal sinus. There was no reported weakness of the facial nerve, and the pulsatile tinnitus disappeared or diminished significantly in all patients [13].

In 1965, Kohut described two new imaging methods to characterize glomus tumors, including polytomography and subtraction angiography. The Massiot polytome produced images of the temporal bone for the first time as small as 1 mm (Fig. 1.19). Subtraction angiography removed the radiologic density of the temporal bone, allowing close visualization of the vasculature (Fig. 1.20). Both of these methods significantly added to the clinical imaging arsenal and increased the accuracy of preoperative assessment for surgical removal of glomus tumors [14].

In 1965, McCabe and Fletcher from the University of Michigan published their approach to diagnosis and management of glomus jugulare tumors. In their report, they described a transcanal hypotympanotomy approach performed under local anesthesia to expose the jugular bulb and establish a diagnosis (Fig. 1.21). Following diagnosis, patients were then managed with radiation. After reviewing 32 cases at Michigan, they stated: "We were amazed at the radiosensitivity of this histologically benign tumor".

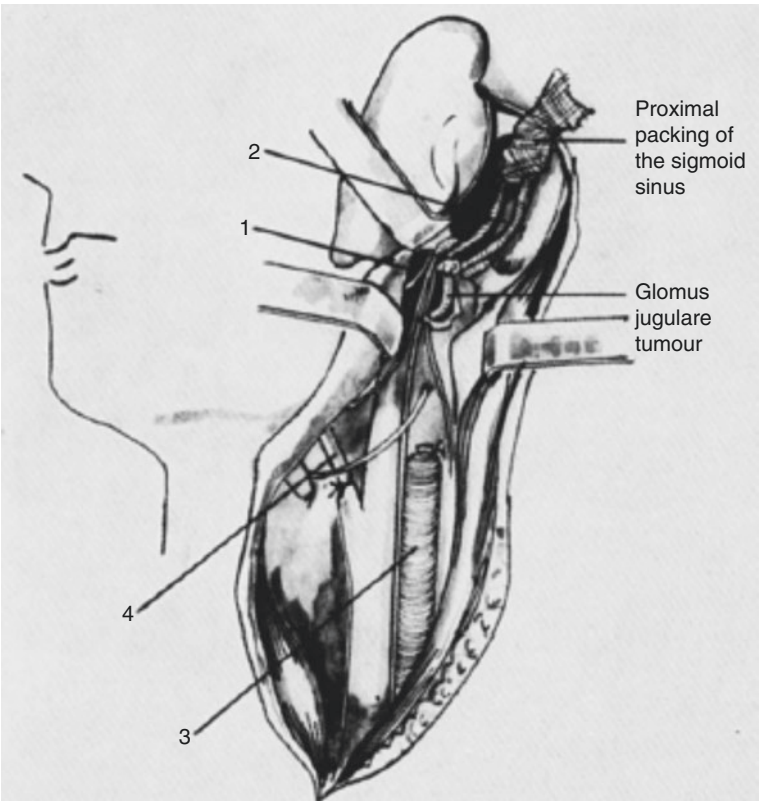

Fig. 1.18 Packing of the sigmoid sinus (From: Gejrot, T. "Surgical treatment of glomus jugulare tumours with special reference to the diagnostic value of retrograde jugulargraphy." *Acta Oto-Laryngologica* 60 (August 1965): 150–68)

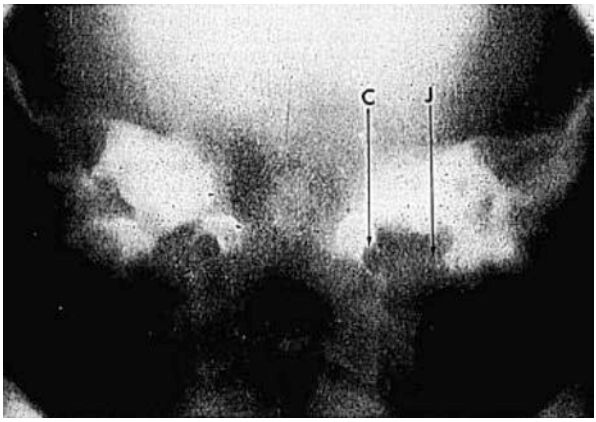

Fig. 1.19 Use of polytome (From: Kohut, R. I., and J. R. Lindsay. "Glomus jugulare tumors. New techniques for determining operability." *The Laryngoscope* 75 (May 1965): 750–62)

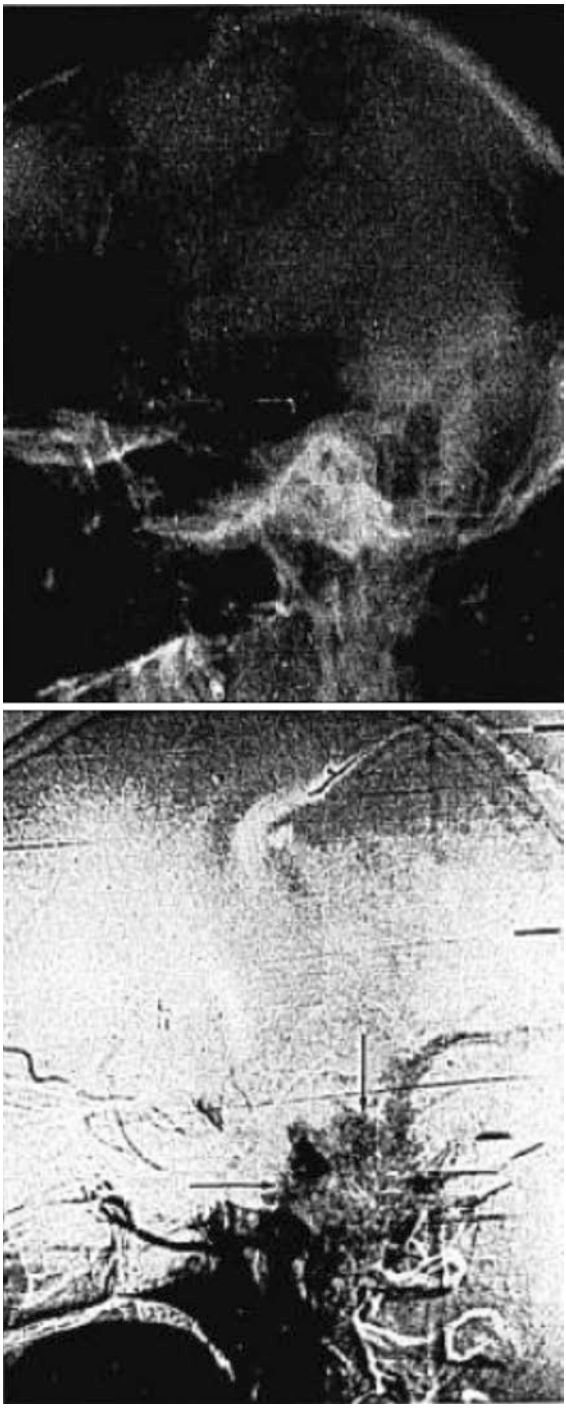

Fig. 1.20 Subtraction angiography (Kohut, R. I., and J. R. Lindsay. "Glomus jugulare tumors. new techniques for determining operability." *The Laryngoscope* 75 (May 1965): 750–62)

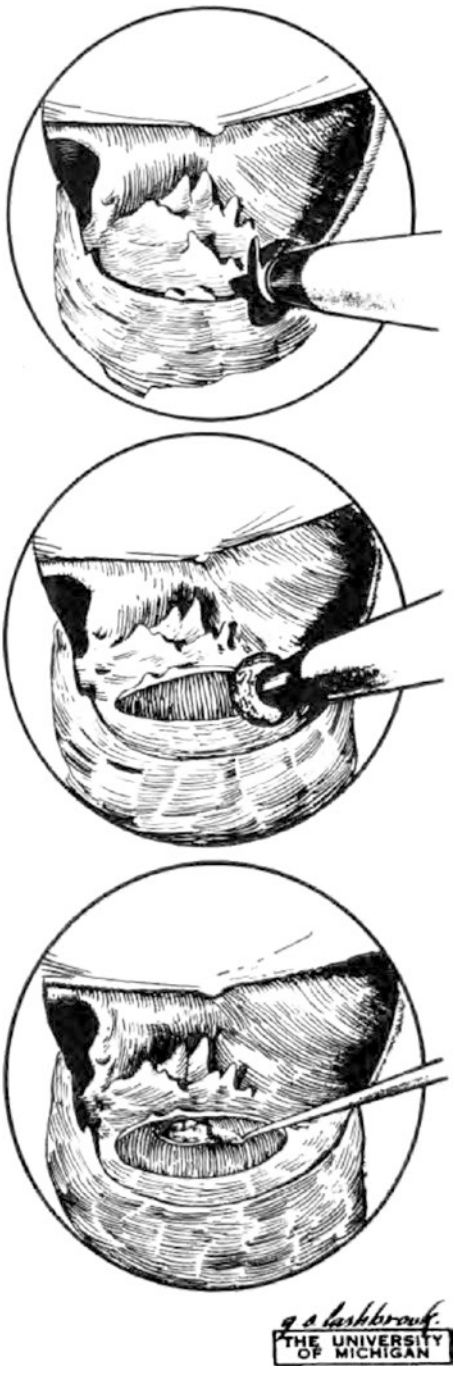

Fig. 1.21 Biopsy technique of McCabe (From: McCabe, B. F., and M. M. Fletcher. "Transtympanic approach to extratympanic (jugular Bulb) chemodectoma." *Transactions - American Academy of Ophthalmology and Otolaryngology. American Academy of Ophthalmology and Otolaryngology* 69, no. 5 (October 1965): 827–31)

In 1968, House described a hearing preservation approach to glomus tumors that preserves the bony canal, ossicles, and facial nerve. House describes a post-auricular approach followed by a simple mastoidectomy. The dissection is carried into the hypotympanum, in what he termed the "extended facial recess" approach where the chorda tympani nerve is sacrificed. Packing is then used to compress the blood supply of the tumor in the hypotympanum, and the tumor is removed with a small curette [15].

In 1969, there was a panel discussion moderated by McCabe with Rosenwasser, House, Carl Hamberger, and Witten where preoperative diagnostic evaluation and surgical techniques were discussed. The majority of participants used tomography and either venography or the venous phase of the arteriogram in order to assess the extent of the tumor preoperatively. In the discussion of surgical approaches, House describes the post-auricular approach with the extended facial recess. Here, he further elaborated on the technique for a more extensive tumor. His approach combines the previous work of Shapiro to extend the approach, find the cranial nerves, and tie off the jugular vein. He packs off the inferior petrosal sinus and then removes the tumor in a similar fashion to what he described in his 1968 paper. There was much disagreement among the group about the radiosensitivity of glomus tumors. McCabe felt that they are radiosensitive based on the experience at Michigan. However, House disagreed. "I think the ones that shrink do so because of an endarteritis and a decrease in their vascularity." He only used radiation for nonoperable tumors. Rosenwasser described the pathology of a postirradiated case, where no tumor cells were found in the specimen. Witten felt that surgery was preferred if the entire tumor could be removed. This round table highlights the opposing points of view on treatment at this time [16].

In 1969, McCabe and Fletcher published their treatment algorithm for 32 cases managed at the University of Michigan. In their report, the authors divided glomus tumors into tympanic, tympanomastoid, petrosal, and extrapetrosal tumors. They recommend complete surgical excision for limited tumors involving the tympanic cavity and radiation only for large extrapetrosal tumors. For intermediate-sized tumors, they recommended radical mastoidectomy followed by radiation to preserve facial nerve function. The majority of patients in their series were alive up to 19 years later with no evidence of tumor growth. However, in their series, they also described three patients with rapidly destructive malignant tumors causing death within 1 year [17].

In 1969, Rosenwasser updated his 1945 case report with 35 subsequent cases, arguing that surgery was the treatment of choice. He reserved radiation for cases with incomplete tumor extirpation or for extensive disease that would require "mutilating" surgery. He concluded by saying "I had thought that 25 years of experience would provide me with the fund of information that would supply all the answers to the many unanswered gaps in our knowledge. Now, I am not so sure but that I won't need another 25 years before I would venture to be arbitrary" [3].

In 1973, multiple reports emerged regarding the sensitivity of glomus tumors to radiation treatment. Newman, at UCSF, reported on 20 patients—14 were treated surgically and 10 of these had a recurrence within 3 years. These patients were then treated with radiation, without evidence of disease recurrence. Those patients who received radiation, either before or after surgery, had no progression of symptoms. The dose varied from 4400 to 5500 rads, five times per week, for 6–8 weeks [18].

A different report that same year from MD Anderson reported similar doses of radiation in 14 people with only one complication of late brain necrosis [19]. Radiation therapy was gaining acceptance as an effective way to halt the growth of glomus tumors.

In 1974, Glasscock described a new surgical technique, which combined the work of Shapiro and the extended facial recess technique of House. He removed the bone over the sigmoid and thinned the bone over the fallopian canal. He then exposed the neck, similar to previous techniques described by Shapiro, ligated the jugular vein, and then packed and opened the sigmoid sinus. Then a Kelly clamp was used to pull the jugular vein under the 11th nerve, and Metzenbaum scissors were used to separate the vein and the carotid artery and avulse the vein, bulb, and tumor (Figs. 1.22 and 1.23). The large hemorrhage of the inferior petrosal sinus was then packed. Using this technique, Glasscock advocated for complete surgical excision as the primary treatment [20].

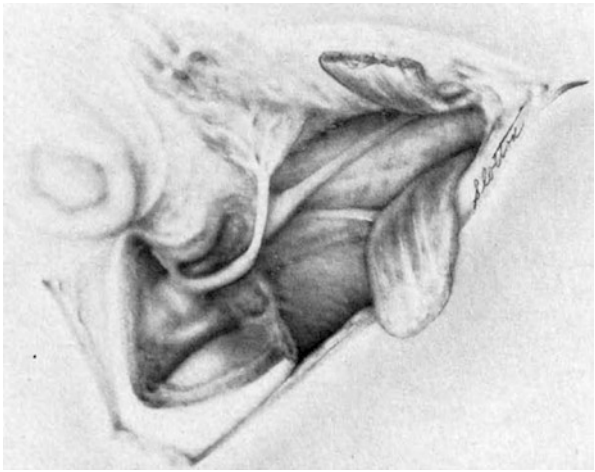

Fig. 1.22 Glasscock's extended technique with removal of the tip of the mastoid (From: Glasscock, M. E., P. F. Harris, and G. Newsome. "Glomus tumors: diagnosis and treatment." *The Laryngoscope* 84, no. 11 (November 1974): 2006–32)

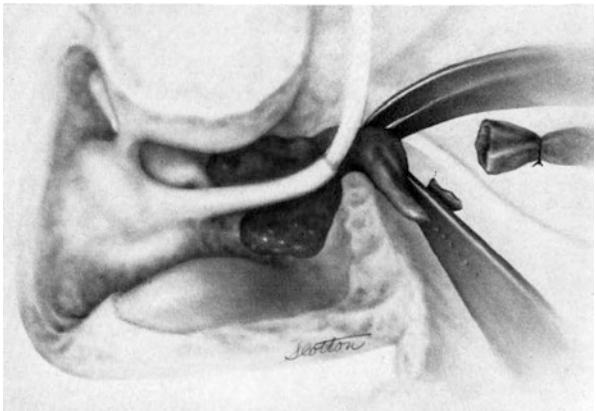

Fig. 1.23 Glasscock, severing of the jugular vein (From: Glasscock, M. E., P. F. Harris, and G. Newsome. "Glomus tumors: diagnosis and treatment." *The Laryngoscope* 84, no. 11 (November 1974): 2006–32)

In 1977, Gardner was the first to suggest a combined approach using a multidisciplinary team that included neurosurgeons. He advocated for total removal using a combined approach through the neck and temporal bone [21].

In 1978, Fisch proposed a new lateral approach to the infratemporal fossa that provides wider and more medial access than ever described. In the type A approach, an+693+3+6. extended parotidectomy incision is made (Fig. 1.24). The facial nerve is identified and dissected, and the external carotid artery is ligated. The ear canal is closed in a blind-sac fashion, and a radical mastoidectomy is performed. The facial nerve is transposed, which gives access to the jugular bulb. This approach requires permanent transposition of the facial nerve, which Fisch felt allowed more space for surgical manipulation and allowed packing of the inferior petrosal sinus without compressing the nerve [22]. Fisch also updates the classification for glomus tumors in 1981 [23].

Along with greater exposure to approach glomus tumors, techniques of selected embolization were refined in order to reduce intraoperative blood loss. In 1979, Simpson and House were the first to describe their experience with preoperative embolization. They thread Gelfoam through a catheter within the carotid artery system. Using this technique, they were able to decrease the average blood loss during surgery from 1000 mL to 400 mL [24]. However, this procedure was not with-

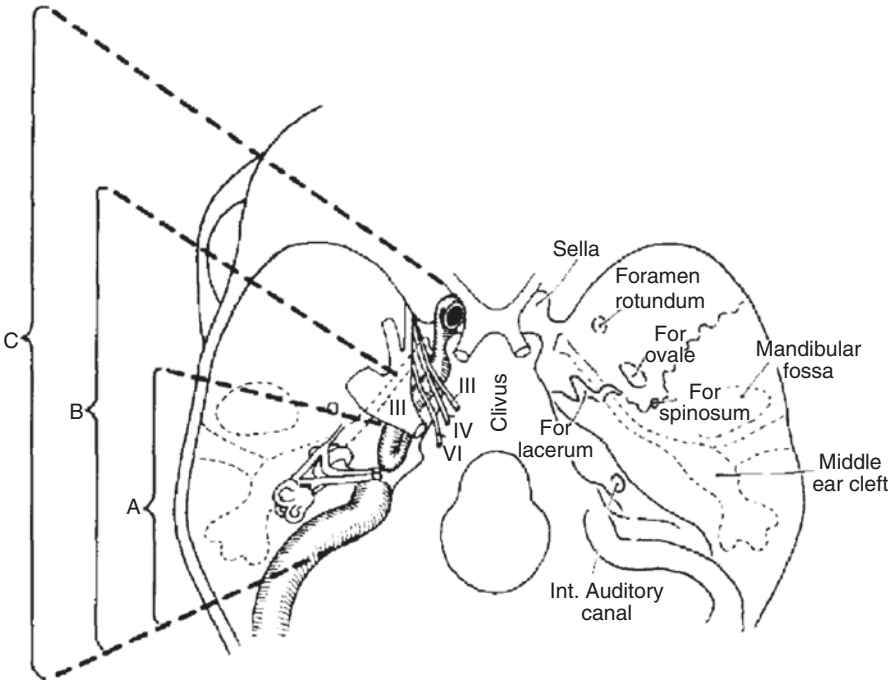

Fig. 1.24 Infratemporal fossa approaches (From: Fisch, U. "Infratemporal fossa approach to tumours of the temporal bone and base of the skull." *The Journal of Laryngology and Otology* 92, no. 11 (November 1978): 949–67)

Cranial nerve palsies (17 Patients).

	Preoperative	Postoperative	Nerve sacrificed
VII	5	17	4
IX	6	15	11
X	8	15	11
XII	6	10	3

Fig. 1.25 Cranial nerve palsies (From: Cece, J. A., W. Lawson, H. F. Biller, A. R. Eden, and S. C. Parisier. "Complications in the management of large glomus jugulare tumors." *The Laryngoscope* 97, no. 2 (February 1987): 152–57)

out its risks, such as A/V shunting of material and stroke. Glasscock, Jackson, and others began adopting this technique, making it a standard treatment for larger tumors [25, 26].

In 1981, Jackson encouraged a return to surgical treatment given the rapid advances in imaging, microscopy, and surgical anesthesia. New CT scanning technologies with contrast permitted high-resolution images that could view both intra- and extracranial contents, and angiography allowed assessment of vascularity, feeding vessels, and concurrent carotid body lesions. Jackson states that involvement of the internal carotid artery or the cranium should not preclude surgical excision and encouraged a multidisciplinary approach with the help of a neurosurgeon and head and neck surgeon [27]. In 1982, Jackson and Glasscock proposed a new classification system and treatment algorithm for glomus tumors advocating for aggressive surgical resection, leaving radiation for the physically infirm or for very extensive lesions that they deemed unresectable [28].

The 1970s and 1980s marked a time where aggressive surgical resection was adopted by most large centers. While radical and complete tumor resection offered tumor control, many patients were left with new or worsening cranial nerve deficits. Cece et al. reported on their complications when removing large glomus tumors, where the majority of patients sustained a new cranial nerve deficit (Fig. 1.25) [29]. Jackson and Glasscock report that permanent cranial nerve deficits occurred in 10–30% of cases [27]. With this, techniques for cranial nerve rehabilitation such as feeding tube placement, cricopharyngeal myotomy, palatal adhesion, and vocal cord injection become a large part of the treatment algorithm.

Beginning in the late 1980s, several groups began adopting more conservative approaches. In 1985, Gardner advocated for initial observation in selected patients given improved imaging for tumor surveillance. In his report of 36 patients, 6 were treated with surgery alone, 14 with radiation alone, and 15 with a combination of radiation and surgery. "We have seen no major complications from the use of X-ray therapy, no major growth of tumor in any patients, and have been impressed with the quality of life in these patients" [30]. In 1988, Howard House reports the case of a woman who lived for 40 years with a glomus tumor following subtotal resection and subsequent radiation. House concludes that radiation can effectively palliate large glomus tumors [31].

In the early 1990s, more systematic reports emerged about the effectiveness of treating glomus tumors with radiation alone. Thirty-eight patients were treated at MD Anderson from 1956 to 1991 using external beam radiation. Fourteen patients were treated with primary radiation, with local control achieved in 79% of cases.

Local control was achieved 91% of the time following surgery, for an overall control rate of 89.5%. Complications of radiation were few and included TMJ disease, a perforated tympanic membrane, and chronic effusion [32]. At the same time, radiosurgery emerged as a technique to treat glomus tumors. This technique permitted precise radiation delivery with minimal collateral radiation injury to surrounding tissue. Foote et al. at the Mayo Clinic were the first to report on the use of radiosurgery to treat patients with unresectable or residual glomus tumors. In this seminal paper, eight of the nine patients demonstrated tumor control, and seven of the nine patients experienced a decrease in their symptoms [33]. These new studies provide the basis for utilizing primary radiosurgery in the treatment of glomus tumors.

The history of jugular paraganglioma treatment has evolved substantially since the 1940s, with Guilds original description. Treatment has closely followed advancements in microsurgical technique and radiation delivery. With a better understanding of the natural history of disease, conservative treatments including primary radiosurgery, subtotal resection, and initial observation have become increasingly used by major centers, in place of radical resection.

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Chapter 2
Surgical Anatomy of Jugular Paraganglioma

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Introduction

Paragangliomas are classified based on location. The carotid body tumor is the most common paraganglioma, arising at the bifurcation of the common carotid artery in the neck. Paragangliomas arising from the vagus nerve, tympanic plexus, and the wall of the jugular bulb are termed vagal, tympanic, and jugular paragangliomas, respectively. Of these, surgical treatment of the jugular paraganglioma is the most challenging. The difficulty is caused by its deep location and surrounding structures including the carotid artery anteriorly, facial nerve laterally, and vertebral artery and jugular process posteroinferiorly. Furthermore, cranial nerves (CNs) IX to XII pass through the jugular foramen and the hypoglossal canal located inferior to the foramen. Surgical resection of jugular paragangliomas, while minimizing neurological complications, requires both a profound understanding of the microsurgical anatomy of the

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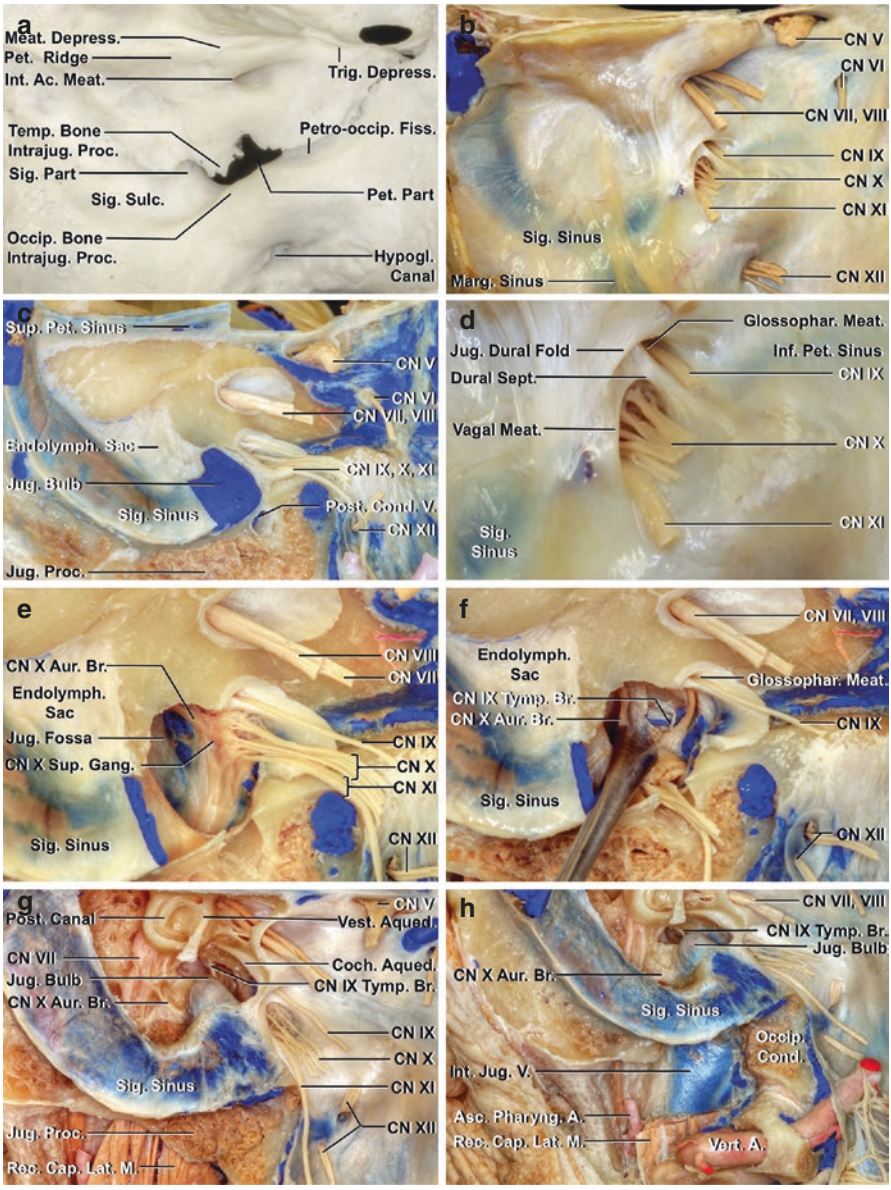
jugular foramen and its surrounding area and selection of an appropriate approach tailored to the extent of disease. In this chapter, cadavers injected with red and blue silicone were dissected to show the basic microsurgical anatomy of the jugular foramen and that specific to the postauricular transtemporal and far-lateral approaches, which are frequently employed in jugular paraganglioma surgery. Specifically, cadavers were dissected in a stepwise manner to understand the intracranial (Fig. 2.1), foraminal (Figs. 2.1, 2.2, and 2.3), and extracranial (Fig. 2.3) anatomy related to the jugular foramen and to show the most relevant surgical views (Figs. 2.4 and 2.5).



Osseous Relationships

The jugular foramen is a hiatus between the temporal bone anterolaterally and occipital bone posteromedially. The petroclival fissure, which separates the petrous portion of the temporal bone and lateral part of the occipital bone, ends at the anteromedial edge of the foramen (Figs. 2.1a and 2.2a). The inferior petrosal sinus courses along the intracranial surface of the fissure, and the inferior petroclival vein courses along its extracranial surface. The occipitomastoid suture, which separates the mastoid part of the temporal bone and squamosal portion of the occipital bone, ends at the posterolateral edge of the foramen. The jugular process, located between the lateral part of the condyle and terminal part of the occipitomastoid suture, forms the posteroinferior border of the jugular foramen (Figs. 2.1b, c, g, h and 2.2). The

Fig. 2.1 Anatomy of the intracranial end of the left jugular bulb and its adjacent area. (**a**) Osseous structures related to the jugular foramen. The jugular foramen sits between the internal auditory canal and hypoglossal canal. The foramen is separated into two parts by the intrajugular processes of the temporal and occipital bones. The petrosal part is the smaller medial part where the pyramidal fossa opens into its superior margin. The sigmoid part is the lateral part where the sigmoid sulcus ends. The petroclival fissure terminates at the anteromedial edge of the foramen. (**b**) The neurovascular relationships of the intracranial end of the jugular foramen and its adjacent area. The foramina for the cranial nerves lie in the anterior wall of the posterior fossa dura. The glossopharyngeal, vagus, and accessory nerves enter into the jugular foramen. The trigeminal nerve enters Meckel's cave. The abducens nerve pierces the dura covering the clivus. The facial and vestibulocochlear nerves enter the internal auditory canal. The hypoglossal nerve enters the hypoglossal canal. (**c**) The dura covering the petrous surface of the temporal bone has been removed. The endolymphatic sac sits on the posterior surface of the petrous bone anterior to the sigmoid sinus. The neural part of the jugular foramen is located between the petrosal and sigmoid parts of the jugular foramen. (**d**) Neurovascular relationships of the intracranial end of the jugular foramen and its adjacent area were shown after removal of the jugular bulb. The glossopharyngeal nerve enters the glossopharyngeal meatus. The vagus and accessory nerves enter the vagal meatus. They are separated by the dural septum. (**e**) The terminal part of the sigmoid sinus and jugular bulb have been removed and the superior margin of the sigmoid part of the jugular foramen and jugular process of the temporal bone have been drilled to expose the course of glossopharyngeal, vagus, and accessory nerves in the foramen. The vagal rootlets form the vagal superior ganglion in the foramen where Arnold's nerve arises. (**f**) Translocating the vagus nerve laterally shows the course of the glossopharyngeal nerve. The superior ganglion of the vagus nerve has been retracted to expose the tympanic branch of the glossopharyngeal nerve. The branch originates from the glossopharyngeal nerve at the external orifice of the jugular foramen. (**g**) Anatomical structures buried in the temporal bone were shown from the posterior cranial fossa. The jugular process and rectus capitis lateralis muscle are obstacles to accessing the jugular bulb. (**h**) Removal of the jugular process and rectus capitis lateralis muscle exposes the posteroinferior surface of the jugular bulb and posterior surface of the internal jugular vein. *A.* artery, *Ac.* acoustic, *Aqued.* aqueduct, *Asc.* ascending, *Aur.* auricular, *Br.* branch, *CN* cranial nerve, *Cap.* capitis, *Coch.* cochlear, *Cond.* condylar, *Cond.* Condyle, *Depress.* depression, *Endolymph.* endolymphatic, *Fiss.* fissure, *Glossophar.* glosopharyngeal, *Hypogloss.* hypoglossal, *Inf.* inferior, *Int.* internal, *Intrajug.* intrajugular, *Jug.* jugular, *Lat.* lateralis, *M.* muscle, *Marg.* marginal, *Meat.* meatal, meatus, *Occip.* occipital, *Petro-occip.* petro-occipital, *Pet.* petrosal, *Post.* posterior, *Proc.* process, *Rec.* rectus, *Sept.* septum, *Sig.* sigmoid, *Sup.* superior, *Trig.* trigeminal, *Temp.* temporal, *Tymp.* tympanic, *V.* vein, *Vert.* vertebral, *Vest.* vestibular

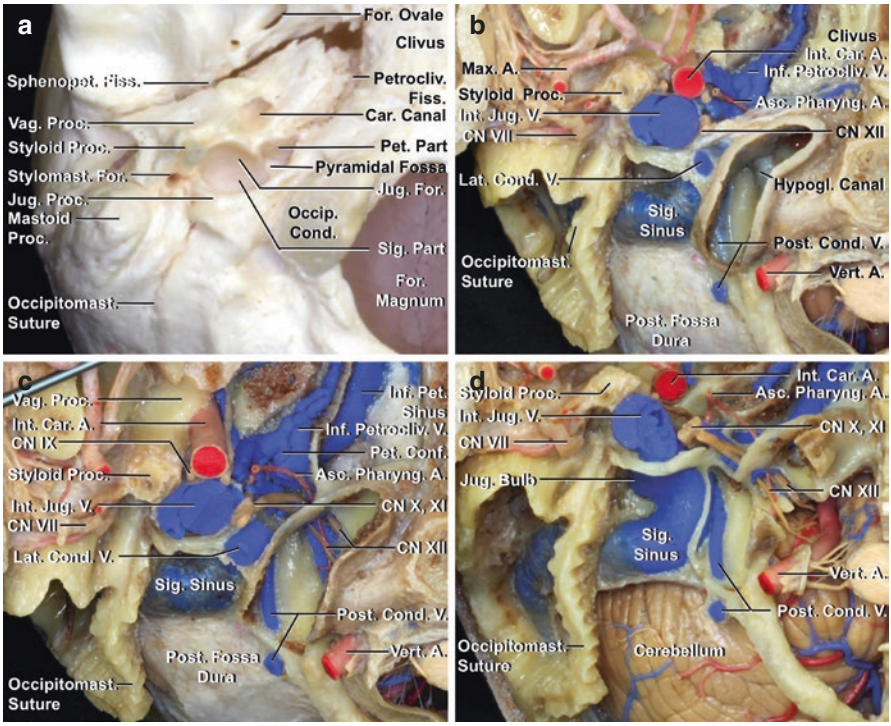


Fig. 2.2 Anatomy of the extracranial end of the jugular bulb and its adjacent area. (**a**) Osseous structures related to the jugular foramen from inferior. The foramen sits behind the carotid canal and styloid process, lateral to the anterior part of the occipital condyle and medial to the styloid foramen. The jugular process forms the posterior surface of the bulb. (**b**) The anatomy of the jugular foramen from inferior. The muscular structures have been removed, and the mastoid process, jugular process, and occipital condyle have been drilled to show the course of the sigmoid sinus. The hypoglossal canal and posterior condylar canal have been skeletonized to show their courses in the occipital condyle and jugular tubercle, respectively. The internal carotid artery courses just anterior to the internal jugular vein. (**c**) The clivus has been drilled to expose the inferior petrosal sinus. The sinus, which courses along the intracranial surface of the petroclival fissure, and the inferior petroclival vein, which courses along the extracranial surface of the fissure, empty into the petrosal confluence before emptying into the internal jugular vein. The lateral condylar vein has been partially removed to expose the course of CN XII and the venous plexus of the hypoglossal canal. The posterior condylar vein empties into the medial surface of the sigmoid sinus. (**d**) The occipital condyle and hypoglossal canal have been drilled to expose the course of the hypoglossal nerve. The alar ligament and dura covering the posterior cranial fossa have been removed. The ascending pharyngeal artery sends the jugular and hypoglossal branches. *A.* artery, *Asc.* ascending, *CN* cranial nerve, *Car.* carotid, *Cond.* condyle, condylar, *Conf.* confluence, *Fiss.* fissure, *For.* foramen, *Hypogl.* hypoglossal, *Inf.* inferior, *Int.* internal, *Jug.* jugular, *Lat.* lateral, *Max.* maxillary, *Occip.* occipital, *Occipitomast.* occipitomastoid, *Pet.* petrosal, petrous, *Petrocliv.* petroclival, *Pharyng.* pharyngeal, *Post.* posterior, *Proc.* process, *Sig.* sigmoid, *Sphenopet.* sphenopetrosal, *Stylomast.* stylomastoid, *Vag.* vaginal, *V.* vein, *Vert.* vertebral

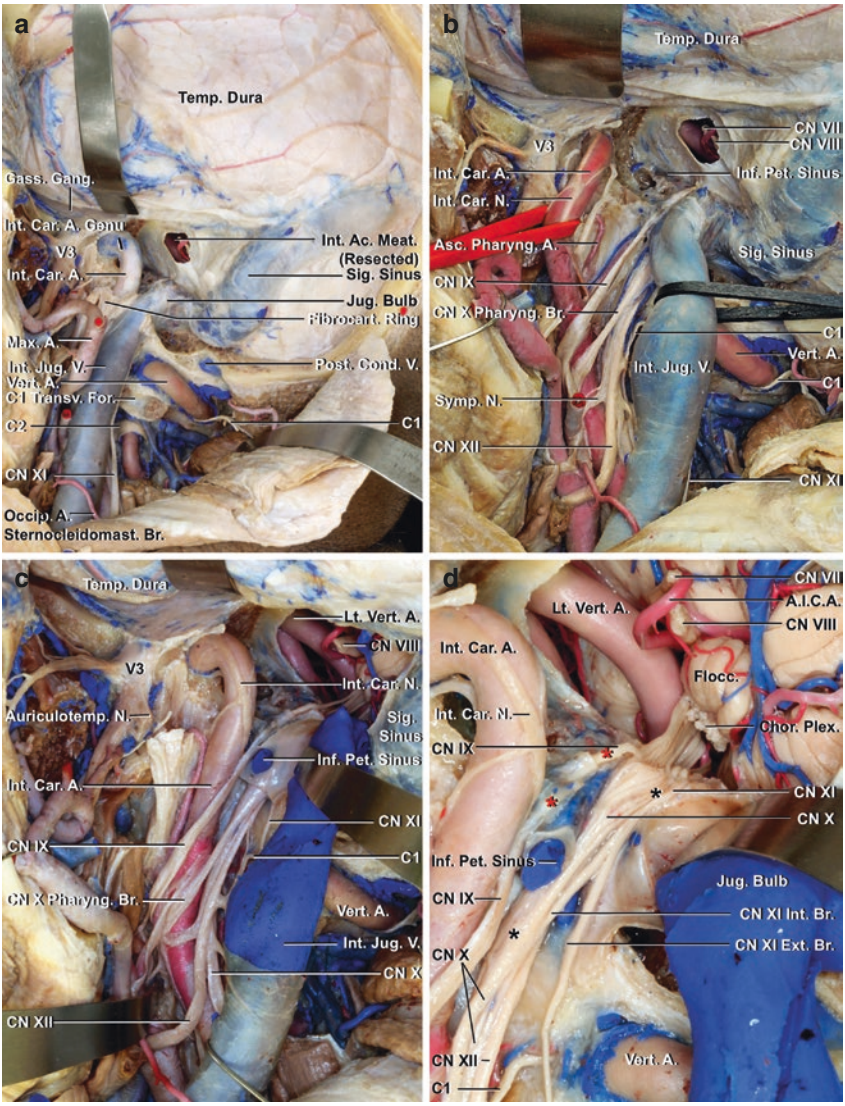


Fig. 2.3 (**a**) The removal of the temporal bone, parotid gland, temporomandibular joint, and pterygoid muscles clearly exposes the neurovascular relationships around the jugular foramen. (**b**). The translocation of the internal carotid artery anteriorly and internal jugular vein posteriorly exposes the course of the lower cranial nerves after they exit the jugular foramen and hypoglossal canal. (**c**) Translocation of the jugular bulb leaving the medial wall of the bulb shows the relationship between the sinuses and cranial nerves. (**d**) Removal of the posterior fossa dura and medial wall of the jugular bulb clearly shows the intracranial, foraminal, and extracranial courses of the lower cranial nerves. *Red* and *black asterisks* indicate the ganglion of the glossopharyngeal and vagal nerves, respectively. *A.* artery, *Ac.* acoustic, *AICA.* anterior inferior cerebellar artery, *Asc.* ascending, *Auriculotemp.* auriculotemporal, *Br.* branch, *Car.* carotid, *CN* cranial nerve, *Cond.* condylar, *Chor.* choroid, *Ext.* external, *Fibrocart.* fibrocartilage, *For.* foramen, *Flocc.* Flocculus, *Gass.* gasserian, *Gang.* ganglion, *Inf.* inferior, *Int.* internal, *Jug.* jugular, *Lt.* left, *Max.* maxillary, *Meat.* meatus, *N.* nerve, *Occip.* occipital, *Pet.* petrosal, *Plex.* plexus, *Post.* posterior, *Pharyng.* pharyngeal, *Sig.* sigmoid, *Sternocleidomast* sternocleidomastoid, *Symp.* Sympathetic, *Temp.* temporal, *Transver.* transverse, *V.* vein, *Vert.* vertebral

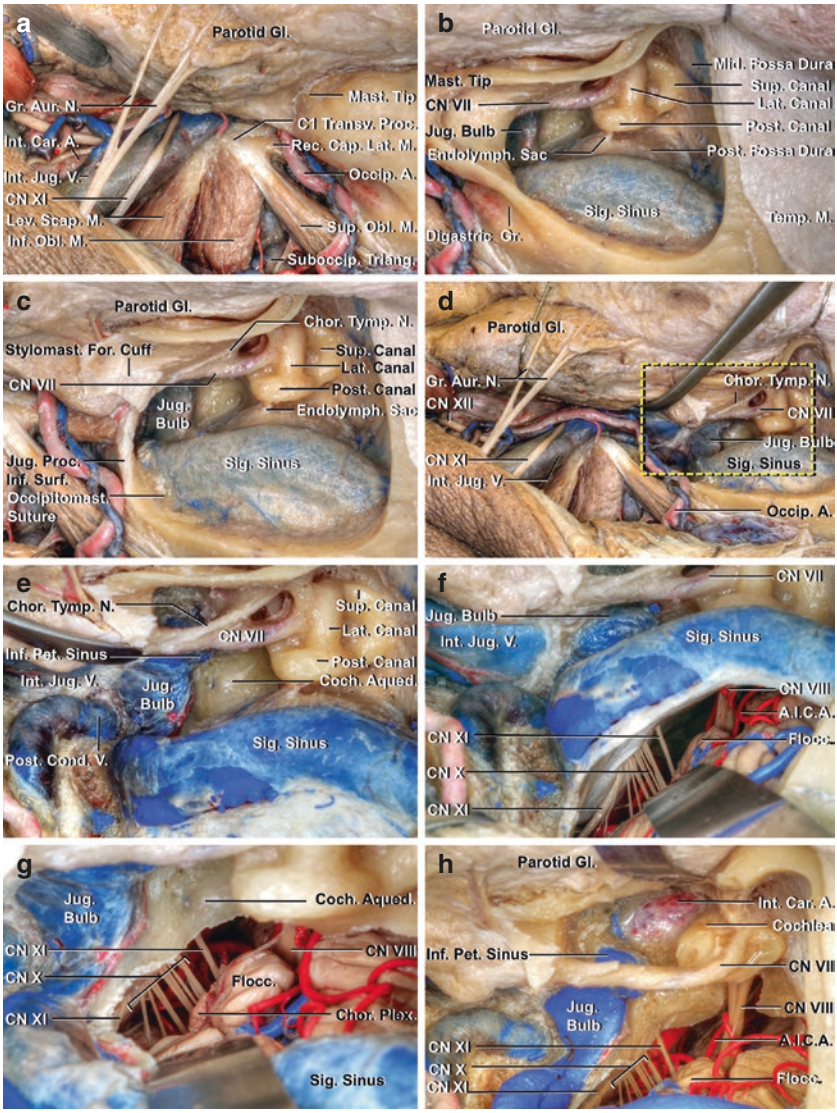


Fig. 2.4 Postauricular transtemporal approach. (**a**) High cervical exposure. (**b**) Infralabyrinthine mastoidectomy. (**c**) The removal of the mastoid tip exposes the insertion of the rectus capitis lateralis muscle into the jugular process. (**d**) Removal of the jugular process and the rectus capitis lateralis exposes the posteroinferior surface of the jugular bulb. (**e**) Enlarged view of the *dotted area* in (**c**) after the Fallopian bridge technique was performed. (**f**) View of the presigmoid approach. (**g**) View of the retrosigmoid approach. (**h**) Removal of the external auditory canal and infracochlear drilling exposes the internal carotid artery medial to the jugular bulb. *A.* artery, *A.I.C.A.* anterior inferior cerebellar artery, *Aur.* auricular, *Aque.* aqueduct, *Cap.* capitis, *Car.* carotid, *Chor.* chorda, choroid, *CN* cranial nerve, *Coch.* cochlear, *Cond.* condylar, *Endolymph.* endolymphatic, *Flocc.* flocculus, *For.* foramen, *Gl.* gland, *Gr.* greater, groove, *Inf.* inferior, *Int.* internal, *Jug.* jugular, *Lat.* lateral, lateralis, *Lev.* levator, *N.* nerve, *M.* muscle, *Mast.* mastoid, *Mid.* middle, *Obl.* oblique, *Occip.* occipital, *Occipitomast.* occipitomastoid, *Pet.* petrosal, *Plex.* plexus, *Post.* posterior, *Proc.* process, *Rec.* rectus, *Scap.* scapula, *Sig.* sigmoid, *Suboccip.* suboccipital, *Sup.* superior, *Surf.* surface, *Stylomast.* stylomastoid, *Temp.* temporalis, *Triang.* triangle, *Tymp.* tympani, *M.* muscle, *Transv.* transverse, *V.* vein

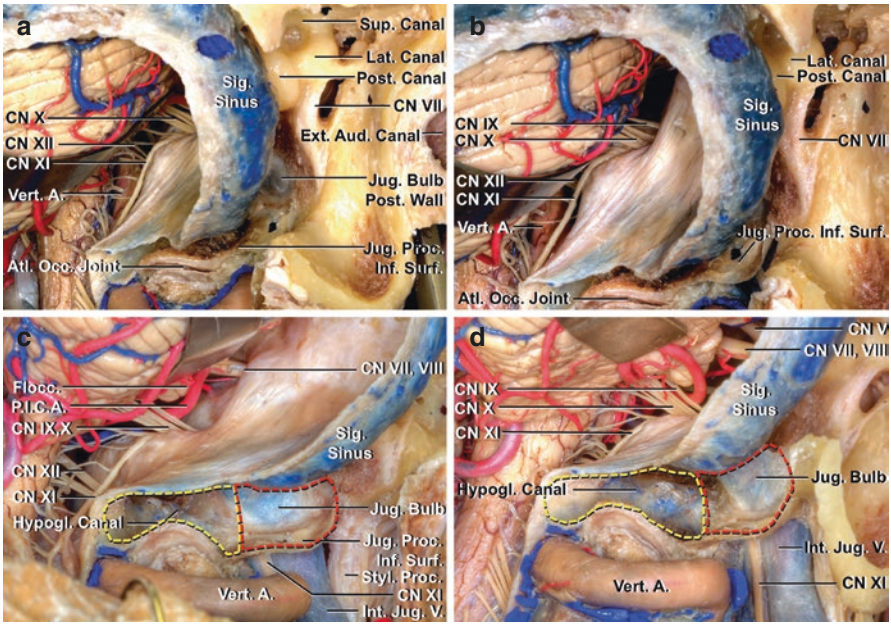


Fig. 2.5 Far-lateral approach. (**a**, **b**) Posterolateral view of the far-lateral approach. (**c**, **d**). Posteroinferior view of the far-lateral approach. *Yellow* and *red dotted lines* indicate the area for the occipital condyle and jugular process, respectively. *A.* artery, *Atl. Occ.* atlanto-occipital, *Aud.* auditory, *CN* cranial nerve, *Ext.* external, *Flocc.* flocculus, *Hypogl.* hypoglossal, *Int.* internal, *Inf.* inferior, *Jug.* jugular, *Lat.* lateral, *P.I.C.A.* posterior inferior cerebellar artery, *Post.* posterior, *Proc.* process, *Sig.* sigmoid, *Styl.* styloid, *Sup.* superior, *Surf.* surface, *V.* vein, *Vert.* vertebral

jugular foramen has three parts: two venous portions including the sigmoid and petrosal and a neural compartment, the intrajugular part. The two venous components, a large lateral part and small medial part, are separated by bony processes, the intrajugular processes of the temporal and occipital bones and intrajugular ridge, which extends forward from the intrajugular process of the temporal bone (Figs. 2.1a, e and 2.2a). The processes are joined by a fibrous or less commonly an osseous bridge, the intrajugular septum, separating the sigmoid and petrosal parts of the foramen [1]. The larger sigmoid part receives drainage from the sigmoid sinus, and the smaller petrous part receives drainage from the inferior petrosal sinus (Figs. 2.1a, b and 2.2a). The pyramidal fossa, a small triangular recess located on the medial side of the intrajugular process of the temporal bone, extends along the anterior surface of the petrous part of the jugular foramen (Figs. 2.1a and 2.2a). Around or in the jugular foramen, the dura of the posterior fossa is attached to the small foramina, mastoid canaliculus, tympanic canaliculus, and cochlear aqueduct. The small foramen on the lateral wall of the jugular fossa is called the mastoid canaliculus, and the auricular branch of the vagus nerve (Arnold's nerve) passes through it (Fig. 2.1e, g). The cochlear canaliculus transmits the perilymphatic duct and cochlear aqueduct; its orifice is located just superior and lateral to where the glossopharyngeal nerve enters the intrajugular part of the jugular foramen. The tympanic canaliculus for Jacobson's nerve, a branch of the glossopharyngeal nerve, is located on or close

to the medial part of the carotid ridge. The carotid ridge separates the carotid canal from the jugular foramen and extends to the intrajugular process of the temporal bone (Figs. 2.1a, e, f and 2.2a) [2].

Arterial Relationships

The major arteries related to the jugular foramen are the internal carotid artery and the ascending pharyngeal artery, which usually arises from the external carotid artery. After bifurcating from the common carotid, the internal carotid artery courses straight upward, posteromedial to the external carotid artery and anteromedial to the internal jugular vein, to reach the skull base (Fig. 2.3a–c). At the level of the entrance of the carotid canal, the internal jugular vein courses just behind the artery. The artery enters into the carotid canal with the carotid sympathetic nerves, ascends, then turns anteromedially to form the posterior genu of the petrous carotid artery (Fig. 2.3a, c, d). The genu is located anteroinferior to the cochlea.

The ascending pharyngeal artery, a branch of the external carotid artery, divides into two major branches: the pharyngeal trunk anteriorly and neuromeningeal trunk posteriorly. Branches from the neuromeningeal trunk include two branches to the dura around the jugular foramen and adjacent area [3, 4]. The hypoglossal branch enters into the hypoglossal canal and the jugular branch into the jugular foramen (Fig. 2.2c, d). After arising from the external carotid artery, the ascending pharyngeal artery ascends straight upward between the internal and external carotid arteries while giving rise to branches to the neighboring muscles, nerves, and lymph nodes [3, 4]. The ascending pharyngeal artery also branches off the inferior tympanic artery, which passes through the tympanic canaliculus along with Jacobson's nerve to reach the tympanic cavity [1].

Venous Relationships

Both intracranial and extracranial drainage empty into the jugular bulb and adjacent part of the jugular vein. The sigmoid part of the jugular foramen receives the drainage from the sigmoid sinus. The sigmoid sinus descends and crosses the occipitomastoid suture, then empties into the sigmoid part, and courses anterior, superior, and slightly lateral to reach the jugular bulb (Figs. 2.1h and 2.2d). The superior surface of the jugular bulb is usually located below the internal auditory canal. It occasionally extends upward to the level of the upper margin of the canal [1]. The bulb is usually larger on the right side, reflecting the larger diameter of the sigmoid sinus on that side [1]. The internal jugular vein starts from the bulb and courses downward posterior to the internal carotid artery and styloid process (Figs. 2.1h, 2.2b, c, and 2.3a). The inferior petrosal sinus courses along the intracranial surface of the petroclival fissure and empties into the petrosal confluence before emptying into the jugular bulb (Figs. 2.2c and 2.3d).

There are several veins connecting the jugular foramen or internal jugular vein with the extracranial venous plexus. The posterior condylar emissary vein passing through the posterior condylar canal, which starts at the center of the condylar fossa, usually empties into the medial part of the sigmoid sinus (Fig. 2.2). The vein connects to the venous plexus around the vertebral artery and sigmoid sinus. The inferior petroclival vein, which courses along the extracranial surface of the petroclival fissure, usually empties into the petrosal confluence (Fig. 2.2b, c). The lateral condylar vein originates from the petrous confluence; courses lateral to the occipital condyle, medial to the internal jugular vein, carotid artery, and CNs IX–XII; and joins the venous plexus around the third segment of the vertebral artery. The venous plexus of the hypoglossal canal, which is also known as the anterior condylar vein, passes through the hypoglossal canal and communicates with the marginal sinus and petrosal confluence (Fig. 2.2b, c). The petrosal confluence has multiple connections with the sigmoid part of the jugular foramen, which usually consists of a large main channel and several small channels. The main channel drains into the medial wall of the jugular bulb between the glossopharyngeal and vagus nerves or directly into the internal jugular vein below the extracranial orifice (Figs. 2.2c and 2.3c) [1].

Neural Relationships

The glossopharyngeal, vagus, and accessory nerves pass through the intrajugular part of the jugular foramen and course along the medial margin of the intrajugular process of the temporal bone to reach the medial wall of the internal jugular vein (Fig. 2.1c, d). The hypoglossal nerve passes through the hypoglossal canal and descends along the medial wall of the internal jugular vein with the vagus and accessory nerves (Figs. 2.1a and 2.2b).

The glossopharyngeal nerve passes through the glossopharyngeal meatus, which is a dural recess located between the jugular dural fold and dural septum, then turns downward and courses along the medial side of the intrajugular ridge to exit the jugular foramen (Figs. 2.1f, 2.2c, and 2.3c). As the nerve courses downward in the high cervical region after it exits the foramen, it courses between the internal carotid artery and internal jugular vein to reach the lateral surface of the internal carotid artery deep to the styloid process (Figs. 2.2c and 2.3c). While the nerve passes through the jugular foramen, it expands at the site of its superior and inferior ganglia (Fig. 2.3d) [1]. Jacobson's nerve arises from the glossopharyngeal nerve at the external orifice of the jugular foramen and passes through the tympanic canaliculus to enter the tympanic cavity where it branches to form the tympanic plexus (Figs. 2.1f–h and 2.3d) [1].

The vagal nerve enters into the vagal meatus inferior to the glossopharyngeal meatus (Fig. 2.1d, e). As it passes through the foramen, its roots gather and form the superior ganglion; this is where the accessory nerve communicates with the vagal nerve (Figs. 2.1e and 2.3d). Arnold's nerve branches off at the level of the superior vagal ganglion and courses lateral in a groove on the anterior wall of the jugular

bulb to reach the lateral wall of the jugular fossa (Figs. 2.1e and 2.3d) [1]. The branch then enters into the mastoid canaliculus, ascends to the mastoid segment of the facial canal, and sends an ascending branch to the facial nerve before turning downward to exit the temporal bone through the tympanomastoid fissure.

The accessory nerve enters the vagal meatus and meets the vagal nerve at the level of the superior vagal ganglion. The accessory nerve then divides into internal and external branches after it exits the jugular foramen. The internal branch joins the vagus nerve, and the external branch descends obliquely between the internal carotid artery and internal jugular vein and then backward across the lateral surface of the vein to reach the sternocleidomastoid and trapezius muscles (Fig. 2.3b–d) [1]. The external branch usually courses along the lateral, but occasionally the medial, surface of the internal jugular vein to reach the muscles. In our dissection, the accessory nerve coursed downward between the internal jugular vein and transverse process of C1 (Fig. 2.3a, b).

Though the hypoglossal nerve passes through its own canal and not the jugular foramen, it joins the glossopharyngeal, vagus, and accessory nerves, which exit the jugular foramen just below the skull, and these nerves descend together along the internal carotid artery and internal jugular vein (Figs. 2.2d and 2.3b–d). After the hypoglossal nerve exits the hypoglossal canal, it descends and turns anteriorly toward the tongue at the level of the transverse process of the atlas (Figs. 2.2d and 2.3c).

Surgical Anatomy for Jugular Paraganglioma: Postauricular Transtemporal Approach and Far-Lateral Approach

To access jugular paragangliomas, Fisch's infratemporal fossa type A approach and its extension are commonly used [5, 6]. The postauricular transtemporal approach is a modification of Fisch's infratemporal fossa type A approach [7]. To clarify the microsurgical anatomy of the jugular foramen and its surrounding structures in the surgical view, cadaveric dissection of the postauricular transtemporal approach has been performed step-by-step for this chapter. If the tumor extends into the posterior cranial fossa, the far-lateral approach and its extension or the transjugular procedures are required. Since many approaches have been reported, surgeons should precisely understand the surgical anatomy of the area and select or combine, if necessary, these approaches based on the tumor location and extension [8–25].

For the postauricular transtemporal approach, the first step is high cervical exposure to control and avoid damage to the internal jugular vein, internal carotid artery, and lower cranial nerves. Detaching the muscles from the mastoid process, including the sternocleidomastoid, semispinalis, longissimus, and digastric muscles, exposes the rectus capitis lateralis muscle, transverse process of C1, and suboccipital triangle. To access the jugular foramen, transverse process of C1, mastoid tip, parotid gland covering the facial nerve, and rectus capitis lateralis are still obstacles (Fig. 2.4a).

Next, an infralabyrinthine retrofacial mastoidectomy is necessary to access the jugular bulb, mainly for the exposure of its superior and lateral aspects (Fig. 2.4b). After exposing the sigmoid sinus, drilling downward along the anterior surface of the sigmoid sinus exposes the jugular bulb. Carefully drilling the bone above the jugular bulb exposes the cochlear aqueduct, a landmark for identifying the glossopharyngeal groove of the temporal bone; the cochlear aqueduct opens into the pyramidal fossa located medial to the glossopharyngeal groove of the temporal bone (Fig. 2.4c and e). Drilling the bone inferiorly into the jugular process can expose the posterior surface of the jugular bulb (Fig. 2.4c). Removing the mastoid tip and drilling the bone along the occipitomastoid suture downward while exposing the sigmoid sinus exposes the insertion of the rectus capitis lateralis muscle into the inferior surface of the jugular process (Fig. 2.4d). In this stage, extreme care should be taken to avoid damage of the sinus, and it is necessary to control the bleeding from the veins connecting to the internal jugular vein, jugular bulb, sigmoid sinus, and anterior condylar confluence. The removal of the jugular process and rectus capitis lateralis are a critical step to expose the posteroinferior aspect of the jugular bulb (Fig. 2.4d, e).

Without anterior rerouting of the facial nerve and removal of the jugular process, the surgical field is limited. Some authors have reported that paragangliomas can be removed without rerouting the facial nerve, but this depends on the case. To gain a wide enough surgical view for access to the paraganglioma and control of the petrous carotid artery, the removal of the styloid process and base of the tympanic bone, temporomandibular joint, parotid gland, pterygoid muscles, and external auditory canal in addition to the anterior rerouting of the facial nerve should be considered. The fallopian bridging technique can provide exposure of the area anterolateral to the jugular bulb and the middle ear cavity. In this dissection, the junction of the inferior petrosal sinus and jugular bulb has been identified (Fig. 2.4e). However, it is extremely difficult to control the petrous carotid artery. After removal of the external auditory canal, infracochlear drilling exposes the petrous carotid artery medial to the jugular bulb (Fig. 2.4h). Both distal and proximal control of the internal carotid artery can be achieved after rerouting the facial nerve anteriorly, which is the basic principle for jugular paraganglioma resection [26–31]. In some cases, the approach without rerouting or minimal inferior rerouting of the facial nerve has been performed by several authors to preserve the facial nerve function (Fig. 2.4e) [32–34].

Intracranial extension of a paraganglioma can be accessed by the addition of the presigmoid, retrosigmoid, or trans-sigmoid approach. Opening the dura in the style of the trans-sigmoid approach is commonly used to attain total resection of the tumor. For this step, a precise understanding of the relationships among the intracranial and extracranial structures of the jugular foramen is crucial. In this chapter, views of the presigmoid and retrosigmoid routes are shown. These approaches can provide access to the area superior and medial to the jugular foramen. For the retrosigmoid approach, the addition of a lateral suboccipital craniotomy is needed to access the lower cranial nerves intracranially. The lateral suboccipital approach (retrosigmoid approach) is one of the most popular procedures to reach the CP

angle. The far-lateral approach is an extensive modification of the lateral suboccipital approach. The basic far-lateral procedure without the drilling of the occipital condyle can reach the intrajugular area where the lower cranial nerves (IX, X, and XI) enter the jugular foramen intracranially.

After detaching the muscles from the superior and inferior nuchal line and reflecting these muscle inferiorly, the condylar fossa, vertebral artery, and the surrounding venous plexus, which is continuous with the posterior condylar emissary vein passing through the condylar canal located superior to the occipital condyle, can be exposed. Then, craniotomy is performed according to the extension of tumor. Furthermore, partial condylectomy can be added if necessary. The far-lateral approach provides enough space to access the lower cranial nerves intracranially (Fig. 2.5). Without removing the jugular process and the rectus capitis lateralis, exposing the jugular bulb may be impossible (Fig. 2.5c, d). To expose the hypoglossal canal and its junction with the medial surface of the internal jugular vein, drilling the occipital condyle is necessary (Figs. 2.2a, b and 2.5b, d). Drilling the jugular process after detaching the rectus capitis lateralis muscle from its inferior surface exposes the posteroinferior surface of the jugular foramen (Fig. 2.5c, d).

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Chapter 3
Presentation and Differential Diagnosis of Jugular Paraganglioma

Stan Pelosi and David W. Chou

Introduction

Jugular paragangliomas (JPs) are the most common tumors found in the jugular foramen. The presenting signs and symptoms of JP vary according to tumor behavior and extent of disease. While they rarely metastasize, JP produce symptoms related to compression, displacement, and invasion of structures adjacent to the jugular foramen and major vasculature. The most common symptoms of JP are ipsilateral hearing loss and pulsatile tinnitus. Less commonly, involvement of cranial nerves VII and IX–XII may result in facial paralysis, dysphagia, hoarseness, and other manifestations. Rarely are symptoms found in isolation. Up to 15% of these tumors are asymptomatic [1].

Overall, JPs exhibit a strong female predilection, occurring up to six times more frequently in females than in males [2–4]. Bilateral tumors are seen in 1–2% of cases [5]. The typical age of presentation is in the fourth or fifth decade of life, though patients may present in teenage years or much later in life [1–3, 6].

Familial paragangliomas occur in 10–30% of all cases of head and neck paraganglioma [1, 7]. Patients with familial paraganglioma may present in their 30s or earlier [8]. Unlike in sporadic cases, familial paragangliomas have an equal sex prevalence [9] and are more likely to be associated with multicentric tumors, most commonly carotid body tumors. There are a number of classification schemes for

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Table 3.1 Fisch classification of jugular paragangliomas [10]

A	Tumor limited to middle ear space
B	Tumor limited to the middle ear or mastoid without involvement of the infralabyrinthine space of the temporal bone
C	Tumor involving infralabyrinthine and apical spaces of temporal bone, with extension into the apex
C1	Tumor with limited involvement of vertical portion of the carotid canal
C2	Tumor invading vertical portion of carotid canal
C3	Tumor invasion of horizontal portion of carotid canal
D1	Tumor with intracranial extension less than 2 cm in diameter
D2	Tumor with intracranial extension greater than 2 cm in diameter

Table 3.2 Glasscock-Jackson classification of jugular paragangliomas [11]

I	Small tumor involving the jugular bulb, middle ear, and mastoid
II	Tumor extending under internal auditory canal; may have intracranial extension
III	Tumor extending into the petrous apex; may have intracranial extension
IV	Tumor extending beyond petrous apex into the clivus and infratemporal fossa; may have intracranial extension

JP. The Fisch classification [10] (Table 3.1) and the Glasscock-Jackson classification [11] (Table 3.2) are most frequently used today and are based on tumor size and extent of disease.

Symptoms

Hearing Loss

Hearing loss is seen in 60–85% of patients [1–3]. Hearing loss is most commonly conductive and results from tumor extension into the middle ear with involvement of the tympanic membrane, ossicular chain or round window. Less commonly, sensorineural hearing loss may result from tumor invasion of the bony labyrinth [1, 4, 5].

Pulsatile Tinnitus

Pulsatile tinnitus is the perception of auditory stimuli that is synchronous with the heartbeat [12]. It is commonly seen in JP as the tumor invades the petrous bone and compresses local neurovascular structures. The incidence of pulsatile tinnitus in patients with JPs is approximately 75% [1, 2].

There are a few hypotheses as to why this phenomenon occurs. It may result from nonlaminar, turbulent blood flow through regional blood vessels which transmit sound to the inner ear [12–14]. Another possibility is that the sound of normal flow is more intensely perceived, whether due to increased bone conduction in the inner ear or decreased conduction of external sounds [14]. Finally, pulsatile movement of the tympanic membrane, ossicles, or round window membrane may result in this symptom.

Cranial Nerve Paralysis

A number of other symptoms are associated with compression of the lower cranial nerves (CN) in the jugular foramen and surrounding structures. Overall, cranial nerve deficits are seen in approximately 40% of patients with JP at time of presentation [15–18]. Encasement and invasion of the facial nerve, most commonly in the mastoid segment, may result in sudden or progressive facial paralysis occurring in up to 25% of cases [2, 19, 20].

Cranial nerves IX, X, XI, and XII may also be involved due to their proximity to the jugular foramen [5]. Signs and symptoms include dysphagia (CN IX), nasal regurgitation, rhinolalia, hoarseness (CN X), shoulder droop (CN XI), and tongue weakness (CN XII). Tongue weakness is most commonly caused by medial growth of tumor into the region of the hypoglossal canal and can be seen in up to 20–40% of patients [2, 21].

Otalgia and Otorrhea

Several published series have described otalgia, occurring in 5–40% of patients [1, 2]. As the tumor expands to include the middle ear space, the Eustachian tube orifice or mastoid antrum may become blocked, resulting in effusion or symptomatic mastoid or middle ear inflammation. Involvement of the tympanic plexus, pressure on the tympanic membrane, or eruption into the external auditory canal may also incite fullness, pressure, or pain. JPs may erode through the tympanic membrane in 14–24% of patients, causing bloody or purulent otorrhea [1, 2].

Papilledema and Vision Loss

In rare instances, JPs may cause hydrocephalus, resulting in papilledema and vision loss. The development of elevated intracranial pressure may occur from intracranial tumor extension with brainstem compression (non-communicating hydrocephalus), occlusion of a dominant venous outflow system, or involvement of bilateral jugular

venous systems in cases of multicentric disease (communicating hydrocephalus). If left untreated, elevated intracranial pressures may lead to vision loss, coma, or death [22, 23].

Cough Syncope

Cough syncope is another unusual presentation of JP. It has been described in a patient with elevated intracranial pressure from communicating hydrocephalus. It was hypothesized that coughing episodes resulted in transient elevations in baseline high intracranial pressure, leading to intermittent tonsillar herniation and syncope [24].

Vertigo

Vertigo is uncommon as a presenting symptom but may result from involvement of the bony labyrinth, vestibulocochlear nerve, or brainstem. There are only a few case reports of patients presenting initially with worsening dizziness as a primary complaint [25, 26].

Catecholamine-Secreting Tumors

Histochemical studies have shown that all paragangliomas secrete catecholamines at some level, but less than 4% secrete enough to cause symptoms [1, 27]. The release of excess catecholamines may cause palpitations, headaches, and uncontrolled hypertension [5, 8, 28–32]. Patients with familial head and neck paragangliomas also have an increased risk of developing abdominal and thoracic pheochromocytomas [9]. Carcinoid syndrome is a rare manifestation of JP, resulting in symptoms of diarrhea, facial flushing, and headaches due to elevated 5-hydroxyindoleacetic acid, the main metabolite of serotonin [33].

Physical Exam

A pulsatile red or purple hypotympanic or mesotympanic mass is a characteristic of JP (Figs. 3.1 and 3.2). When the entire circumference of the tumor can be seen on otoscopy, the diagnosis of a glomus tympanicum can be made. However, it is impossible to distinguish a glomus tympanicum and JP on physical examination

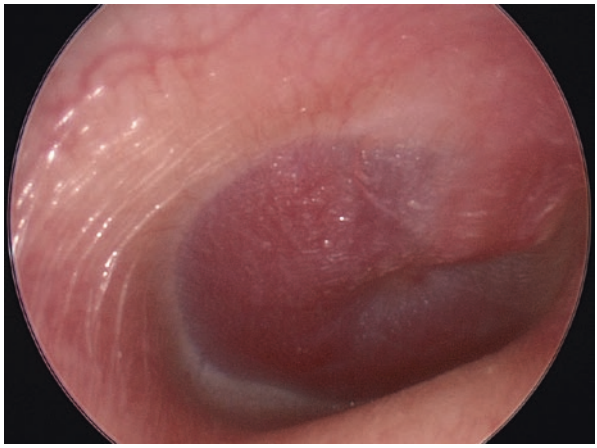

Fig. 3.1 Jugular paraganglioma presenting as retrotympanic mass involving most of the middle ear space (*Courtesy of George Wanna, MD*)

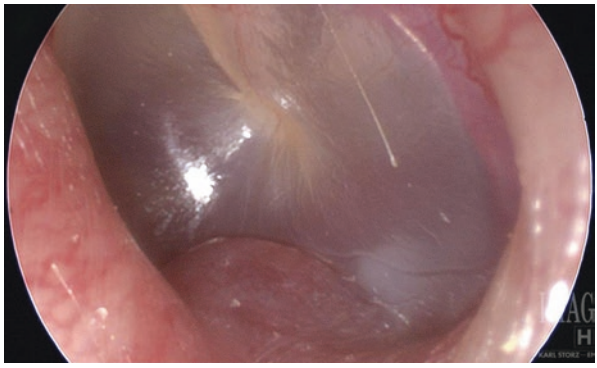

Fig. 3.2 Jugular paraganglioma involving the hypotympanum (*Courtesy of George Wanna, MD*)

alone when the inferior aspect of the tumor extends below the tympanic ring into the hypotympanum—in such cases, additional imaging is required to determine the extent of the tumor. The "rising sun" sign has been used to describe the red appearance of a tumor seen on otoscopy when it ascends from the floor of the middle ear. The tumor may often develop prominent canal vasculature surrounding the mass, likened to sunrays. The retrotympanic mass may initially pulsate more vigorously, and then blanch with positive pressure using pneumatic otoscopy, a finding known as Brown's sign (pulsation sign). Some tumors can erode through the tympanic membrane, whereby an inflamed polypoid growth in the medial external auditory canal can be seen [2, 5]. Aquino's sign refers to blanching and decreased pulsation of the mass with manual compression of the ipsilateral carotid artery. Additionally, an audible bruit may be auscultated in the mastoid or infra-auricular region.

Multicentric paragangliomas develop in 10–20% of sporadic tumors and in up to 80% of familial cases [24]. Head and neck paragangliomas may arise from other

locations aside from the jugulotympanic region, including paraganglia of carotid bodies (most common), or along vagal, distal laryngeal or facial nerves or from the sympathetic chain. Cervical head and neck paragangliomas commonly present with an asymptomatic neck mass, which can be pulsatile [34].

Differential Diagnosis

Jugular paragangliomas are the most frequently occurring tumors of the jugular foramen, accounting for at least half of lesions of the jugular foramen [6]. The differential diagnosis includes benign and malignant neoplasms as well as vascular lesions that are most easily differentiated by neuroimaging [6, 35]. A case series of 106 patients who underwent surgery for jugular foramen lesions are identified, in order of incidence: paragangliomas, schwannomas, meningiomas, chondrosarcoma, carcinoma, aneurysmal bone cyst, chordoma, cholesteatoma, chondroma, lymphangioma, and inflammatory granuloma [6].

After paragangliomas, schwannomas and meningiomas are the next most common tumors of the jugular foramen [6]. Lower cranial nerve schwannomas may present with palate insufficiency, hoarseness, dysphagia, dysarthria, as well as weakness of the trapezius and sternocleidomastoid muscles [35]. The imaging of schwannomas is unique compared to JP and meningioma. Specifically, CT commonly demonstrates a widened jugular foramen with smooth borders, and lower cranial nerve schwannoma generally does not invade the middle ear or mastoid. MRI usually demonstrates a round neoplasm, potentially with a dumbbell appearance between the posterior fossa and upper neck. Schwannomas are characteristically isointense of T1 imaging, iso- to hyperintense on T2 imaging, and avidly enhance with gadolinium. In most cases, schwannomas do not develop prominent flow voids.

Meningiomas that are centered in the jugular foramen are considered primary jugular foramen tumors, while secondary meningiomas develop elsewhere in the posterior fossa but extend into the jugular foramen. Primary meningiomas are characterized by invasive growth into the skull base often involving the middle ear, jugular tubercle, hypoglossal canal, occipital condyle, and clivus [35]. A great majority of patients with meningiomas present with lower cranial nerve deficits and most commonly report a history of hoarseness and dysphagia [6]. Compared to schwannomas and JP, meningioma usually exhibits dural “tails” or tapering of the peripheral tumor margin with the surrounding dura. Meningiomas are also commonly associated with hyperostosis of the underlying skull base, best demonstrated on CT.

Finally, JPs are found centered on the jugular foramen, with invasive ill-defined margins resulting in a moth-eaten appearance in the bone on CT. JPs nearly always involve the middle ear space to some degree. Distinguishing JP and isolated glomus tympanicum can be challenging in some cases. Generally, erosion of the bone over the jugular bulb or demineralization of the jugulo-carotid spine indicates a JP, while strict involvement of the tympanic cleft suggests an isolated tympanic paraganglioma. T1- and T2-weighted MRI commonly exhibits prominent flow voids in the

substance of the tumor, reflecting the great vascularity of the tumor. Conventional angiography may assist in evaluation when the diagnosis remains in question. Vascular abnormalities in the middle ear can also present with similar features to JP. A dehiscent high-riding jugular bulb can present with conductive hearing loss, pulsatile tinnitus, and a purple mass in the hypotympanum [36, 37]. Similarly, an aberrant or laterally displaced carotid artery may also present similarly [38].

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Chapter 4
Imaging of Jugular Paragangliomas

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Abbreviations

CBT	Carotid body tumors
CT	Computed tomography
FLAIR	Fluid-attenuated inversion recovery
HN-PGL	Head and neck paraganglioma
J-PGL	Jugular paraganglioma
MD-CTA	Multidetector CT angiography
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography/computed tomography
PPGL	Pheochromocytomas paragangliomas
SDH	Succinate dehydrogenase gene
STIR	Short tau inversion recovery
TRICKS	Time-resolved imaging of contrast kinetics technique

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Aim and Scope

This chapter aims at defining the ideal imaging evaluation for jugular paraganglioma (J-PGL). Relevant imaging modalities are reviewed in separate sections to emphasize their recent developments. Recommendations are then stressed to help skull-base surgeons in elaborating an individualized plan of imaging at each step: initial workup, wait and scan monitoring, preoperative planning, and post-therapeutic surveillance.

Introduction

Jugular paragangliomas (J-PGL) involve a limited anatomical area rich in critical neural and vascular structures. Reliable bony landmarks are precisely identifiable on computed tomography scan (CT scan) of the petrous bone. Soft tissue is best assessed on magnetic resonance imaging (MRI) of the skull base. Both imaging modalities have considerably evolved leading to increased spatial resolution. Similarly, increasing knowledge in contrast uptake patterns results in improving temporal resolution. Both evolutions result in improved diagnostic certainty of J-PGL and lower the risk of misdiagnosing other pathologies (i.e., meningioma, schwannoma, meningeal hemangiopericytoma). The choice of the imaging technique (CT, CT angiography, MRI, MRI angiography) depends mainly on the initial clinical presentation and suspected diagnosis. A J-PGL is usually suspected in the presence of a vascular middle ear mass associated with a pulsatile tinnitus and/or lower cranial palsy (dysphonia, swallowing disorder, choking). A conductive hearing loss indicates an extension to the mesotympanum with or without ossicular chain involvement. In large J-PGL, other clinical signs may be present (e.g., sensorineural hearing loss, facial palsy). The clinician will choose the ideal imaging modality to detect the suspected pathology and to study its size and extensions. In the absence of lower cranial nerve involvement, imaging is still needed in most cases to classify the paraganglioma between tympanic or jugular. Additional imaging studies including functional imaging are necessary to precisely elaborate on a personalized plan of treatment. Indeed, recent advances in the genetics of pheochromocytomas/paragangliomas (PPGL) highlight the need for thorough initial workup. The uncertainty of the natural history requires selecting a reasonable workflow for a potentially lifelong follow-up. The imaging evaluation is critical to the selection and planning of therapeutic options and should therefore be familiar to any physician in charge of J-PGL patients.

Jugular paragangliomas are benign neoplasm arising from the adventitia of the jugular vein at the level of the jugular foramina. This rare tumor belongs to the larger family of pheochromocytoma/paragangliomas (PPGL), a homogeneous group of tumor pathology potentially located at multiple sites. J-PGL accounts for the second most common head and neck paraganglioma, preceded by carotid body tumors (CBT). Due to its location at initiation, J-PGL frequently involves multiple lower cranial nerves in the pars nervosa of the jugular foramina or at the skull base

in the infratemporal fossa. Intraluminal growth will often involve the inferior petrosal sinus, proximal sigmoid sinus, or jugular vein. Extraluminal extension progressively invades the internal carotid artery wall, facial nerve at the fallopian canal, middle/external ear, or otic capsule. J-PGL may also extend to the neck along the jugular vein or cranial nerves or to the cerebellopontine angle. Genetic predisposition to paraganglioma development is now well described with syndromes preferentially affecting the cervical area or association of adrenal and extra-adrenal locations. Considering the prevalence of genetic predisposition, a patient presenting with an apparently isolated J-PGL may benefit from a genetic evaluation and/or imaging screening. The development and diagnosis of malignant PGL are subject to debate. The presence of PGL in lymphatic tissue or vertebrae suggests metastatic spread rather than de novo onset. In large cohort of patients, malignancy has been reported in approximately 7.7% of patients [1].

CT Imaging

Computed Tomography

High-resolution CT imaging is the best technique for demonstrating characteristic bony destructive skull-base changes (Fig. 4.1a–d). CT angiography aids in the diagnosis of glomus tumors with peak tumor opacification appearing at the arterial phase [1].

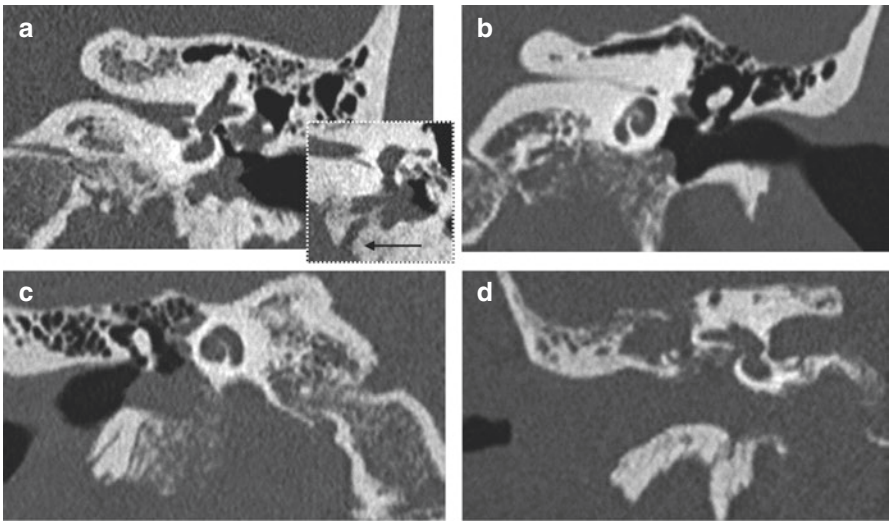


Fig. 4.1 Jugular paraganglioma arises from the jugular bulb. It frequently involves the surrounding bone and extends to the hypotympanum through the Jacobson's canal (*black arrow*, **a**). Bone destruction is a well-documented CT characteristic of skull-base tumors. J-PGL classically causes an erosive or permeative pattern at a late stage. Typical extensions are shown in (**a–d**). This figure highlights the different patterns of extension with increasing bony erosion involving the hypotympanum, mesotympanum, infracochlear area, tympanal bone, and sulcus tympanicum

The goal of the imaging is:

1. To narrow the differential diagnosis. The most frequent lesions in the jugular foramen region are jugular paraganglioma (60–80%), schwannoma/neuromas, and meningiomas (both approximately 10%) [2]. Rarely, primary bone (giant cell tumor, chondrosarcoma, and chondroblastoma) and masses within the subarachnoid space (epidermoid cyst) can also affect this region. Jugular foramen metastasis and pseudotumor have been described as well as dehiscent jugular bulb [3].
2. To define the extension of the lesion. Multidetector CT angiography (MD-CTA) has expanding capabilities including isotropic multiplanar reconstruction, improved temporal and spatial resolution, and angiographic analysis [2]. The same exam can assess bony erosion, tumor extension, and contrast agent uptake at the arterial and venous phases.

CT is the best exam to look at the normal anatomy of the jugular foramen. The lateral (pars vascularis) and medial (pars nervosa) can be well defined and compared to the healthy side. The intrajugular process which is typically dividing these two compartments can be visualized if ossified. It joins the jugular process of the occipital bone to the jugular spine of the petrous temporal bone. Both of these structures can be eroded by the lesion. The analysis of the tumor in the coronal plane allows to distinguish between hypotympanic and tympano-jugular forms of paraganglioma which is of the utmost importance in the treatment plan. CT is able to detect an erosion of the carotid canal, the fallopian canal, the ossicles, and the inner ear. Irregular erosive enlargement of the jugular foramen is typical of a jugular paraganglioma. Suggestive CT findings include jugular foramen enlargement (length plus width >20 mm) predominantly involving the pars nervosa with irregular bony margins and erosion of the jugular bulb and vascular crest. In contrast, jugular foramen schwannomas are well-circumscribed tumors that tend to push rather than invade structures. Thus, bony changes typically demonstrate an enlarged foramen with more regular and smooth margins. The mean radiodensity of J-PGL is 210 HU compared with 69 HU for neuromas [4]. Of note, some critical area should be assessed from the beginning since less than 1 mm growth may be sufficient to hamper the prognosis (e.g., facial nerve, cochlea, CPA angle) (Figs. 4.2 and 4.3). The association of MRI imaging alongside contrast uptake timing with CT angiography can more accurately characterize the lesion (Fig. 4.4).

CT Angiography (Figs. 4.5 and 4.6)

At the authors' center, helical CT angiography is performed to allow 3D reconstruction on a Philips Brilliance 40-slice scanner. Acquisition comprises a double spiral with arterial and venous phases using the following parameters: pitch, 1; table speed, 2 mm/s; slice thickness, 0.6 mm; and reconstruction every 0.3 mm, acquisition time (variable as a function of the number of rows), 120 kV, 250 mAs. Contrast

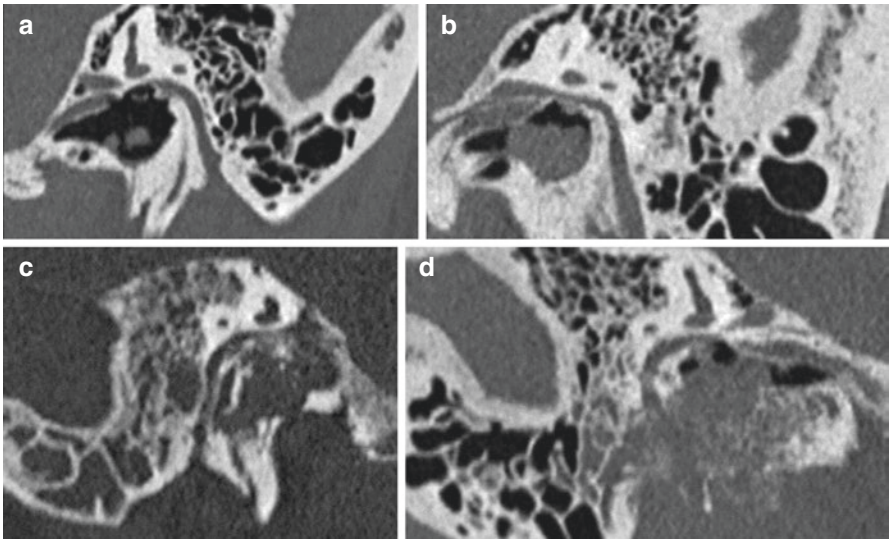


Fig. 4.2 The extension in the area surrounding the fallopian canal is determined using reconstruction along the course of the intratympanic and mastoid segment of the facial nerve from high-resolution temporal bone CT imaging. (**a**) left temporal bone CT-scan. Intact fallopian canal. (**b**) left temporal bone CT-scan. Hypotympanic tumor and decreased density of the bone surronding the fallopian canal. (**c**) right temporal bone CT-scan. erosion of the surronding bone respecting fallopian canal. (**d**) right temporal bone CT-scan. Bone destruction affecting the fallopian canal

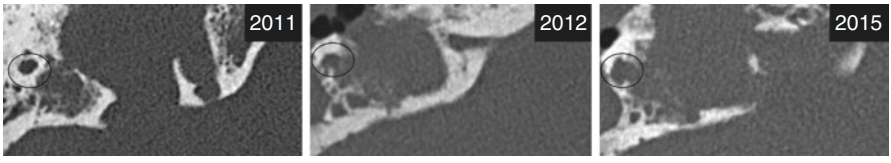


Fig. 4.3 Progressive erosion of the fallopian canal during the follow-up of a SDH-D-related jugular paraganglioma. Note the increasing erosion at risk of epineural spread

agent is injected by a power injector with the following parameters: 120 cc to 3 cc/s and then 30 cc to 1 cc/s and start time of 30 s for the first arterial spiral and 70 s for the second venous spiral. Vessels are well opacified during the two acquisitions with this type of injection. For tumors with arterial contrast enhancement, such as paragangliomas, the first spiral will be used for reconstruction, while, for tumors with later contrast enhancement (meningiomas or neuromas), the second spiral will be used for reconstruction [1]. With this workup, CT angiography avoids the need to perform invasive catheter angiography for diagnostic purpose. Christie et al. found that the mean radiodensity of the paragangliomas was 210 HU (range 117–371 HU) compared with 69 HU (range 58–98 HU) for the neuromas when using a MD-CTA (64-slice CT scanner system (Philips Medical Systems, Cleveland, OH, USA)) with

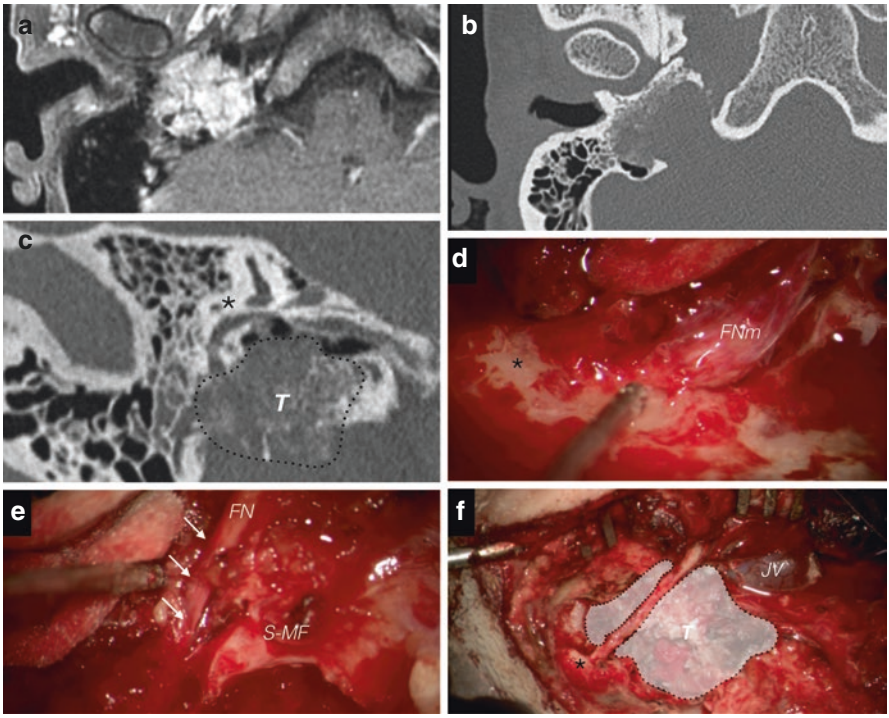


Fig. 4.4 Epineural spread of a jugular foramen paraganglioma in a SDH patient revealed by a facial paresis associated with conductive hearing loss. (**a**) Axial post-contrast T1 MR imaging showing intense gadolinium uptake of a tumor surrounding the facial nerve. (**b**) Axial high-resolution CT scan of the temporal bone showing bony erosion of the tumor raising from the jugular foramina and extending to the mastoid. (**c**) Involvement of the facial nerve at the stylomastoid foramina. (**d**) Surgical view of the mastoid segment of the facial nerve (FNm) with edematous change (*black asterisk*: lateral semicircular canal). (**e**) The facial nerve is freed off of tumor at the stylimastoid foramina (S-MF). (**f**) The facial nerve is preserved and anteriorly rerouted for further tumor resection (T)

120 kV and 400 mAs and 60 ml of contrast medium (Iobitridol, 350 mg iodine/ml; Xenetix, Guerbet, Roissy, France). Since both arterial and venous uptakes are necessary, imaging was started 40 s after the start of the contrast medium injection. The pitch was set at 0.891 with a detector configuration of 4 1.25 or 64 0.625 mm. A 50% overlap of the reconstructed axial sections was achieved with a section width of 1 mm and 0.5 mm increment (Fig. 4.7).

Jugular vein analysis on CT angiography (compression, occlusion, tumor infiltration) brings up important information when a surgical treatment is scheduled. This can influence the surgical planning (e.g., sacrifice of the jugular vein to ensure adequate tumor removal) (Fig. 4.5c, e, f). If computer-assisted navigation is scheduled for surgery, a dedicated CT evaluation is required to ensure the best possible registration (Fig. 4.8).

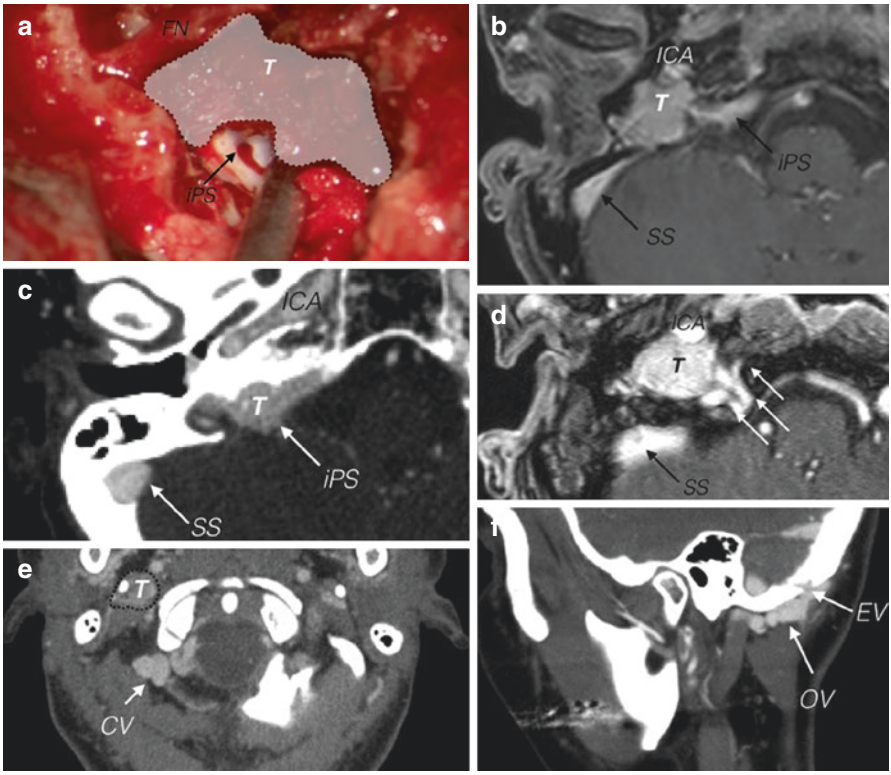


Fig. 4.5 Venous anatomy relevant to J-PGL (FN, facial nerve; T, tumor; iPS, inferior petrosal sinus; ICA, internal carotid artery; SS, sigmoid sinus; CV, condylar vein; EV, emissary vein; OV, occipital vein). (**a**) Surgical view during the opening of the jugular bulb. The J-PGL is involving the outer part of the vein and the medial plane is free of tumor. Note the opening of the inferior petrosal sinus medially to the tumor. (**b**) Inferior petrosal sinus may be enlarged on the side of the tumor. It is important to assess its volume prior to surgery since it may be a source of an important bleeding. (**c**) Intraluminal extension of the J-PGL into the inferior petrosal sinus. This extension might be difficult to safely resect during surgery since it would hamper the functional prognosis of the lower cranial nerves. (**d**) The hypoglossal canal should as well be assessed since it may provide collateral venous drainage to the tumor that can be exposed to increased bleeding during surgery when dissecting the medial wall of the internal carotid artery. (**e**) Collateral drainage through the condylar vein. (**f**) Collateral drainage through the emissary vein and occipital vein

MR Imaging

Diagnosis of PGL with MRI

Typical MRI demonstrates low signal on T1-weighted images and an intermediate to high signal on T2-weighted MRI images. The presence of tumor flow voids often referred to as “salt-and-pepper” appearance is characteristic of the condition but not specific. Flow signal voids in the tumor are well seen on spin-echo sequences.

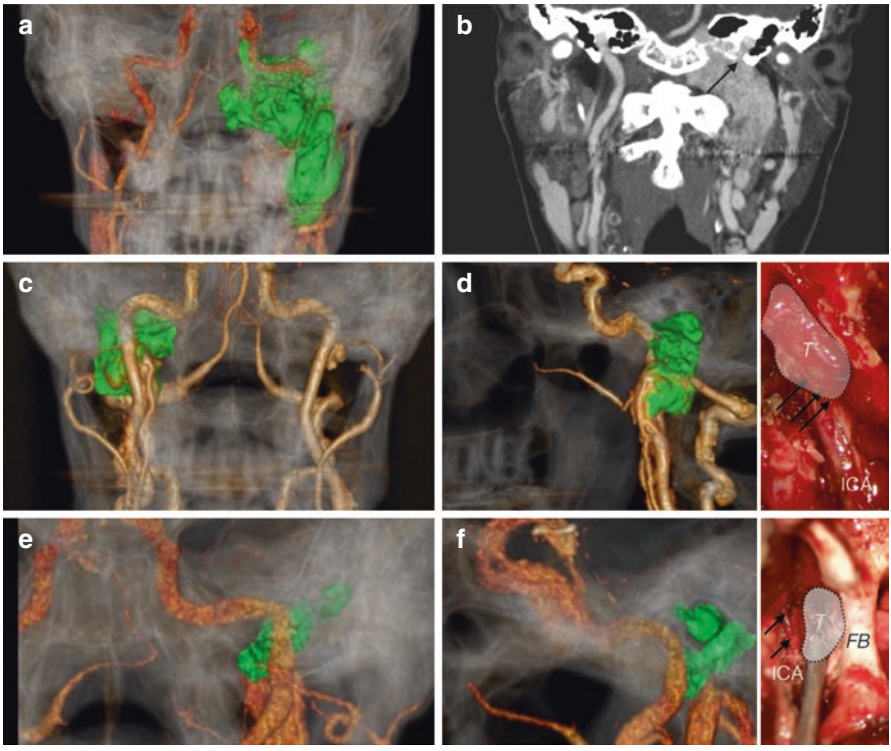
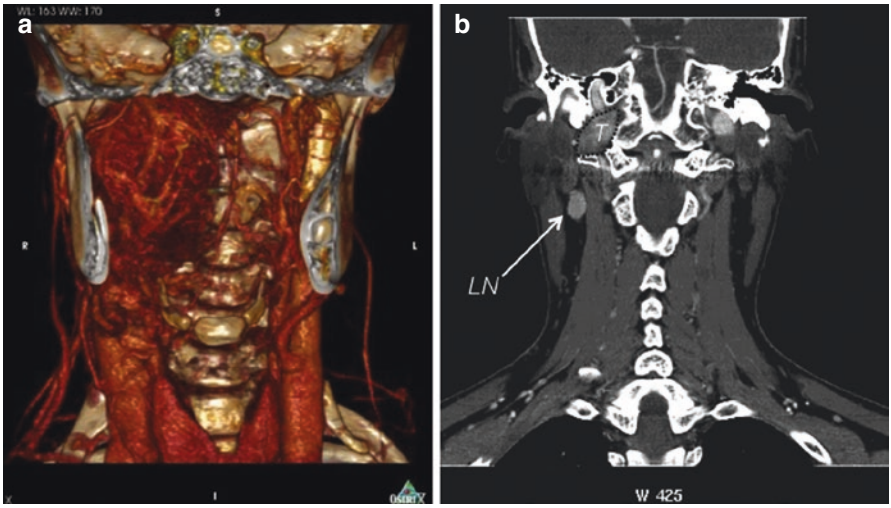


Fig. 4.6 Internal carotid artery (ICA) involvement assessed using CT angiogram with 3D reconstruction. (**a** and **b**) Internal carotid artery thrombosis, (**c** and **d**) extension of the J-PGL spreading in the adventitia of the ICA (T, tumor; *black arrows*, tumor removal is obtained by developing the plane in the vessel adventitia), and (**e** and **f**) adhesion of the J-PGL at the posterior border of the ICA. During surgery, the posterior limit of the ICA is easily identified with limited exposure and progressively freed off of tumor (modified Fisch technique without facial nerve rerouting and partial external auditory canal (EAC) resection eligible for reconstruction of the EAC)



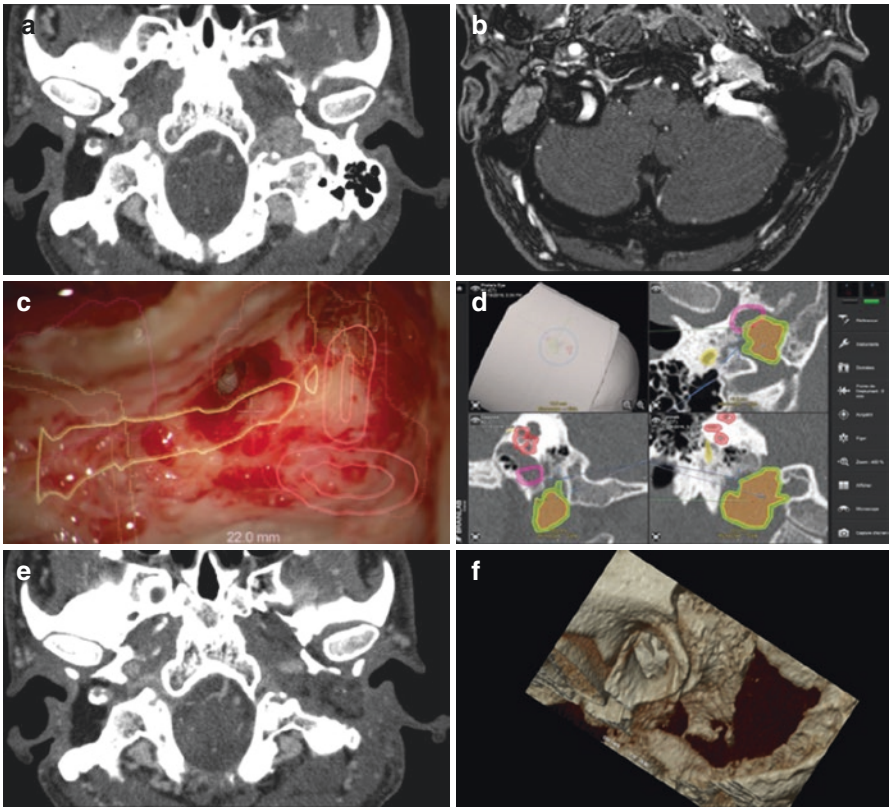


Fig. 4.8 Interest of computer-assisted navigation system during skull-base surgery for adapting the approach and eventual hybrid surgery (combined postoperative radiosurgery) using BrainLab Curve system. (**a**) T1 post-contrast MRI, (**b**) CT angiogram at the arterial time, preoperative aspect growing jugular paraganglioma on the *left side* followed over 6 years with an average tumor growth of 1 mm/year. (**c**) Preoperative view with multivision (Zeiss, Pentero 900 microscope) projecting the facial nerve (*yellow*), otic capsule (*red*), internal carotid artery (*pink*), and tumor (*orange* and *green*). (**d**) Multiplanar reconstruction during surgery is used to assess the extent of tumor resection. (**e**) Axial postoperative CT angiogram through the jugular foramen confirming an apparently complete resection. (**f**) Three-dimensional reconstruction of the lateral skull base showing the preserved and skeletonized external auditory canal

Fig. 4.7 (**a**) Malignant paragangliomas with aggressive feature involving the cervical spine, occiput, and skull base diagnosed on lymph node biopsy in a teenage girl with no familial history of PPGL. (**b**) Vagal paraganglioma with new onset of tumor in the spinal nerve area in SDH-B mutation carrier

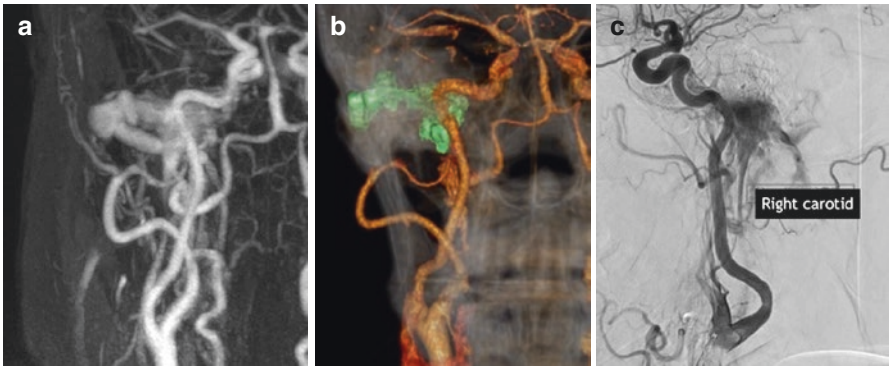


Fig. 4.9 Multimodal imaging for the assessment of a large jugular paraganglioma diagnosed in front of recurring arterial bleeding from the *right ear*. (**a**) MR angiogram, (**b**) CT angiogram with 3D reconstruction, (**c**) selective arteriography prior to embolization

(STIR) and fluid-attenuated inversion recovery (FLAIR). Christie et al. state that the expanding capabilities of MD-CTA, including isotropic multiplanar reconstruction, improved temporal and spatial resolution and angiographic analysis has thrown doubt into the previously accepted case for MRI superiority [4] (Fig. 4.9).

Overall, in view of the literature, we should consider MRI in patients with metastatic PPGL, for the detection of skull-base and neck paragangliomas, in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations requiring lifelong monitoring, and those with recent excessive radiation exposure) [6].

PGL Detection in SDHx Patients (Fig. 4.10)

MRI is widely used for the detection of HN-PGL. Knowing the lack of sensitivity of biochemical markers for HN-PGL, an imaging screening is recommended for carrier of predisposition syndrome associated with SDHx mutations [7, 8]. MRI scans of head and neck region could be performed according to the Dutch surveillance guidelines: follow-up every 3 years on a 1.5 Tesla scanner with 4 mm coronal and axial pre- and post-contrast T1-weighted sequences covering the posterior skull base and neck, as well as a dynamic contrast-enhanced MRA from the aortic arch to skull base [9]. Further development of protocols used in this background has occurred. In Gimenez-Roqueplo et al., the authors described the sensitivity of MRI in the diagnosis of HN-PGL occurring in a genetic setting. They used magnetic resonance imaging (MRI) to detect HN-PGL. The volume explored was from the skull base (including petrous bone) to the lower neck, with a 4-mm slice thickness. MRI sequences included transverse and sagittal plane T1-weighted spin-echo images, T2-weighted fast spin-echo images, and T2-weighted fast spin-echo with fat

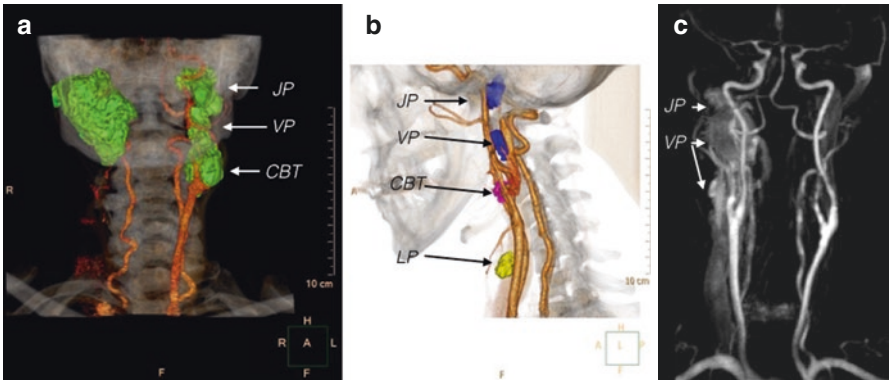


Fig. 4.10 Predisposition to pheochromocytomas and paragangliomas accounts for multiple localizations (JV, jugular paraganglioma; VP, vagal paraganglioma; CBT, carotid body tumor; LP, laryngeal paraganglioma). (**a, b**) CT angiograms with 3D reconstruction. (**c**) Post-contrast MR angiography used in the follow-up of a SDH-D patient

saturation images. After IV contrast injection of gadolinium chelate (0.1 mmol/kg body weight, gadoteric acid; Dotarem Guerbet, Aulnay-sous-Bois, France), a fast spin-echo T1-weighted sequence with fat saturation and three-dimensional time-of-flight angiography projection images were obtained. In the expert reading for detection of all paragangliomas or pheochromocytomas, head and neck MR angiogram plus TAP CT scan had a higher sensitivity than any other imaging modality at 91.7% (95% CI, 84.2–96.3) [8]. To decrease scan time, a short protocol was proposed making possible the combination of the head and neck screening MRI with the thoracic, abdominal, and pelvic (TAP) MRI screening recommended by the clinical practice guideline from the endocrine society. In this instance, a post-contrast 3D MR angiography at arterial phase is sufficient for the detection of HN-PGLs. It could be associated with post-contrast T1-weighted sequence in the protocol that provides additional diagnostic detail that assists in localizing HN-PGL. A MIP of 8–10 mm is essential to depict subcentimetric tumors by differentiating them from small vascular branches. The authors state that screening of HN-PGL in SDHx mutations carriers could be performed with only a post-contrast 3D MR angiography at arterial phase and a post-contrast T1 weighted with fat saturation sequence [10].

Functional Imaging

Functional imaging is useful to determine whether additional HN-PGL is present after the diagnosis of an isolated JPGL. In this instance, MRI is inferior to [^{18}F] FDOPA PET/CT [5]. It has low uptake in the brain and salivary glands. Therefore, it is currently recommended that all patients with HN-PGL be screened with functional imaging. [^{18}F] FDOPA PET-CT is yet the preferred modality to investigate

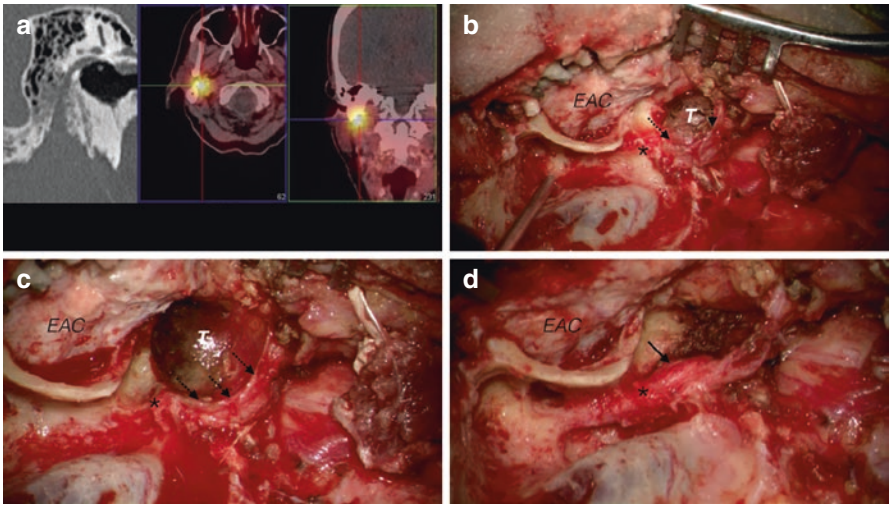


Fig. 4.11 Imaging and surgery of a facial nerve paraganglioma non-SDH related. (**a**) Note the erosion pattern centered on the fallopian canal at the stylomastoid foramina. (**a**) This sporadic paraganglioma demonstrates a strong uptake at octreoscan imaging. (**b**–**d**) Surgical resection of the tumor with a postauricular approach (EAC, external auditory canal; *black asterisk*, stylomastoid foramina; *black arrow*, facial nerve)

PGL and is superior to [^{18}F] FDG PET-CT except in SDH-B carriers [11]. Indeed, studies have found this exam to be very sensitive and specific for the detection of HN-PGL. It has shown a moderate to high uptake in particular in SDHx patients. Its use is meanwhile limited by its accessibility mostly in selected centers. The sensitivity is of interest for the detection of multiple localizations in SDHx patients or for the assessment of metastatic spread.

^{111}In-pentetreotide scintigraphy (Fig. 4.11) and ^{123}I-MIBG scintigraphy modalities are frequently used to assess PPGL. ^{111}In-pentetreotide scintigraphy has higher sensitivity although it is limited due to its lack of spatial resolution, it has proven to be useful in metastatic disease [12]. ^{123}I-MIBG scintigraphy has low overall sensitivity but high specificity in clinical practice of paraganglioma detection particularly in adrenal disease, familial paraganglioma/pheochromocytoma syndromes, and recurrent or malignant disease and is a highly valuable tool for the visualization of secreting tumors [13], though it has little efficacy in the detection of HN-PGL [12].

Tips

- Screen for multiple localizations: team up for a multidisciplinary approach to guide initial imaging workup.
- Monitor the natural history prior to treatment when asymptomatic. A yearly schedule is safe after detection.

- Use of less invasive, time relevant imaging techniques.
- Identify at risk extensions justifying high-resolution CT scan.
- Consider preoperative imaging for surgical planning to assess technical limitations for each treatment modality.

Pitfalls

- Forget to check for an associated pheochromocytoma and/or metabolic secretion: consider [^{18}F] FDOPA PET-CT or [^{18}F] FDG PET-CT in SDH-B patients.
- Inaccurate diagnosis due to inadequate imaging: combination of MRI and MD-CTA is useful for the diagnosis.
- Unnecessary repetition of radiating exams particularly in genetic PPGL-prone syndromes: use post-contrast 3D MR angiography at arterial phase and a post-contrast T1 weighted with fat saturation sequence when possible.

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Chapter 5
The Natural History of Jugular Paraganglioma

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Introduction

Jugular paragangliomas (JP) are uncommon, slow growing, highly vascular primary neoplasms of the temporal bone that develop from chief cells located in the adventitia of the jugular bulb [1–5]. The great majority of extra-adrenal paraganglioma reside in the abdomen, while only 10% are located in the head and neck—carotid body tumors (CBT) being most common, followed by JP and vagal paraganglioma (VP). Most JP are solitary, nonsecreting, and benign, while less than 5% are associated with catecholamine release or malignant character, and up to 17% of patients display multiple paragangliomas [6]. JP exhibit a female predominance and most commonly manifest during the fourth to fifth decades of life with symptoms of unilateral pulsatile tinnitus, conductive hearing loss, and less commonly lower cranial neuropathy. Owing to the rare prevalence and insidious growth, many patients endorse a long duration of preceding symptoms and are found to have advanced disease at diagnosis [1, 2].

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Following the refinement of infratemporal fossa surgical approaches and with improved access to advanced imaging modalities, the great majority of patients with JP treated in the 1980s and 1990s received upfront microsurgery with the goal of complete tumor removal [6–9]. However, even when performed by an experienced skull base surgical team, most patients with moderate to large JP were left with conductive hearing loss, transient or permanent facial nerve paralysis, and worsening lower cranial neuropathy following gross total resection [7, 10–12]. These outcomes led several pioneering groups to seek other treatment alternatives including subtotal tumor removal, stereotactic radiation, and observation; however, it was not until years later that these strategies gained more widespread acceptance [13].

Historically, radiation was largely reserved for recurrent disease, patients with advanced medical comorbidities, or palliation [12]. Part of this was driven by early clinical studies showing that radiation had little direct effect on tumor cells but also from concerns over using conventional nonconformal external beam radiation in the treatment of benign disease [14–16]. Primarily beginning in the 1990s, evidence emerged that stereotactic radiation therapy provided a viable treatment alternative to microsurgical resection, with a lower upfront risk of cranial neuropathy [17]. With time, the treatment paradigm for JP in the United States has evolved, and today many centers have adopted a strategy of upfront radiation treatment. Coinciding with the upsurge in radiation use, many centers now utilize aggressive subtotal tumor removal in patients with large JP as a method to reduce tumor volume while limiting morbidity [3, 18–21]. Still others have considered combined modality therapy—resecting middle ear tumor to improve conductive hearing loss and reduce or abolish pulsatile tinnitus while using stereotactic radiation to treat residual disease [19]. This strategy also carries the theoretical advantage of lowering the radiation dose to the cochlea. Together, these recent evolvements demonstrate that preservation of function has taken precedence to "surgical cure" from radical resection.

Since the primary treatment objectives of SRS are to halt tumor growth and mitigate worsening cranial neuropathy, rather than disease eradication, it is important to compare the results of SRS with the natural course of disease in order to delineate benefit. Akin to vestibular schwannoma, quoted rates of tumor control and cranial nerve outcomes following SRS are difficult to interpret without knowledge regarding the baseline natural history of untreated JP [22, 23]. Unfortunately, studies detailing the clinical course of untreated JP are sparse and needed [2, 23, 24]. Such information is particularly valuable toward counseling patients of advanced age, poor surgical candidacy, and subjects with limited symptoms. Herein, we review our experience with conservative management of JP and summarize other relevant reports. It is important to note that this chapter specifically discusses JP and not tympanic paraganglioma (i.e., glomus tympanicum). The latter arises from the tympanic plexus and is generally confined in the middle ear and mastoid. In these patients, we usually still advocate upfront tumor resection given the low risks of surgery and benefits of hearing improvement and relief of pulsatile tinnitus [25].

Natural History of Jugular Paraganglioma

To the best of the authors' knowledge, there have been only four major studies to date that have evaluated the clinical behavior and growth pattern of untreated JP [2, 13, 23, 24]. These studies come from experienced skull base centers and represent a small selected subpopulation of patients, which introduces selection bias and may limit generalizability. Furthermore, these studies did not utilize true three-dimensional volumetric analysis from segmentation, which is an important consideration given the irregular and often ill-defined tumor margin within the skull base. Despite limitations, these case series provide the best information to date on the natural history of JP.

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In 2015, Carlson et al. reviewed a 20-year experience at Vanderbilt University [2]. During this time period, there were 16 JP, in 15 patients, which received observation with serial MRI after initial diagnosis and had a minimum of 24 months of clinical follow-up. This represented a selected cohort of patients and fewer than 10% of all JP managed at the author's center between 1995 and 2015. The most common reasons for conservative management were advanced age and patient preference, while five patients refused intervention despite receiving recommendations for treatment, and two had bilateral skull base paragangliomas (Fig. 5.1).

The primary outcomes of interest were disease progression and treatment. Tumor volume was analyzed using three perpendicular axes using the ellipsoid volume calculation [24]. Growth was defined as a minimum 20% volume increase on consecutive imaging [24, 26].

Overall, the median age at diagnosis was 70 years (38–80 years) and 12 of 15 patients were women (Table 5.1). Hearing loss (12; 75%) and pulsatile tinnitus (11; 69%) were the most common symptoms, while vagal (6; 38%), accessory (3; 19%), and hypoglossal (2; 12%) paralyses were less common at diagnosis (Tables 5.2 and 5.3). The median duration between symptom onset and diagnosis was 31 months (range 0–144 months).

Six (38%) JP had growth through the medial wall of the jugular bulb with intracranial extension at the time of diagnosis (Table 5.4). The median tumor volume was 2.7 cm^3 (range 0.9–19.9 cm^3) and the median linear size was 2.0 cm (1.4–3.9 cm). There was no statistically significant correlation between age and tumor size at diagnosis ($p = 0.53$). Over a median imaging follow-up of 58 months (range 24–144 months), seven (58%) tumors were stable, while five (42%) enlarged with a median growth rate of 0.8 mm/year (range 0.6–1.6 mm/year) or 0.44 cm^3/year (0.14–0.87 cm^3/year). There was no age difference between the cohort of

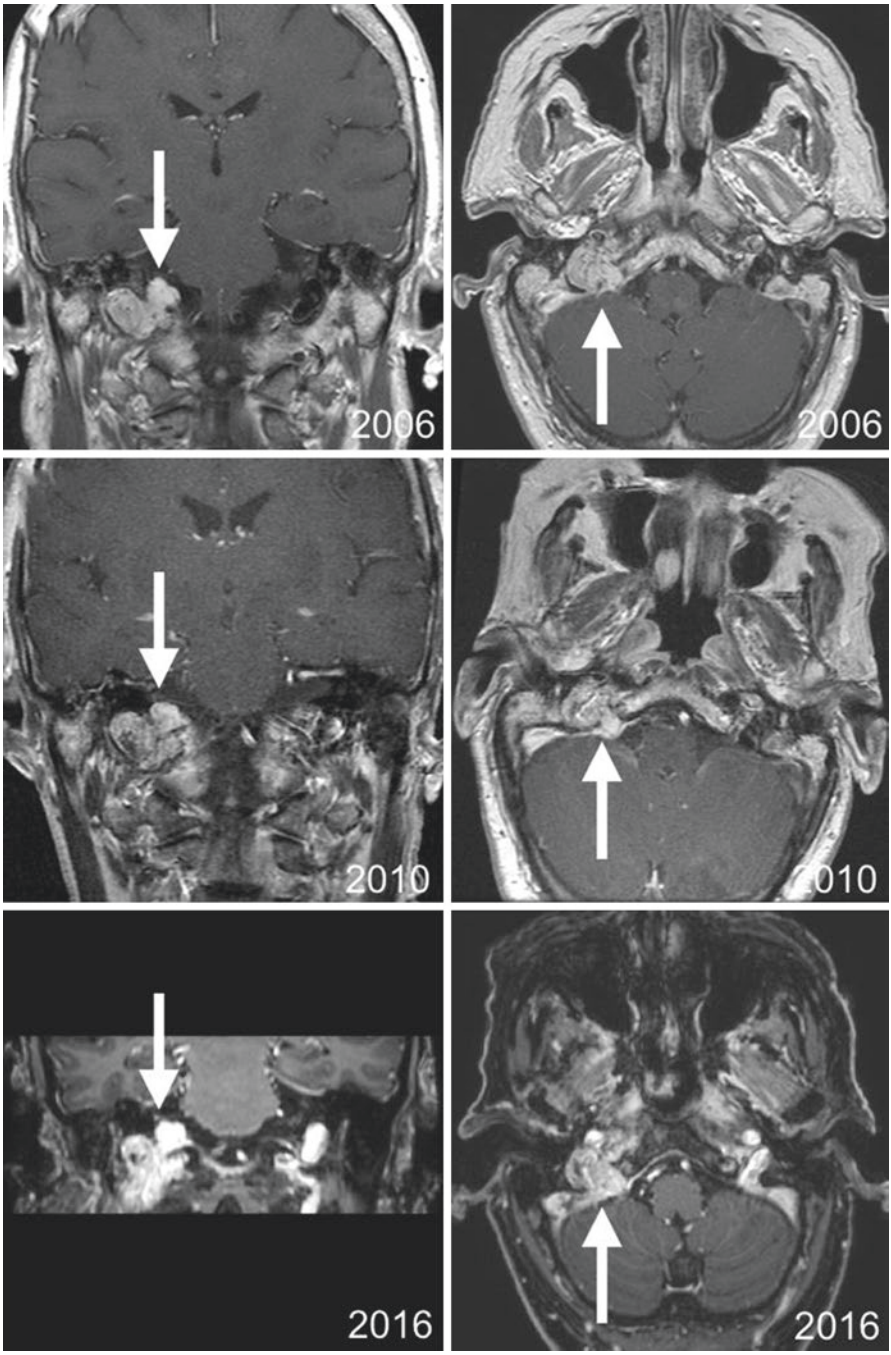

Fig. 5.1 Serial axial and coronal gadolinium enhanced T1-weighted MRI sequences of a right-sided JP demonstrating stable tumor size over the course of 10 years of observation

Table 5.1 Baseline features, interventions, and follow-up on 16 jugular paraganglioma tumors, 15 patients, initially managed with conservative observation

Baseline features			Intervention(s)			Clinical follow-up	
Age	Sex	Multiple tumors[a]	Resection	Radiation	Vocal cord procedure	Duration	Status and age
69.6 years	F, 12 (80%)	Y, 3 (20%)	Y, 1 (6%)	Y, 1 (6%)	Y, 5 (31%)	7.2 years	AWD, 13 (87%), 69.7
(Range, 38–80)	M, 3 (20%)	N, 12 (80%)	N, 15 (94%)	N, 15 (94%)	N, 11 (69%)	(Range, 2.0–13.2)	DUC, 2 (13%), 80.1

[a]At least one additional skull base or cervical paraganglioma present
AWD alive with disease, *DUC* death from unrelated cause, *F* female, *M* male, *N* no, *Y* yes

Table 5.2 Baseline and progression of symptoms during course of observation in 16 jugular paraganglioma tumors, 15 patients, initially managed with conservative observation

Status	Hearing loss	Pulsatile tinnitus	Bloody otorrhea	Vertigo	Dysphonia	Dysphagia
Never present	4 (25%)	5 (31%)	14 (88%)	12 (75%)	9 (56%)	10 (63%)
Stable	6 (38%)	11 (69%)	0 (0%)	2 (13%)	4 (25%)	4 (25%)
Progressed	6 (38%)	0 (0%)	0 (0%)	1 (6%)	2 (13%)	1 (6%)
New deficit	0 (0%)	0 (0%)	2 (13%)	1 (6%)	1 (6%)	1 (6%)

Table 5.3 Baseline and progression of cranial neuropathy during course of observation

	Carlson et al. 2015					Prasad et al. 2014	
Status	CN 7	CN 10	CN 11	CN 12	CNs 10, 11, 12 combined	CN 7	CNs 10, 11, 12 combined
Never present	15 (94%)	8 (50%)	11 (69%)	11 (69%)	8 (50%)	21 (91%)	13 (57%)
Stable	0 (0%)	4 (25%)	2 (13%)	1 (6%)	2 (12.5%)	2 (9%)	2 (9%)
Progressed	0 (0%)	2 (13%)[a,b]	1 (6%)	1 (6%)	2 (12.5%)[a]	0%	1 (5%)
New deficit	1 (6%)	2 (13%)	2 (13%)	3 (19%)	4 (25%)	0%	7 (30%)

CN cranial nerve
[a]One patient had progression of vagal paralysis and new onset of hypoglossal paralysis occurred immediately following radiotherapy
[b]One patient had an ipsilateral vagal paraganglioma threatening cranial nerve 10 function

patients with growing and stable tumors (median 67 vs. 69, $p = 0.27$). However, patients with growing JP had a longer duration of follow-up (median 87 vs. 44 months; $p = 0.07$).

At a median clinical follow-up of 86 months (24–158 months), 6 (38%) patients experienced progressive hearing loss, 2 (12.5%) developed bloody otorrhea, pulsatile

Table 5.4 Literature review on the natural history of jugular paragangliomas

Study	Number of cases	Median age, year	Stage at diagnosis (Fisch type)	Volume at diagnosis, cm^3	Max linear growth rate, mm/year (range)	Volumetric growth rate, cm^3/year (range)	Stable or regression at follow-up	Progression at follow-up	Mean follow-up, years (range)
Carlson et al. 2015	16	69.6	C: 10 (62%) D: 6 (38%)	2.7	0.8 (0.6–1.6)	0.4 (0.1–0.9)	7 (58%)[e]	5 (42%)[e]	4.8 (2.0–12.0)[a]
Prasad et al. 2014[b]	23	69	C: 15 (65%) D: 8 (35%)	NA	NA[c]	NA	15 (65%)	8 (35%)	5.1
Jansen et al. 2000[d]	11	NA	NA	0.8	0.79	NA[e]	5 (45%)	6 (55%)	3.8

[a]Only includes the 12 patients with radiographic follow-up
[b]Only includes the 23 patients with follow-up longer than 3 years
[c]Average growth rate was not reported. Growth rate was >3 mm/year in 1 (4%) tumor and <3 mm/year in 7 (31%) tumors
[d]May include glomus tympanicum (Fisch type A or B)
[e]Tumor volume was measured in this study but not reported

tinnitus remained stable in all patients, 8 (50%) maintained normal vagal function, and 11 (69%) maintained normal accessory and hypoglossal function. New or progressive lower cranial nerve paralysis developed in less than a third of cases, and only one (6%) experienced partial facial paresis. Four (25%) patients underwent type 1 thyroplasty with arytenoid adduction, and one (6%) received injection laryngoplasty. No patients required feeding tube, tracheostomy, or ventriculoperitoneal shunt placement. At last follow-up, none of the 15 patients experienced death from disease.

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In 2014, Prasad et al. reviewed 47 patients with JP (Fisch type C and D) who were managed conservatively and analyzed for tumor response and facial and lower cranial nerve status on follow-up [23]. Of these, 32 (68.1%) were older than 65 years. Tumor volume was measured by its diameter in two perpendicular planes; however, these values were not reported. Tumor growth was determined by the increase in the maximum linear dimension on follow-up and stratified into two groups: slow-growing (<3 mm/year) and fast-growing (>3 mm/year) tumors.

In 24 patients, duration of follow-up was less than 3 years, and the authors found that tumor size remained stable in 22 patients (92%). In the remaining 23 patients with follow-up of longer than 3 years (median, 61 months), tumor size remained stable in 12 (52%), regressed in 3 (13%), and progressed in 8 (35%) patients (Table 5.4). This decrease in tumor control after 3 years underscores the slow, indolent growth of JP and the need for long-term follow-up. In a literature review presented by Prasad et al., tumor stability or regression after radiotherapy ranges from 76% to 100%; however, this must be analyzed in the context of the 65% tumor control rate achieved with observation alone as concluded in their study. Of the eight (35%) patients with progressive tumors, seven were slow growing and were managed with continued observation, while one fast-growing tumor was treated with radiotherapy. Only seven (30%) patients developed a new lower cranial nerve deficit. Two subjects had facial paresis at time of diagnosis, and no patient experienced new onset or progression of facial weakness during the course of observation (Table 5.3).

The authors propose a treatment algorithm whereby surgery is the treatment of choice for patients younger than 65 years with Class C and D JPs. For patients older than 65 years, an initial wait-and-scan approach is taken to identify the growth rate of the tumor. Slow-growing tumors can be observed with little risk given the low incidence of new cranial nerve deficits and the ability for the contralateral nerves to simultaneously compensate for any loss of function. Fast-growing tumors, on the other hand, may necessitate radiotherapy or minimally aggressive (subtotal) resection.

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In a seminal paper published in 1992, van Der Mey and colleagues reported their experience with 108 patients with head and neck paragangliomas evaluated over a 32-year period [13]. Within this cohort were 52 jugulotympanic paragangliomas, of which 13 were untreated (observed), 16 underwent gross total resection, and 23 underwent subtotal resection. Although tumor growth rates and quantitative comparison of cranial nerve morbidity between groups were not described, the authors argued that for many patients with JP, radical surgery does not improve survival and results in greater cranial neuropathy. They emphasized that cervical paragangliomas, such as carotid body tumors and vagal paragangliomas, could be removed with minimal morbidity and therefore upfront treatment seems valid. In contrast, because of the potential morbidity posed by resection of JP, an initial wait-and-see policy is justified until progressive cranial nerve palsy or intracranial growth ensues. Because surgical intervention did not seem to prolong life expectancy in their series, the authors believe that the goal of treatment should be to reduce morbidity in patients with JP, rather than eradicate disease. Of course, notably, this study was limited by the era of imaging and lack of modern stereotactic radiation therapy delivery in their treatment algorithm.

In a later series from 2000 by the same center, Jansen et al. reviewed 11 jugulotympanic tumors that were conservatively observed [24]. Tumor volume was analyzed using three perpendicular axes using the ellipsoid volume calculation, and the average volume was 0.8 cm^3 (equating to a ~ 1.1 cm diameter). After a mean follow-up of 3.8 years, 55% of tumors demonstrated radiologic progression (defined as a minimum 20% volume increase on consecutive imaging) with a median growth rate of 0.79 mm/year and a median tumor doubling time of 13.8 years (Table 5.4). In an analysis of all head and neck paragangliomas including jugulotympanic, carotid body, and vagal paragangliomas, the authors observed a biphasic growth pattern, whereby growing tumors were more likely to be intermediate in size compared to very small or large tumors. Jugulotympanic paragangliomas, however, tended to be smaller and exhibit a more indolent growth pattern compared to these other head and neck paragangliomas. None of the jugulotympanic paragangliomas caused cranial nerve palsy; however, hearing loss and tinnitus were present in nine (81.8%) patients. However, in this study, it is not clear how many of the observed tumors were glomus tympanicum (Fisch type A and B) rather than JP (Fisch type C and D). Given that none of the patients exhibited any cranial neuropathies and the average tumor size was small, it suggests that at least a fraction of tumors were glomus tympanicum.

Natural History of Other Head and Neck Paragangliomas

Given overlapping similarities and the potential for multifocal disease, it is pertinent to also review the literature regarding the natural history of other head and neck paragangliomas, beyond JP. In particular, two studies in the modern era provide

valuable information regarding the biological behavior of untreated CBT and VP. In 2000, Jansen et al. examined 20 CBTs and 17 VPs, and volumetric change was estimated using the ellipsoid equation [24]. After an average follow-up for 4.5 years, 60% of CBT exhibited growth, the median linear growth rate was 0.83 mm/year, and median doubling time was 7.13 years. Of the 17 VP, the mean follow-up period was 4.6 years, 65% exhibited growth, the median growth rate was 1.0 mm/year, and the median doubling time was 8.9 years. Within these cases, the authors observed no significant difference in growth rates between sporadic and hereditary cases. Finally, in approximately 80% of cases, symptoms did not change over the course of follow-up, even in the setting of growth.

In 2012, Langerman and colleagues characterized growth patterns of untreated asymptomatic cervical paragangliomas—28 CBT and 19 VP—that were evaluated between 1993 and 2010 at Vanderbilt University [4]. The mean age at diagnosis was 56 years, and the mean follow-up was 5 years. Within this cohort, reasons for observation included patient preference (35%), advanced age (28%), and preexisting contralateral cranial nerve deficits (26%). Given limitations in available imaging, three-dimensional volumetric analysis was not performed. Overall 42% of tumors remained stable in size, 38% grew, and 20% reduced in size. Of the tumors that exhibited growth, the average growth rate was only 0.2 cm/year. Characteristics between CBT and VP were not described. In this review, the authors stressed the importance of close follow-up and consideration for intervention should pain, rapid growth, or adenopathy develop. Collectively, these two studies further validate an initial trial of observation for head and neck paraganglioma in select patients.

Comparison of Radiation Therapy and Observation

Within the last 5 years, there have been several large studies reporting the outcomes of stereotactic radiation therapy for JP. In 2011, a meta-analysis identified 869 patients from 109 studies that underwent subtotal resection alone, gross total resection alone, subtotal resection with adjuvant stereotactic radiosurgery, and radiosurgery alone [20]. Overall, tumor control was highest in those that received radiosurgery alone (95%) compared to gross total resection (86%) and subtotal resection (69%). Additionally, new or worsening cranial nerve paralysis involving IX, X, and XI occurred more frequently following gross total resection compared to radiosurgery. In 2011, Guss et al. performed a meta-analysis examining 19 studies with 335 JP cases [27]. Among the 11 studies with a minimum of 36 months of follow-up, 95% achieved clinical control, and 96% achieved tumor control. In this study, Gamma Knife radiosurgery, LINAC, and CyberKnife all achieved similar rates of tumor control across subjects. In a large multicenter study from the North American Gamma Knife Consortium, Sheehan et al. found that overall tumor control was achieved in 93% of patients at last follow-up [2], with an actuarial tumor control rate of 88% at 5 years [21]. Pulsatile tinnitus was improved in

approximately half of subjects, and new or worsening cranial nerve deficits were seen in 15% of patients.

Based on the current limited data, cranial nerve outcomes appear roughly comparable for stereotactic radiation therapy and observation of JP, and both modalities provide superior functional outcomes compared to radical tumor resection. Additionally, long-term tumor control is greater for radiation and microsurgery compared to observation. However, at least half of JP do not grow initially following diagnosis, and the average growth rate for enlarging tumors is usually less than 1 mm per year [2, 23]. Combining our data with Prasad et al., only 8% of observed JP underwent treatment during the course of follow-up [2, 23]. Notably, however, we also found that there was a trend toward higher rates of tumor progression in patients that were followed longer—a finding that was also reported by Prasad and colleagues. Collectively, these data support the option of an initial observation period for selected patients. Since most of these patients in these cohorts are of advanced age and because long-term follow-up is limited, we cannot yet safely conclude that observation should be routinely recommended for young patients who may have more aggressive disease and who are expected to live for many decades still.

Discussion

Without high-level evidence supporting one treatment strategy over others, the management of JP and other head and neck paragangliomas remains controversial. The axiom—primum non nocere, above all, do no harm—is particularly relevant to JP, where the treatment itself may result in greater morbidity to the patient than the disease over time. Regardless of treatment biases between centers, it is clear that management of JP is highly nuanced and driven by factors such as chronological age, overall health and functional status, tumor size, symptoms, multifocality, and patient preference among other factors.

In which patients can observation be considered? Since a significant proportion of JP do not grow after initial diagnosis and because the average growth rate among growing tumors is slow, observation is theoretically an option in many cases. Nonoperative treatment may be particularly attractive for patients with advanced age, poor health status, short-life expectancy, bilateral head and neck paraganglioma, contralateral lower cranial nerve paralysis, poor pulmonary reserve, and minimal or no symptoms. Some exceptions requiring operative treatment include large tumors resulting in brainstem compression, rapidly progressive symptoms, cases where the tumor has erupted into the ear canal, or in rare cases of suspected malignancy or refractory catecholamine secretion. Operative intervention is also appealing in younger patients with smaller tumors where the prospect of complete resection with “cure” and minimal morbidity is high.

It is evident that the treatment paradigm of JP and other head and neck paragangliomas is evolving with the pendulum swinging toward conservatism, including subtotal removal, radiation therapy, or initial observation. Defining optimal use of these

strategies is becoming increasingly important, as a higher number of incidental presymptomatic lesions are being diagnosed as a result of greater MRI availability and more widespread use of screening protocols for at-risk individuals [1]. While it is often more straightforward to delimit treatment between radical resection and a nonoperative strategy, the decision between observation and stereotactic radiation therapy is more ambiguous. This difficulty is primarily fueled by the paucity of studies evaluating the natural history of JP and the highly selected nature of these limited cohorts. Additionally, long-term data regarding outcomes following radiation therapy are greatly needed. It is clear in the literature that radiosurgery alters the natural course of many benign skull base and intracranial tumors; however, paralleling the vestibular schwannoma literature, upfront radiation therapy likely takes credit for tumor control in a percentage of JP that were not destined to grow [22]. And at least for vestibular schwannoma, most studies do not suggest that proactive radiation therapy is protective—the rate of progression to non-serviceable hearing and other cranial neuropathies is still higher in patients that undergo radiation therapy compared to observed tumors [28, 29].

At least in the short term, one of the advantages of initial observation is that it spares the expenses and risk of treatment in the subset of patients that ultimately do not need intervention. Additionally, for patients that are observed and then treated with radiation or surgery after growth is seen, the cumulative number of years a patient lives with the adverse effects from treatment is fewer. Furthermore, physiological compensation for lower cranial nerve paralysis is more satisfactory with progressive loss of function from disease, rather than abrupt loss that may develop following treatment. An initial trial of observation also elucidates the clinical behavior of the tumor prior to treatment, since this may ultimately influence treatment selection. For example, if a tumor exhibited very rapid growth, the patient and physician may be more inclined to proceed with surgical treatment rather than radiation. One final consideration that is not frequently cited when discussing radiation therapy for JP is the theoretical risk of malignant transformation, which may be higher in the subgroup of patients that already harbor an underlying germline mutation in a tumor suppressor gene (e.g., SDH, vHL, NF1).

Currently, there is a lack of reliable clinical markers that can be used to predict future tumor behavior. In the future, perhaps genetic testing and disease-related biomarkers may be used to predict tumor behavior and guide counseling. In recent years, several genetic alterations in the succinate dehydrogenase gene have been identified in up to a third of head and neck paragangliomas [1]. Factors suggesting a possible underlying germline mutation include male sex, younger age, family history, and multicentric disease. Alterations in SDHD predict a high risk for multiple head and neck paraganglioma, and variations in SDHB are associated with a higher risk for malignancy.

Based on the available data, we are reluctant to endorse a specific treatment protocol or management decision tree. Until better evidence exists, management should be individualized according to patient and tumor-related factors. The data presented in this chapter support that conservative observation is a valid initial option for select patients, particularly those with advanced age, limited life expectancy, and minimal or no symptoms.

Summary

Among selected cohorts of patients with JP, a notable percentage of tumors remain stable after initial diagnosis. Even when growth is seen, most JP exhibit indolent progression of approximately 1 mm/year. Therefore, initial observation of JP is a viable consideration in many cases, particularly for patients with minimal or no symptoms, bilateral tumors, poor health status, or advanced age. Careful patient counseling and close radiological follow-up are mandatory. Further studies with larger, unselected cohorts are required to compare tumor control and function preservation between stereotactic radiation therapy and observation.

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Chapter 6
Perioperative Considerations in the Management of Jugular Paragangliomas

Robert J. Yawn and David S. Haynes

Introduction

Surgical extirpation of jugular paragangliomas (JPs) can present a complex challenge in the perioperative setting. Because of the vascular nature of these tumors and the close proximity to critical neurovascular structures, specific challenges in perioperative management must be anticipated prior to surgery. Additional concerns arise because of the potential for these tumors to secrete catecholamine and serotonin metabolites or be associated with pheochromocytoma. Appropriate management often employs a multidisciplinary approach partnering endocrinologists, anesthesiologists, and surgeons in the perioperative period. The goal of this chapter is to discuss specific challenges that JP presents in the perioperative setting by presenting an algorithm for the evaluation and management of patients through the entire surgical process, from initial workup to surgical resection and into the immediate postoperative period. Long-term postoperative management, including cranial nerve rehabilitation, and medical therapy of secreting tumors will be discussed in detail in other chapters.

Preoperative Evaluation

Jugular paragangliomas are vascular tumors primarily arising from paraganglia cells derived from the neural crest found within the adventitia of the jugular bulb [1]. Because of their origin and function within the autonomic nervous system, these

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cells have the ability to secrete norepinephrine, epinephrine, and dopamine, with the majority of secreting tumors producing norepinephrine. The literature is somewhat varied on reported prevalence of catecholamine secretion in JP, but most studies estimate clinically significant excess catecholamine secretion to occur in 4–8% of tumors [1–4]. This is complicated by the fact that patients may have elevated levels of serum catecholamines in the absence of clinical symptomatology [5]. Furthermore, cases with multicentric paraganglioma may have concomitant abdominal or thoracic pheochromocytoma. Thus, clinical suspicion should be high for secretion even in the absence of symptoms, as this can impact the perioperative management.

While norepinephrine remains the most commonly secreted hormone, rarely JPs have the capacity to secrete other products, including 5-hydroxytryptamine (serotonin) and other precursor compounds to histamine [6]. Excess production of serotonin can produce classic symptoms of carcinoid syndrome, including diarrhea, facial flushing, and headaches. One of the earliest reports of carcinoid syndrome produced by a JP was by Farrior and colleagues in 1980 [7]. Manipulation of a secreting tumor intraoperatively can precipitate high levels of histamine or serotonin release leading to hypotension and shock. Further complicating this factor is that catecholamines can also potentiate and exacerbate these effects [6]. Excess histamine can also cause intraoperative bronchoconstriction, which can be treated effectively with β-agonists or with anticholinergic pharmacotherapy as histamine-potentiated bronchoconstriction is mediated through cholinergic pathways [8, 9].

Preoperative identification of patients with catecholamine or serotonin-secreting tumors is paramount (Fig. 6.1). Some studies suggest screening all patients with

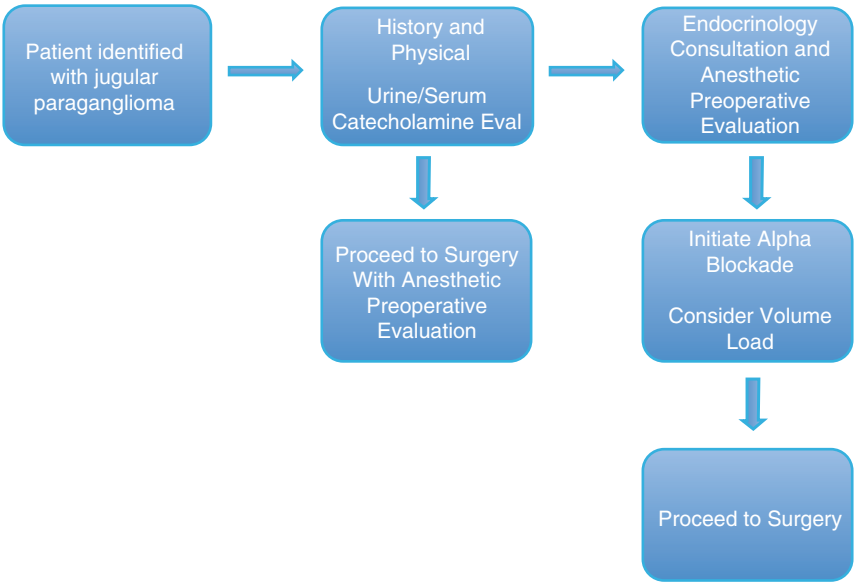

Fig. 6.1 Flow chart detailing the preoperative process in jugular paraganglioma management

JPs, whereas others recommend only screening patients that are symptomatic, knowing there is a risk of a tumor producing excess catecholamines that are ultimately subclinical in nature [6, 10, 11]. Suggestive symptoms may include hypertension, sweating, flushing, history of myocardial infarction, palpitations, and diarrhea. Screening for catecholamine secreting tumors can be performed via urine and serum analysis. A detailed description of endocrinologic management and preoperative management of secreting tumors is discussed in Chap. 7.

Jugular paragangliomas are highly vascular tumors, and therefore the potential for high-volume intraoperative blood loss during tumor resection is a concern that should be discussed between the surgeon and anesthetic team prior to surgery. Excess circulating catecholamines can cause chronic vasoconstriction, leading to a smaller circulating blood volume. With tumor resection and normalization of catecholamine levels, even small amounts of hemorrhage can lead to clinically significant hypotension intraoperatively, and some anesthesiologists prefer to volume load patients prior to surgery to prevent this complication. Furthermore, all patients should receive a type and screen before surgery to ensure timely transfusion if required. Additional concerns for the surgeon include the close proximity of dural venous sinuses including the sigmoid sinus and inferior petrosal sinus. In order to reduce intraoperative blood loss, many surgeons perform preoperative embolization as some studies have shown improved resection rates and decreased intraoperative tumor bleeding [12, 13]. Embolization is not without controversy, as one small study reported a 25–50% reduction in blood flow to the tumor on arteriography, but did not show any difference in embolized patients versus non-embolized in operative time, intraoperative blood loss, or extent of resection. Additionally within this study, embolized patients had higher rates of complications, believed to be associated with embolization [14]. Other studies have also suggested a higher risk of post-embolization cranial neuropathy (facial nerve, lower cranial nerves) because of overlapping blood supply of tumor and cranial nerves [15, 16]. While less common, there have even been reports of cardiac arrest and hypertensive crisis during embolization of JP, thought to result from tumor necrosis and subsequent spillage of catecholamines [1, 17].

Elevated intracranial pressure is a rare finding in patients with JP since tumors are often extradural or have limited involvement of the posterior fossa. However, since these tumors arise from the jugular bulb, obstruction of the venous outflow tract from tumor growth or treatment may lead to elevated intracranial pressure and rarely irreversible vision loss in patients with long-standing symptoms [18]. Tumors have also been shown to masquerade as benign intracranial hypertension (pseudotumor cerebri) even in cases without significant intracranial extension [19, 20]. Preoperative head imaging, assessment for papilledema, or lumbar puncture with opening pressure should be considered in patients with symptoms concerning for hydrocephalus including headache, imbalance, vision changes, urinary incontinence, or memory impairment.

Patients with history of head and neck surgery, imaging concerning for extensive tumor involvement of cranial nerves, or symptoms suggestive of lower cranial neuropathy should be evaluated for deficits, as preoperative cranial nerve palsy and vocal fold paresis should be identified preoperatively in order for intraoperative and postoperative planning.

Intraoperative Management

Standard anesthetic monitoring should be used in all cases. Additionally, an arterial line, Foley catheter, and central venous catheter for volume monitoring should also be placed. Patients with preoperative known increases in intracranial pressure can have lumbar drains placed as an adjunct. Central venous catheter placement should be performed with preoperative knowledge of tumor involvement. Venous access should be obtained from large venous vessels away from the disease so as not to catheterize a jugular vein involved by tumor. In anticipation for blood loss, two large-bore intravenous lines should also be placed to facilitate blood product transfusion if necessary. Volume status should be monitored, and fluid resuscitation performed aggressively as pressures can vary widely with tumor manipulation and resection with subsequent normalization of catecholamine levels in patients with secreting tumors.

Vasopressor administration should also be considered as tumor dissection commences, because normalization of catecholamine levels can cause severe hypotension [1]. Calcium-channel blockers and sodium nitroprusside can be used for intraoperative hypertension as they are typically fast acting [21]. Known injury of cranial nerves during surgical resection should be communicated to the anesthesia team in order to prepare for extubation in the setting of lower cranial nerve injury. In the setting of gastroparesis, nasogastric suction should be frequently performed to minimize the risk of postoperative aspiration.

Postoperative Management

Postoperative management will depend on several factors, including operative time, blood loss, operative complications, and catecholamine secretion. Patients should be monitored in a neurointensive care unit. Clinicians should be aware that normalization of chronically elevated catecholamine levels can lead to postoperative hypotension as well as hypoglycemia, and invasive blood pressure monitoring and frequent blood glucose monitoring are necessary for the first 48 h postoperatively.

Clinicians should be aware of the increased risk of postoperative ileus in patients undergoing JP resection. This is thought to result from increased levels of cholecystokinin (CCK) levels in these patients and impaired gastric emptying in the postoperative setting [6]. Jackson and colleagues postulate that the high rates of postoperative ileus and delayed gastric emptying in these patients is related to a combination of factors, including increased cholecystokinin that rapidly equilibrates to normal levels. While CCK is normalized, CCK receptors have been chronically upregulated, and a relative under-occupation of these receptors postoperatively leads to delayed gastric emptying, ileus, and lower levels of gallbladder contraction [22]. This can be especially troublesome with the addition of lower cranial nerve paralysis placing patients at high risk of aspiration and dysphagia. The use of a nasogastric tube postoperatively when ileus is suspected can be helpful in mitigating these symptoms prior to nausea, emesis, and aspiration.

Lower cranial nerve paralysis from disease or treatment, particularly injury to the vagus nerve, can lead to loss of sensation, tone, and motor function within the upper aerodigestive tract. Even in cases where a preoperative vagal paralysis was identified, it is not uncommon to have worsening swallow function following surgery. The mechanism behind this observation may be loss of residual pharyngeal tone or injury to other lower cranial nerves that contribute to coordinated swallow. Rates of aspiration postoperatively have been reportedly as high as 25%, and thus swallowing function should be evaluated in the postoperative setting and measures should be taken to avoid aspiration pneumonia [5, 6]. Vocal fold paresis is common in JP, and subsequent injection medialization is necessary for some patients to improve voice quality and cough [23]. Postoperative acute airway obstruction from vocal cord paralysis is rare, because deficits are usually unilateral. As stated in the introduction, the rehabilitation of long-standing postoperative cranial neuropathy is outside of the scope of this chapter and will be discussed in later chapters of the text.

Known injury to lower cranial nerves can place patients at high risk of aspiration, especially in the setting of increased risk of gastroparesis and ileus with chronically elevated catecholamines, as was previously discussed. Patients should have frequent nasogastric suctioning. Swallow function should be evaluated in all patients prior to the initiation of oral feeding. Clinicians should also be aware that postoperative edema in the first few days after resection can result in delayed cranial neuropathy, and high clinical suspicion for aspiration should be present throughout the postoperative period.

Conclusion

Jugular paragangliomas present a complex challenge for a variety of reasons related to tumor pathophysiology. Identification of patients with catecholamine secreting-tumors and proper preoperative management allows for the minimization of perioperative risk associated with operative resection. Multidisciplinary teams, including surgeons, endocrinologists, and anesthesiologists, are recommended for optimal outcomes in these complex patients.

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Chapter 7
Endocrinologic Management of Skull Base Paraganglioma

William F. Young Jr.

Introduction

Catecholamine-secreting tumors are rare, with an annual incidence of 2–8 cases per 1 million people [1–3]. When we reviewed all patients diagnosed at Mayo Clinic with benign paraganglioma between the years 1978 and 1998, 80% (189 of 236 patients) had neck and skull base paragangliomas: 117 carotid body tumors, 46 glomus jugulare tumors, and 26 glomus vagale tumors [4]. Catecholamine hypersecretion was documented in 6 (8.3%) of the 72 patients with glomus jugulare or vagale tumors [4] Thus, although not common, the risk of associated catecholamine hypersecretion in the clinical setting of skull base paragangliomas is clinically significant [5]. Reviewed herein are the clinical presentation of patients with catecholamine-secreting tumors, case-detection testing for catecholamine hypersecretion, the role for obtaining imaging studies outside of the neck, and preoperative preparation for patients with catecholamine-secreting skull base paragangliomas.

Clinical Presentation of Patients with Catecholamine-Secreting Skull Base Paragangliomas

The symptoms listed in Table 7.1 are caused by the pharmacologic effects of excess concentrations of circulating catecholamines [6]. The associated hypertension may be sustained or paroxysmal, and patients whose catecholamine-secreting tumor is

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Table 7.1 Signs and symptoms associated with catecholamine-secreting tumors[a]

Spell-related signs and symptoms
Anxiety and fear of impending death
Diaphoresis
Dyspnea
Epigastric and chest pain
Headache
Hypertension
Nausea and vomiting
Pallor
Palpitation (forceful heartbeat)
Tremor
Chronic signs and symptoms
Cold hands and feet
Congestive heart failure—dilated or hypertrophic cardiomyopathy
Constipation
Diaphoresis
Dyspnea
Ectopic hormone secretion-dependent symptoms (e.g., CRH/ACTH, GHRH, PTHrP, VIP)
Epigastric and chest pain
Fatigue
Fever
General increase in sweating
Grade II–IV hypertensive retinopathy
Headache
Hyperglycemia
Hypertension
Nausea and vomiting
Orthostatic hypotension
Painless hematuria (associated with urinary bladder paraganglioma)
Pallor
Palpitation (forceful heartbeat)
Tremor
Weight loss
Not typical of pheochromocytoma
Flushing

ACTH adrenocorticotropic hormone, *CRH* corticotropin-releasing hormone, *GHRH* growth hormone-releasing hormone, *PTHrP* parathyroid hormone-related peptide, *VIP* vasoactive intestinal polypeptide

[a]Adapted from Young WF Jr. Pheochromocytoma, 1926–1993. *Trends Endocrinol Metab.* 1993;4:122–127. [6]

diagnosed in the presymptomatic stage may have normal blood pressure. The lability in blood pressure can be attributed to episodic release of catecholamines, chronic volume depletion, and impaired sympathetic reflexes. Symptoms of orthostatic hypotension (e.g., light-headedness, presyncope, syncope) may dominate the presentation, especially in patients with epinephrine- or dopamine-predominant tumors [7]. Unique clinical presentations of skull base paragangliomas include neck mass, hearing loss, pulsatile tinnitus, lower cranial nerve palsies, and obstruction of jugular venous outflow with resultant increased intracranial pressure and papilledema [8–12].

Episodic symptoms associated with catecholamine hypersecretion may occur in spells, or paroxysms, that can be extremely variable in presentation but typically include forceful heartbeat, pallor, tremor, headache, and diaphoresis [13, 14]. The spell may start with a sensation of a "rush" in the chest and a sense of shortness of breath, followed by a forceful heartbeat and a throbbing headache. Peripheral vasoconstriction associated with a spell results in cool or cold hands and feet and facial pallor. Increased sense of body heat and sweating are common symptoms that occur toward the end of the spell. Spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., β-adrenergic antagonists, metoclopramide, anesthetic agents), or exercise. Spells may occur multiple times daily or as infrequently as once monthly. The typical duration of a catecholamine-secreting tumor spell is 15 to 20 min, but it may be much shorter or last several hours. However, the clinician must recognize that most patients with spells do not have a catecholamine-secreting tumors. [14].

Catecholamine-secreting paragangliomas are found where there is chromaffin tissue: along the para-aortic sympathetic chain, within the organ of Zuckerkandl (at the origin of the inferior mesenteric artery), in the wall of the urinary bladder, and along the sympathetic chain in the neck or mediastinum [4]. Paragangliomas in the skull base and neck region usually arise from parasympathetic tissue and typically do not hypersecrete catecholamines and metanephrines. Paragangliomas in the lower mediastinum, abdomen, and pelvis usually arise from sympathetic chromaffin tissue and usually do hypersecrete catecholamines and metanephrines.

Biochemical Testing for Catecholamine Hypersecretion

All patients with skull base paragangliomas should have biochemical testing for catecholamine hypersecretion (Fig. 7.1) [5, 13]. Preoperative screening is indicated because up to 8% of skull base paragangliomas are functional [4], which poses a risk for anesthetic and surgical induction of a hypertensive crisis [13, 15, 16]. The index of suspicion for a catecholamine hypersecretion from a skull base paraganglioma should be high in the following scenarios: resistant hypertension, spells with associated pallor, a family history of paraganglioma, a genetic

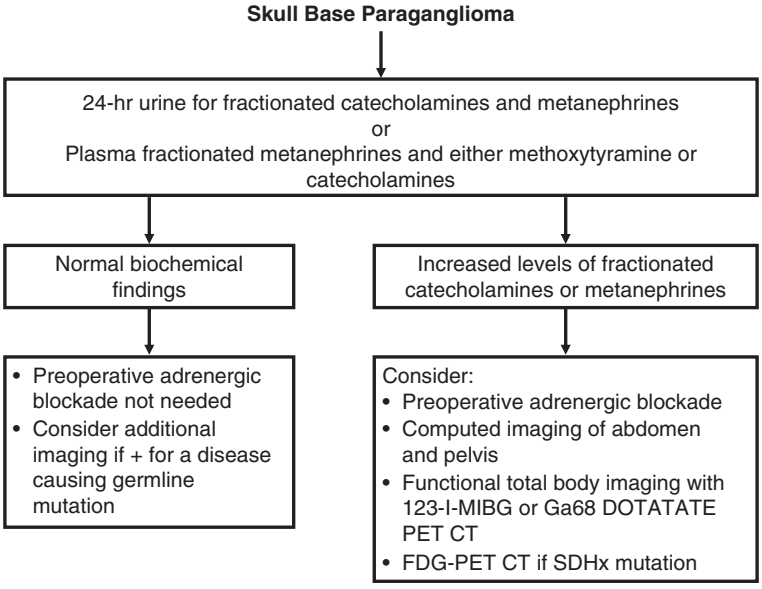

Fig. 7.1 Case-detection testing of catecholamine-secreting skull base paragangliomas. *CT* computed tomography, *DOTATATE* 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate, *FDG* fluorodeoxyglucose, *^{123}I-MIBG* iodine ^{123}I-labeled metaiodobenzylguanidine, *PET* positron emission tomography

syndrome that predisposes to paraganglioma (e.g., germline succinate dehydrogenase [*SDHx*] mutation), and a past history of resected pheochromocytoma or paraganglioma [17, 18].

The metabolism of catecholamines is primarily intratumoral, with formation of metanephrine from epinephrine and normetanephrine from norepinephrine [19]. Most reference laboratories now measure fractionated catecholamines (dopamine, norepinephrine, and epinephrine) and fractionated metanephrines (metanephrine and normetanephrine) by tandem mass spectrometry or high-performance liquid chromatography with electrochemical detection [20–22]. These techniques have overcome the problems with fluorometric analysis, which included false-positive results caused by α-methyldopa, labetalol, sotalol, and imaging contrast agents.

The most reliable case-detection strategy for catecholamine hypersecretion is the measurement of fractionated metanephrines and catecholamines in a 24-h urine collection (sensitivity, 98%; specificity, 98%) [15, 23]. Measurement of urinary or plasma dopamine (as part of fractionated catecholamines) or plasma methoxytyramine (the primary dopamine metabolite) can be very useful in detecting the rare skull base paraganglioma with selective dopamine hypersecretion [23, 24]. It is important to recognize that plasma metanephrine fractions are not direct metabolites of dopamine and may be normal in the setting of a dopamine-secreting tumor [7, 23, 25]. In addition, in some patients with dopamine-secreting paragangliomas, the 24-h urinary dopamine concentration may not be increased due to the sulfation of dopamine in the kidney. Thus, in addition to measurement of fractionated

Table 7.2 Medications that may increase measured levels of fractionated catecholamines and metanephrines

Tricyclic antidepressants (including cyclobenzaprine)
Levodopa
Drugs containing adrenergic receptor agonists (e.g., decongestants)
Amphetamines
Buspirone and antipsychotic agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs (e.g., illicit drugs)
Illicit drugs (e.g., cocaine, heroin)
Ethanol

metanephrines in the blood or urine, a case can be made for measurement of fractionated plasma catecholamines or plasma methoxytyramine (Fig. 7.1).

Although it is preferred that patients not receive any medication during biochemical testing, treatment with most medications may be continued. Tricyclic antidepressants are the drugs that interfere most frequently with the interpretation of catecholamines and metanephrines. To effectively screen for catecholamine-secreting tumors, treatment with tricyclic antidepressants and other psychoactive agents listed in Table 7.2 should be tapered and discontinued at least 2 weeks before any hormonal assessments.

Imaging Studies: Localization of Synchronous Thoracic, Abdominal, or Pelvic Paragangliomas

Imaging of the chest, abdomen, or pelvis is not needed in most patients with skull base paragangliomas. However, imaging outside of the neck is indicated in two clinical settings: apparent catecholamine-secreting skull base paraganglioma (because the catecholamine hypersecretion may actually be from a synchronous paraganglioma not located in the skull base) and known disease-causing germline mutation (e.g., *SDHx*) because these patients are at high risk of multiple paragangliomas and pheochromocytoma (Fig. 7.1). In those clinical settings, computed tomography (CT) or magnetic resonance imaging of the abdomen and pelvis should be obtained (sensitivity, >95%; specificity, >65%) [13, 26]. The most common locations of catecholamine-secreting paragangliomas include superior abdominal para-aortic region, 46%; inferior abdominal para-aortic region, 29%; urinary bladder, 10%; mediastinum, 10%; head and neck, 3%; and pelvis, 2% [4].

In addition to the computed abdominal and pelvic imaging, functional total body imaging should be considered in patients with apparent catecholamine-secreting skull base paragangliomas. One option for functional total body imaging is ^{123}I-labeled metaiodobenzylguanidine (MIBG). This radiopharmaceutical agent accumulates preferentially in catecholamine-producing tumors; however, this imaging study is not as sensitive as was initially hoped (sensitivity, 80%; specificity,

99%) [27, 28]. It is important for the clinician to recognize the medications that may interfere with ^{123}I-MIBG uptake (e.g., tricyclic antidepressants, labetalol, calcium channel blockers) and have the patient discontinue them before imaging is performed [29]. In addition, somatostatin-based gallium 68 (68-Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE) for positron emission tomography (PET) CT is a very sensitive imaging agent to detect paragangliomas [30–32]. Where available, 68-Ga DOTATATE PET-CT is replacing ^{123}I-MIBG as a functional total body imaging option to screen for additional paragangliomas or metastatic disease. Finally, due to activation of aerobic glycolysis in patients with pheochromocytoma or paraganglioma associated with *SDHx* mutations, PET scanning with 18F-fluorodeoxyglucose (FDG) is the ideal imaging technique for localization of primary and metastatic tumors in patients with *SDHx* mutations [33, 34].

Preoperative Preparation for Patients with Catecholamine-Secreting Skull Base Paragangliomas

Patients with nonfunctioning skull base paragangliomas do not need preoperative adrenergic blockade. However, some form of preoperative pharmacologic preparation is indicated for all patients with catecholamine-secreting paragangliomas, including those who are asymptomatic and normotensive [13, 35–37]. Combined α- and β-adrenergic blockade is one approach to control blood pressure and prevent intraoperative hypertensive crises [6]. α-Adrenergic blockade should be started 7–10 days preoperatively to normalize blood pressure and expand the contracted blood volume. A longer duration of preoperative α-adrenergic blockade is indicated for patients with recent myocardial infarction, catecholamine cardiomyopathy, or catecholamine-induced vasculitis. Blood pressure should be monitored with the patient in the seated and standing positions twice daily. Target blood pressure is low-normal blood pressure for age (e.g., <120/80 mm Hg in the seated position), with systolic blood pressure greater than 90 mm Hg (standing); both targets should be modified on the basis of the patient's age and comorbid disease. Orthostasis is not a goal of treatment, but rather a side effect. Therefore, on the second or third day of α-adrenergic blockade, patients are encouraged to start a diet high in sodium content (≥5000 mg/day) because of the catecholamine-induced volume contraction and the orthostasis associated with α-adrenergic blockade. This degree of volume expansion may be contraindicated in patients with congestive heart failure or renal insufficiency. After adequate α- adrenergic blockade has been achieved, β-adrenergic blockade is initiated, typically 2–3 days preoperatively.

α-Adrenergic Blockade

Phenoxybenzamine is the preferred drug for preoperative preparation to control blood pressure and arrhythmia. It is an irreversible, long-acting, nonspecific α-adrenergic blocking agent. The initial dosage is 10 mg once or twice daily, and the

Table 7.3 Orally administered drugs used to treat pheochromocytoma

Drug	Initial dosage, mg/day[a] (maximum)	Side effects
α-adrenergic blocking agents		
Phenoxybenzamine	10[b] (100)[b]	Postural hypotension, tachycardia, miosis, nasal congestion, diarrhea, retrograde ejaculation, fatigue
Prazosin	1 (20)[c]	First-dose effect, dizziness, drowsiness, headache, fatigue, palpitations, nausea
Terazosin	1 (20)[b]	First-dose effect, asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations, somnolence
Doxazosin	1 (20)	First-dose effect, orthostasis, peripheral edema, fatigue, somnolence
Combined α- and β-adrenergic blocking agent		
Labetalol	200[b] (1200)[b]	Dizziness, fatigue, nausea, nasal congestion, impotence
Calcium channel blocker		
Nicardipine sustained-release	30[b] (120)[b]	Edema, dizziness, headache, flushing, nausea, dyspepsia
Catecholamine synthesis inhibitor		
α-Methyl-ρ-L tyrosine (metyrosine)	1000[c] (4000)[c]	Sedation, diarrhea, anxiety, nightmares, crystalluria, galactorrhea, extrapyramidal symptoms

[a]Given in two doses daily
[b]Given in three or four doses daily
[c]Given once daily unless otherwise indicated

dose is increased by 10–20 mg in divided doses every 2–3 days as needed to control blood pressure and spells (Table 7.3). The final dosage of phenoxybenzamine is typically between 20 and 100 mg daily. The patient should be warned about the orthostasis, nasal congestion, retrograde ejaculation in men, and marked fatigue that occur in almost all patients. With their more favorable side effect profiles and lower cost, selective α1-adrenergic blocking agents (e.g., prazosin, terazosin, doxazosin) are preferable to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., for metastatic pheochromocytoma) [38].

β-Adrenergic Blockade

The β-adrenergic antagonist should be administered only after α-adrenergic blockade is effective because with β-adrenergic blockade alone, severe hypertension or cardiopulmonary decompensation may occur due to the unopposed α-adrenergic stimulation [39]. Preoperative β-adrenergic blockade is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α-adrenergic blockade. The clinician should exercise caution if the patient is asthmatic or has congestive heart failure. Chronic catecholamine excess

can produce a myocardiopathy that may become evident with the initiation of β-adrenergic blockade, resulting in acute pulmonary edema [39]. Therefore, when the β-adrenergic blocker is administered, it should be used cautiously and at a low dose. For example, a patient is usually given 10 mg of propranolol every 6 h to start. On the second day of treatment, the β-adrenergic blockade (assuming the patient tolerates the drug) is converted to a single long-acting dose. The dose is then increased as necessary to control the tachycardia (goal heart rate is 60–80 beats per minute).

Catecholamine Synthesis Inhibitor

Metyrosine should be used with caution and only after other agents have been ineffective or in patients in whom tumor manipulation will be marked or if destruction is planned (e.g., radiofrequency ablation of metastatic sites) [40, 41]. Although some centers advocate that this agent should be used routinely preoperatively, most reserve it primarily for patients who cannot be treated with the typical combined α- and β-adrenergic blockade protocol for cardiopulmonary reasons. Metyrosine inhibits catecholamine synthesis by blocking the enzyme tyrosine hydroxylase [40]. The side effects of metyrosine can be disabling; with long-term therapy, they include sedation, depression, diarrhea, anxiety, nightmares, crystalluria and urolithiasis, galactorrhea, and extrapyramidal signs. Metyrosine may be added to α- and β-adrenergic blockade if the resection will be difficult (e.g., malignant paraganglioma) or if destructive therapy is planned (e.g., radiofrequency ablation of hepatic metastases). Our typical protocol with short-term preprocedure preparation is to start with metyrosine 250 mg every 6 h on day 1, 500 mg every 6 h on day 2, 750 mg every 6 h on day 3, and 1000 mg every 6 h on the day before the procedure, with the last dose (1000 mg) given on the morning of the procedure. With this short-course therapy, the main side effect is hypersomnolence.

Calcium Channel Blockers

Calcium channel blockers, which block norepinephrine-mediated calcium transport into vascular smooth muscle, have been used successfully at several medical centers to preoperatively prepare patients with pheochromocytoma [42]. Nicardipine is the most commonly used calcium channel blocker in this setting; the starting dose is 30 mg twice daily of the sustained-release preparation [43, 44]. Nicardipine is given orally to control blood pressure preoperatively and if needed is given as an intravenous infusion intraoperatively. Although there is less collective experience with calcium channel blockers than with α- and β-adrenergic blockers, when calcium channel blockers are used as the primary mode of antihypertensive therapy, they may be just as effective [44, 45]. Clearly, the exclusive use of calcium channel blockers for the perioperative management of patients with catecholamine-secreting tumors does not prevent all hemodynamic changes; however, its use has been associated with low morbidity and mortality [45]. The main role for this class of drugs

may be either to supplement the combined α- and β-adrenergic blockade protocol when blood pressure control is inadequate or to replace the adrenergic blockade protocol in patients with intolerable side effects.

Acute Hypertensive Crises

Acute hypertensive crises may occur before or during an operation, and they should be treated with intravenously administered sodium nitroprusside, phentolamine, or nicardipine. Sodium nitroprusside is an ideal vasodilator for intraoperative management of hypertensive episodes because of its rapid onset of action and short duration of effect. It is administered as an intravenous infusion at 0.5–5.0 μg/kg of body weight per minute and adjusted every few minutes for target blood pressure response; to keep the steady-state thiocyanate concentration below 1 mmol/L, the rate of a prolonged infusion should be no more than 3 μg/kg per minute. Phentolamine is a short-acting, nonselective α-adrenergic blocker that is available in lyophilized form in 5-mg vials. An initial test dose of 1 mg is administered and is followed, if necessary, by repeat 5-mg boluses or continuous infusion. The response to phentolamine is maximal 2–3 min after a bolus injection and lasts 10–15 min. Nicardipine can be started at an infusion rate of 5 mg/h and titrated for blood pressure control (the infusion rate may be increased by 2.5 mg/h every 15 min up to a maximum of 15.0 mg/h).

Anesthesia and Surgery

Surgical resection of a catecholamine-secreting paraganglioma is a high-risk surgical procedure, and an experienced surgeon-anesthesiologist team is required. The last oral doses of α- and β-adrenergic blockers can be administered early in the morning on the day of the operation. Fentanyl, ketamine, and morphine should be avoided, because they potentially can stimulate catecholamine release from a pheochromocytoma [46]. Also, parasympathetic nervous system blockade with atropine should be avoided because of the associated tachycardia. Anesthesia may be induced with intravenous injection of propofol, etomidate, or barbiturates in combination with synthetic opioids [46]. Most anesthetic gases can be used, but halothane and desflurane should be avoided. Hemodynamic variables must be monitored closely. If the patient has congestive heart failure or decreased cardiac reserve, monitoring of pulmonary capillary wedge pressure is indicated.

Hypotension may occur during and after surgical resection of a catecholamine-secreting paraganglioma, and it should be treated with fluids and colloids and then intravenous pressor agents if necessary. Postoperative hypotension occurs less frequently in patients who have had adequate preoperative α-adrenergic blockade and volume expansion. Because hypoglycemia can occur in the immediate postoperative period, blood glucose levels should be monitored, and fluid given intravenously should contain 5% dextrose.

Long-Term Postoperative Follow-Up

Approximately 1–2 weeks after surgery, 24-h urinary fractionated catecholamines and metanephrines should be measured. If the levels are normal, the resection of the catecholamine-secreting paraganglioma should be considered complete. Increased levels of fractionated catecholamines and metanephrines detected postoperatively are consistent with residual tumor (i.e., a second primary lesion or occult metastases). Biochemical testing for 24-hour urine catecholamines and metanephrines should be re-checked annually for life because the initial tumor may have been malignant and it can take many years to detect. In addition, underlying germline mutations may predispose to additional paragangliomas over time.

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Chapter 8
Surgical Management of Class C and D Tympanojugular Paragangliomas

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Introduction

Tympanojugular paragangliomas (TJPs) have always presented a challenge to surgeons due to the fact that these tumors are vascular and locally aggressive and involve important neurovascular structures like the jugular bulb (JB), the internal carotid artery (ICA), and the facial and the lower cranial nerves (LCNs, CN IX, X, XI, XII). Owing to their indolent nature, they often present late with cranio-temporo-cervical extensions rendering them inoperable in the past. However, significant developments in the last couple of decades have changed this scenario. A thorough anatomical and surgical mapping of the skull base and descriptions of various rational approaches, in addition to technological improvements in neuromonitoring, neuroanesthesia, and neuroradiology, have made surgical removal of skull base tumors technically feasible and safer. Fisch originally classified TJPs into classes A, B, C, and D according to location and extension based on high-resolution computed tomography (HRCT) examination. This was subsequently modified by Sanna [1] to include subclassifications and an additional class V to include tumors that involve the vertebral artery (VA) (Table 8.1).

TJPs, being trans-cranio-temporo-cervical in nature, demand that the surgeon has a thorough understanding of skull base anatomy and surgical techniques for

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Table 8.1 Modified Fisch classification of the temporal bone paragangliomas (TBPs)

Tympanomastoid paragangliomas (TMPs)	Class A	Tumors confined to the middle ear	
		A1	Tumor margins clearly visible on otoscopic examination
		A2	Tumor margins not visible on otoscopy. Tumors may extend anteriorly to the Eustachian tube and/or to the posterior mesotympanum
	Class B	Tumors confined to the tympanomastoid cavity without destruction of bone in the infralabyrinthine compartment of the temporal bone	
		B1	Tumors involving the middle ear with extension to the hypotympanum
		B2	Tumors involving the middle ear with extension to the hypotympanum and the mastoid
		B3	Tumors confined to the tympanomastoid compartment with erosion of the carotid canal
Tympanojugular paragangliomas (TJPs)	Class C	Tumors extending beyond the tympanomastoid cavity, destroying bone of the infralabyrinthine and apical compartment of the temporal bone, and involving the carotid canal	
		C1	Tumors with limited involvement of the vertical portion of the carotid canal
		C2	Tumors invading the vertical portion of the carotid canal
		C3	Tumors with invasion of the horizontal portion of the carotid canal
		C4	Tumors reaching the anterior foramen lacerum
	Class D	Tumors with intracranial extension	
		De1	Tumors up to 2 cm dural displacement
		De2	Tumors with more than 2 cm dural displacement
		Di1	Tumors up to 2 cm intradural extension
		Di2	Tumors with more than 2 cm intradural extension
		Di3	Tumors with inoperable intradural extension
	Class V	Tumors involving the VA	
		Ve	Tumors involving the extradural VA
		Vi	Tumors involving the intradural VA

effectively dealing with them. Surgical management of TJPs has steadily yielded better results over the last couple of decades after the description of the infratemporal fossa (ITFA) type A approach by Fisch and colleagues [2] and the addition of extensions to it [3, 4]. The introduction of techniques like intra-arterial stenting of the ICA at our center in 2003 has made surgery possible even in cases that were previously considered inoperable. However, surgery in this complex region is still fraught with danger, requiring the ability to accurately assess varied interrelated factors, their impact on the ultimate result, and their management. In this chapter, we summarize the various techniques and refinements in skull base surgery and neuroradiology that can be used to yield very satisfactory results in the management of C1 to C4 TJPs.

Choosing the Right Approach to the Jugular Fossa

The jugular fossa is a highly complex anatomical area closely related to critical neurovascular structures. To achieve optimal exposure while minimizing its morbidity is the goal of all skull base surgeries. To obtain proximal and distal exposure of the major vessels is an important basic principle in the management of all vascular tumors [5–7]. This dictum above all should determine the degree of exposure required in the management of TJPs, due to their invariable involvement of the ICA.

Two critical points to consider when obtaining adequate surgical exposure are whether the facial nerve (FN) needs mobilization and whether the middle ear can be preserved. These issues form the core argument in the treatment of jugular fossa pathology. It is not the intracranial extension that is the primary consideration that has to be taken into account while selecting an approach, but the degree and nature of ICA involvement. Most of the documented approaches that avoid FN rerouting limit the degree of exposure of the intrapetrous ICA and certainly limit any ability to safely remove bone around this vessel, which is usually required in the management of C2–C4 TJP. For alternate pathologies of the jugular fossa, more "conservative" approaches in relation to both the FN and middle ear structures can often be utilized.

This ITFA type A has been the mainstay of surgery for TJPs ever since it was described by Fisch and Pillsbury in 1979 [8]. The ITFA type A is designed to allow access to the jugular foramen area, the infralabyrinthine and apical compartments of the petrous bone, the vertical segment of the internal carotid artery, and the upper jugulocarotid space (Fig. 8.1a). The approach is designed primarily for extensive extradural lesions involving these areas. The key point in this approach is the anterior transposition of the FN to provide optimal control of the targeted areas (Fig. 8.1b). The other structures that prevent lateral access to these areas are shown in Fig. 8.1c. Besides the FN they include the tympanic bone, the digastric muscle, and the styloid process. These structures are removed to allow an unhindered lateral access. The morbidity associated with the classic ITFA type A includes conductive hearing loss, temporary or permanent FN dysfunction due to permanent anterior rerouting of the nerve, and temporary masticatory difficulties.

In the recent past, many authors have favored the technique of retaining the FN in situ without rerouting it in the ITFA type A and/or attempt to conserve the external auditory canal in the resection of jugular fossa tumors [9–16]. Unfortunately, however, these reports often do not clearly differentiate between vascular and nonvascular tumors nor do they discuss the stage of the paragangliomas treated. It is the involvement of the intratemporal ICA and the infiltrative nature of the pathology that dictates the surgical approach. While it is true that some smaller tumors could be removed this way [17], it is incorrect to apply the principle for all classes of TJPs. The involvement of the intratemporal ICA and the infiltrative nature of the pathology must dictate the surgical approach. Hypotympanic approaches to small C1 tumors are employed by some surgeons for minimal jugular fossa involvement, but the risk of limited ICA exposure and the lack of proximal and distal control of the

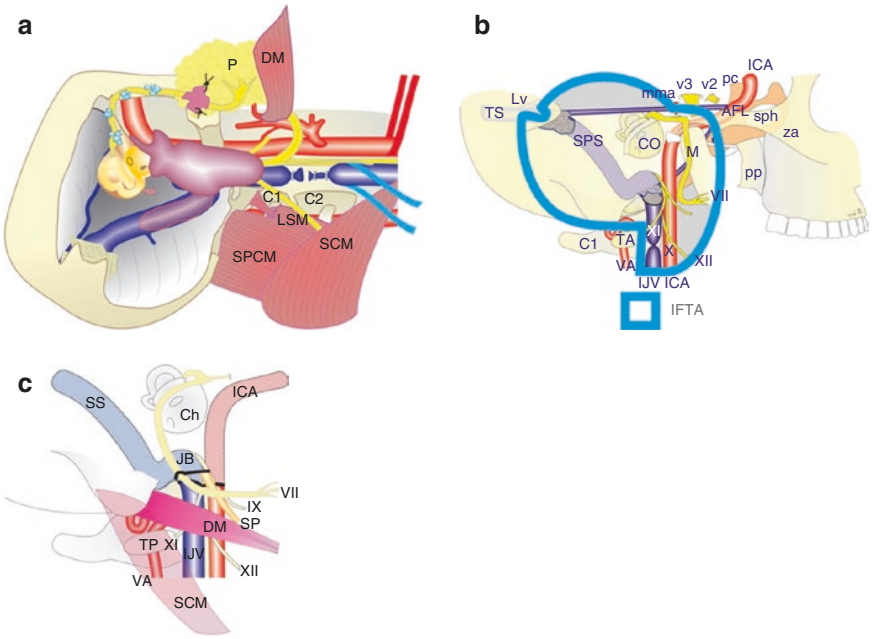

Fig. 8.1 Illustrations for ITFA type A. (**a**) An illustration of surgical view in ITFA. (**b**) An illustration of surgical limit in ITFA. (**c**) An illustration of obstacles to approach the jugular bulb. *ICA* internal carotid artery, *sph* sphenoid sinus, *za* zygomatic arch, *pc* clinoid process, *V2* maxillary branch of trigeminal nerve, *V3* mandibular branch of trigeminal nerve, *pp*. pterygoid plate, *M* mandible, *Co* cochlea, *sps* superior petrosal sinus, *Lv* vein of Labbe, *TS* transverse sinus, *ev* emissary vein, *OC* occipital condyle, *TA* transverse process of atlas, *C1* atlas, *C2* axis, *VA* vertebral artery, *VII* FN, *IX* glossopharyngeal nerve, *XI* spinal accessory nerve, *XII* hypoglossal nerve, *IJV* internal jugular vein, *FN* facial nerve, *TP* transverse process of the atlas, *DM* posterior belly of the digastric muscle, *SCMM* sternocleidomastoid muscle, *SP* styloid process, *JB* jugular bulb, *Co* cochlea, *SpCM* splenius capitis muscle, *LSM* levator scapulae muscle, and *P* parotid gland

jugulosigmoid system can be significant [18–21]. The assertion that a purely infralabyrinthine approach, with preservation of the middle ear and the FN left in situ, is a safe and effective approach for most TJP is erroneous as limited anterosuperior exposure creates the risk of residual tumor and the potential for catastrophic injury to the ICA. These approaches that are essentially a variation of the petro-occipital trans-sigmoid approach certainly have their indications and are suitable for addressing minimally invasive and minimally vascularized jugular fossa pathology. They can also be considered for early class C1 TJPs, with predominantly posterior disease, and class B3 tumors [22]. The majority of TJPs, which are in close proximity to the ICA, require an ITFA to facilitate safe removal of the tumor [22, 23]. Circumferential dissection of the FN in its vertical segment with preservation of a thin bony coverage is referred to as a fallopian bridge technique [23, 24]. This technique allows access to the jugular bulb on either side of the FN [25] and can be applied with either preservation or elimination of the EAC and middle ear structures

[23]. However, this technique still limits anterior control, and there remains a small risk of FN injury due to possible fracture of the fallopian bridge.

FN mobilization also allows safe removal of the styloid process and complete removal of the tympanic bone, which is invariably infiltrated in TJP. This would provide for optimal control of the upper parapharyngeal space, the ICA, and the LCN. The true results of facial function following rerouting must be analyzed in comparison to tumor recurrence rates and associated morbidity when the FN is not mobilized. We strongly feel that the relatively mild facial dysfunction associated with anterior rerouting from the geniculate ganglion is a small price to pay for improved access which provides definitive vascular control and ultimately reduces recurrence rates [2].

A purely retrosigmoid approach that is commonly used to manage LCN schwannomas and posterior fossa meningiomas does not allow safe removal of tumor that extends into the jugular foramen and is therefore a common cause for recurrence. Hence a transjugular approach is usually necessary in the management of jugular foramen pathology and is essential to allow excision of lesions that have true extension into the jugular foramen and further down into the parapharyngeal space [26]. It is generally in the rare case where sacrifice of the jugulosigmoid system is not possible as detected on preoperative assessment, in which conservative measures like a retrosigmoid approach may be considered.

Preservation of the jugulosigmoid system has been also described for jugular fossa pathology, when it has been compressed but not invaded. The suprajugular approach, essentially a presigmoid and infralabyrinthine approach, involves dissection of the infralabyrinthine air cell tract, with an opening of the dura between the labyrinth and the jugular bulb, allowing improved access up to the jugular foramen [27]. The pneumatization pattern of the temporal bone plays a large role in the amount of room that can be gained in this area. Evidently, while preservation of the jugulosigmoid system has been described for dumbbell tumors of the LCN [28], this might not allow complete removal of the tumor. As mentioned, a transjugular approach is usually necessary in management of JF pathology and is essential to allow excision of lesions that have true extension into the jugular foramen and further into the parapharyngeal space [26]. It is only in the rare case where sacrifice of the jugulosigmoid system is not possible as detected on preoperative assessment, in which these more conservative measures should be considered.

The use of the far or extreme lateral approaches with various extensions has been proposed for accessing the jugular fossa to preserve the middle ear and leave the FN in situ and even avoidance of drilling the petrous bone at all [10, 13, 15, 29–33]. It must be remembered that the far-lateral approach was initially developed to access lesions of the craniocervical junction and ventral lower brain stem in order to limit brain stem retraction and pathology without significant involvement of the temporal bone [27, 30, 34, 35]. However, this approach by itself limits the control of the intrapetrous carotid and the ability to widely remove infiltrated bone. The real advantage in this approach lies in improved exposure of the intradural extension. In summary these techniques are useful adjuncts to the ITFA, especially in C2–C4 tumors.

The subtemporal-infratemporal approach was initially described by Sekhar for the removal of extradural lesions of the mid to upper clivus and involvement of the petrous ICA [36]. It is a preauricular approach that, when used in isolation, represents an anterior approach to the jugular fossa. While it avoids the necessity to reroute the FN, it requires resection of the mandibular condyle and mobilization of the petrous ICA and gives limited exposure to the bony margins of the jugular fossa. It has no role as a sole approach for lesions of the jugular fossa. In combination with an IFTA, it is essentially the same as an ITFA type B and is employed to control the area medial to the horizontal intrapetrous ICA [5, 37]. The classic ITFA type A is the most favored approach for class C1 and certain class C2 tumors, and the ITFA type A with extensions can be used to manage class C2–C4 tumors.

Rationale of the Infratemporal Fossa Approach Type A

This approach is designed to allow access to the jugular foramen area, the infralabyrinthine and apical compartments of the petrous bone, the vertical segment of the internal carotid artery, and the upper jugulocarotid space. The approach is designed primarily for extensive extradural lesions involving these areas. The key point in this approach is the anterior transposition of the FN to provide optimal control of the targeted areas. The other structures that prevent lateral access to these areas are shown in Fig. 8.1c. Besides the FN they include the tympanic bone, the digastric muscle, and the styloid process. These structures are removed to allow an unhindered lateral access.

Surgical Steps

A postauricular skin incision is performed (Fig. 8.2). A small, anteriorly based musculoperiosteal flap is elevated to help in closure afterward. The external auditory canal is transected and closed, and the FN is identified at its exit from the temporal bone

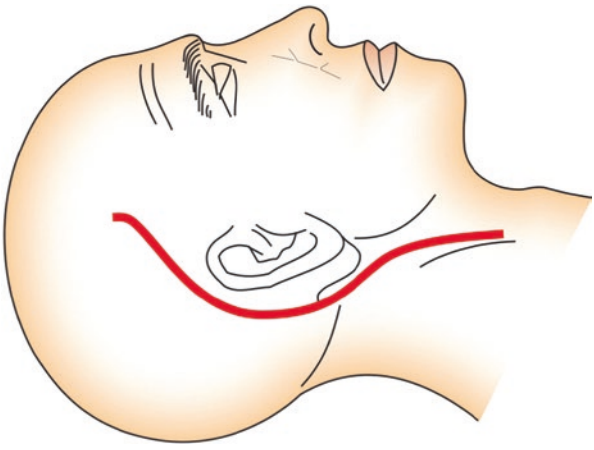

Fig. 8.2 Incision for infratemporal fossa approach type A

(Figs. 8.3 and 8.4). The main trunk is found at the perpendicular bisection of a line joining the cartilaginous pointer to the mastoid tip. The main trunk is traced in the parotid until the proximal parts of the temporal and zygomatic branches are identified. The posterior belly of digastric muscle and the sternocleidomastoid muscle are divided close to their origin. The internal jugular vein and the external and internal carotid arteries are identified in the neck. The vessels are marked with umbilical tape. The skin of the external auditory canal, the tympanic membrane, the malleus, and the incus is removed. A canal wall down mastoidectomy is performed, with removal of the bone anterior and posterior to the sigmoid sinus. The FN is skeletonized from the stylomastoid foramen to the geniculate ganglion. The last shell of bone is removed using a double-curved raspatory. The suprastructure of the stapes is preferably removed after cutting its crura (Fig. 8.5). The inferior tympanic bone is widely removed, and the mastoid tip is amputated using a rongeur. A new fallopian canal (arrow) is drilled in the root of the zygoma superior to the Eustachian tube (Fig. 8.6). The FN is freed at the level of the stylomastoid foramen using strong scissors. The soft tissues at this level are not separated from the nerve (Fig. 8.7). The mastoid segment is next elevated using a Beaver knife to cut the fibrous attachments between the nerve and the fallopian canal. The tympanic segment of the nerve is elevated carefully, using a curved

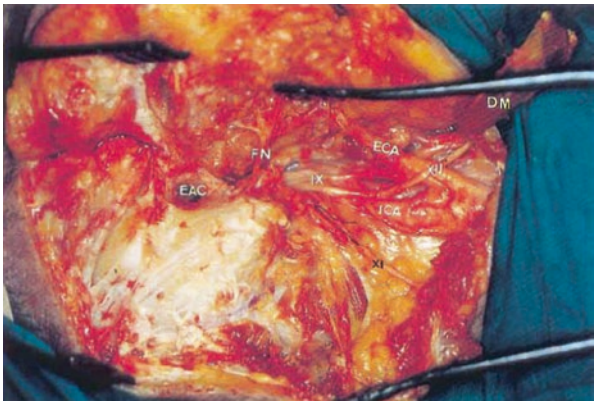

Fig. 8.3 Exposure of Infratemporal Fossa Approach Type A after blind sac closure of the external auditory canal. *DM* digastric muscle, *EAC* external auditory canal, *ECA* external carotid artery, *FN* facial nerve, *ICA* internal carotid artery, *IX* glossopharyngeal nerve, *XI* spinal accessory nerve, *XII* hypoglossal nerve

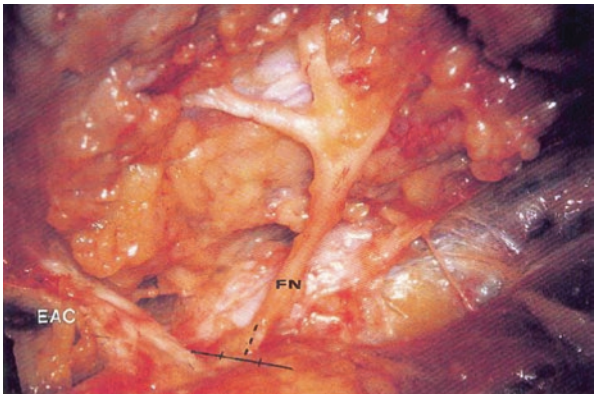

Fig. 8.4 The facial nerve is identified at the stylomastoid foramen. *EAC* external auditory canal, *FN* facial nerve

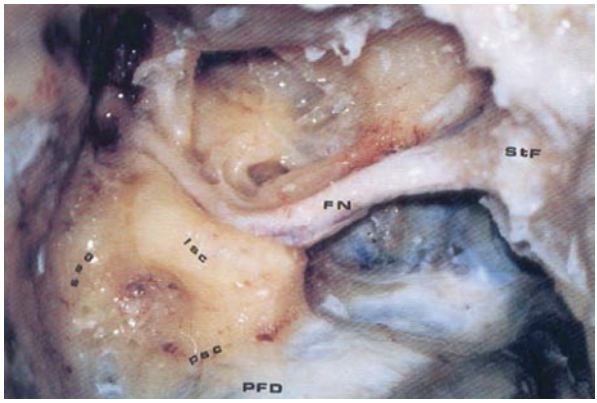

Fig. 8.5 The tympanic and mastoid segements of the facial nerve are skeletonised. *FN* facial nerve, *PFD* posterior fossa dura, *LSC* lateral semicircular canal, *psc* posterior semicircular canal, *ssc* superior semicircular canal, *StF* stylomastoid foramen

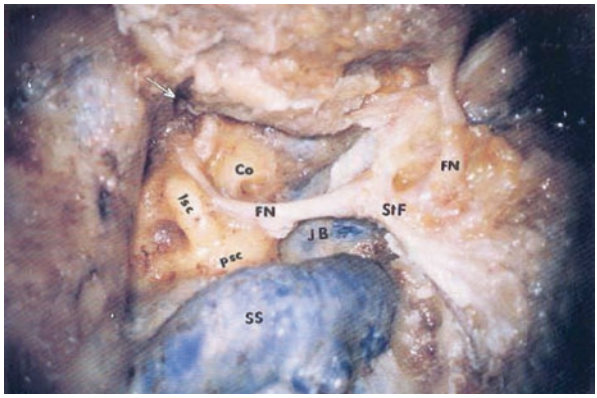

Fig. 8.6 The facial nerve from the geniculate ganglion to the terminal branches in the parotid are skeletonised. *Co* cochlea, *FN* facial nerve, *JB* jugular bulb, *PFD* posterior fossa dura, *LSC* lateral semicircular canal, *psc* posterior semicircular canal, *StF* stylomastoid foramen

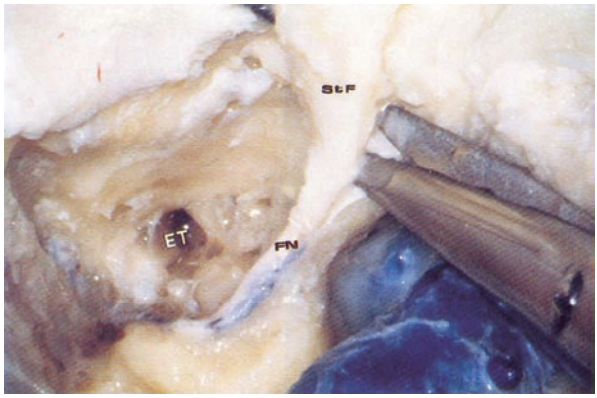

Fig. 8.7 The facial nerve is released at the stylomastoid foramen. *ET* Eustachian tube, *FN* facial nerve, *StF* stylomastoid foramen

raspatory, until the level of the geniculate ganglion is reached. A non-toothed forceps is used to hold the soft tissue surrounding the nerve at the stylomastoid foramen, and anterior rerouting is carried out (Fig. 8.8). A tunnel is created in the parotid gland to secure the transposed nerve (Fig. 8.9). The tunnel is dosed around the nerve using two

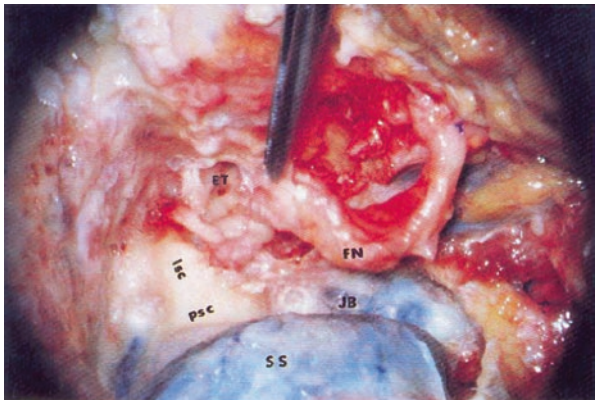

Fig. 8.8 The facial nerve is carefully elevated from its canal. *ET* Eustachian tube, *FN* facial nerve, *JB* jugular bulb, *LSC* lateral semicircular canal, *psc* posterior semicircular canal, *SS* sigmoid sinus

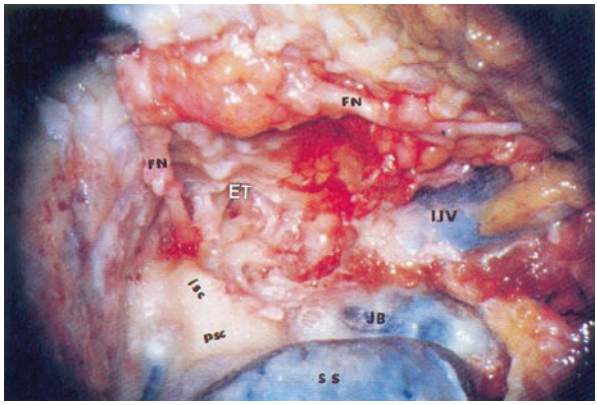

Fig. 8.9 The facial nerve is re-routed by stitching the cuff of tissue at the stylomastoid foramen to the parotid gland. *ET* Eustachian tube, *FN* facial nerve, *IJV* internal jugular vein, *JB* jugular bulb, *LSC* lateral semicircular canal, *psc* posterior semicircular canal, *SS* sigmoid sinus

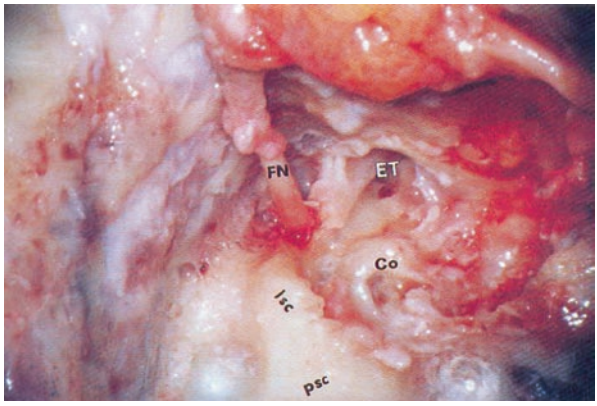

Fig. 8.10 The nerve is glued to the canal created for it at the root of the zygoma. *Co* cochlea, *ET* Eustachian tube, *FN* facial nerve, *LSC* lateral semicircular canal, *psc* posterior semicircular canal

sutures. A closer view shows the FN in its new bony canal, just superior to the Eustachian tube. The nerve is fixed to the new bony canal using fibrin glue (Fig. 8.10). Drilling of the infralabyrinthine cells is completed, and the vertical portion of the

internal carotid artery is identified (Fig. 8.11). The mandibular condyle is separated from the anterior wall of the external auditory canal using a large septal raspatory. The Fisch infratemporal fossa retractor is applied, and the mandibular condyle is anteriorly displaced, with care being taken not to injure the FN. The anterior wall of the external auditory canal is further drilled, thus completing the exposure of the vertical portion of the internal carotid artery. A small incision is made in the posterior fossa dura just behind the sigmoid sinus, through which an aneurysm needle is passed. Another incision is made just anterior to the sinus to allow for the exit of the needle (Fig. 8.12). The sinus is closed by double ligation with a Vicryl suture (Fig. 8.13). Suture closure of the sinus, however, may lead to gaps in the dural incision, with a higher risk of cerebrospinal fluid leakage postoperatively. Alternatively, the sigmoid sinus can be closed with Surgicel extraluminal packing (Fig. 8.14). The structures attached to the styloid process are severed. The styloid is fractured using a rongeur and is then cut with strong scissors (Figs. 8.15 and 8.16). The remaining tough fibrous tissue surrounding the internal carotid artery at its ingress into the skull base is carefully removed using

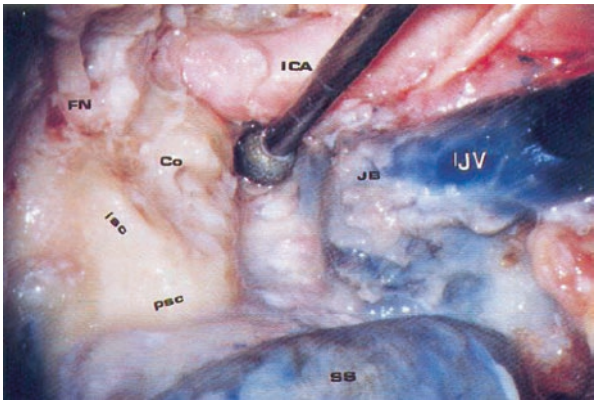

Fig. 8.11 The hypotympanic bone and the petrous bone below the cochlea is drilled out. *Co* cochlea, *FN* facial nerve, *ICA* internal carotid artery, *IJV* internal jugular vein, *JB* jugular bulb, *LSC* lateral semicircular canal, *psc* posterior semicircular canal, *SS* sigmoid sinus

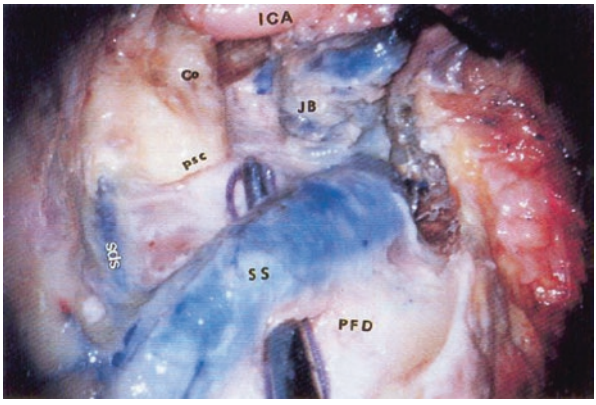

Fig. 8.12 The sigmoid sinus is completely skeletonised and a proximal control is achieved. *Co* cochlea, *FN* facial nerve, *ICA* internal carotid artery, *JB* jugular bulb, *PFO* posterior fossa dura, *psc* posterior semicircular canal, *sps* superior petrosal sinus, *SS* sigmoid sinus

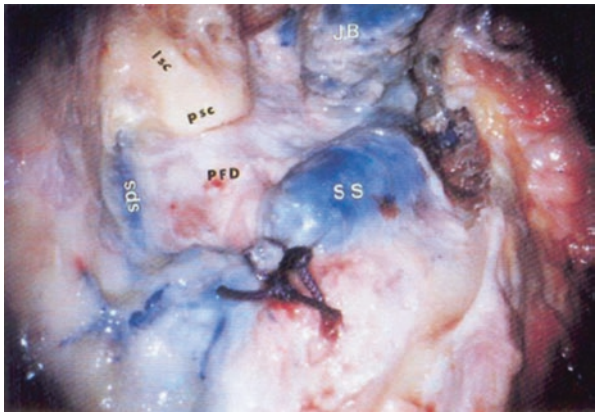

Fig. 8.13 The sigmoid sinus is ligated. *JB* jugular bulb, *LSC* lateral semicircular canal, *PFO* posterior fossa dura, *psc* posterior semicircular canal, *sps* superior petrosal sinus, *SS* sigmoid sinus

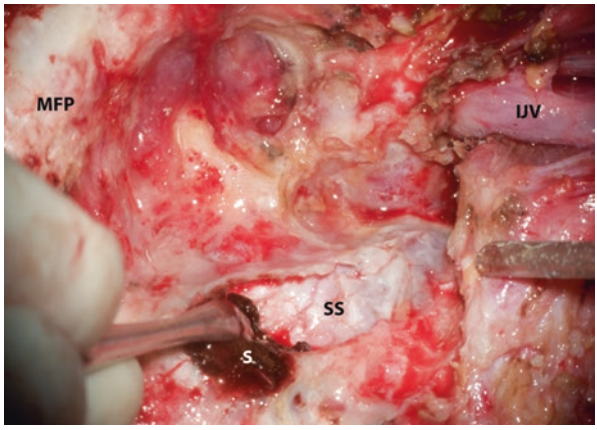

Fig. 8.14 Another technique is to achieve a sigmoid sinus closure is to do an extra and intra-luminal packing. *MFP* middle fossa plate, *S* Surgicel, *SS* sigmoid sinus, *IJV* internal jugular vein

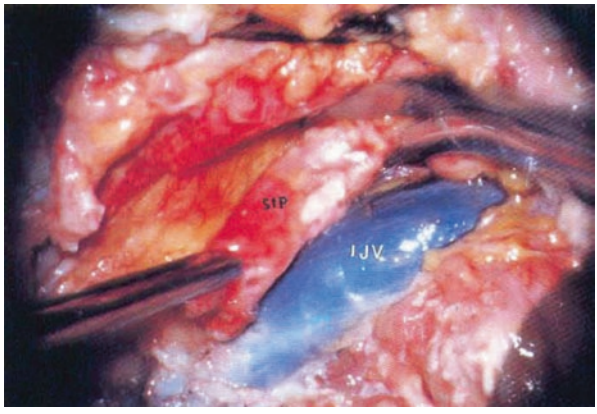

Fig. 8.15 The styloid process is identified and excised from its muscular attachments. *IJV* internal jugular vein, *SP* styloid process

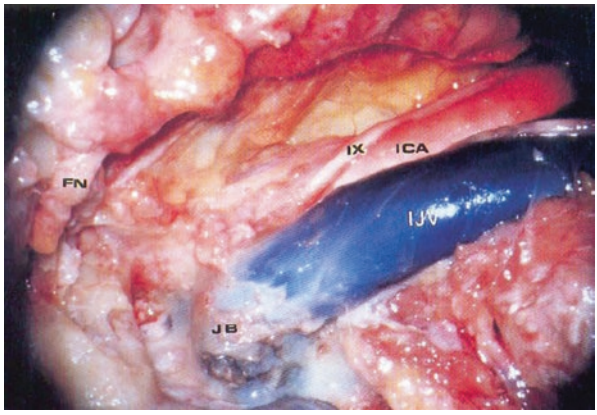

Fig. 8.16 The field after removal of the styloid process. *FN* facial nerve, *ICA* internal carotid artery, *IJV* internal jugular vein, *JB* jugular bulb, *IX* glossopharyngeal nerve

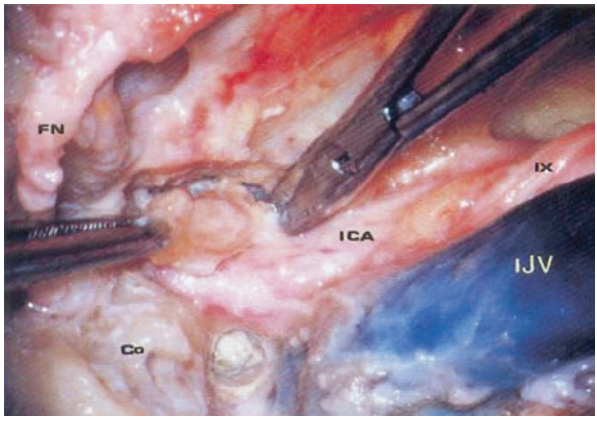

Fig. 8.17 The internalcarotid artery is skeltonised at the carotid foramen drilling all around the vertical portion of the petrous carotid artery. *Co* cochlea, *FN* facial nerve, *ICA* internal carotid artery, *IJV* internal jugular vein, *IX* glossopharyngeal nerve

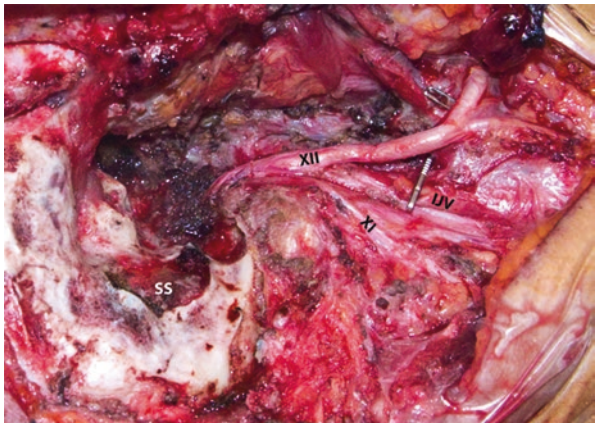

Fig. 8.18 The surgical field exposing the area of the tumor. *XI* spinal accessory nerve, *XII* hypoglossal nerve, *IJV* internal jugular vein, *SS* sigmoid sinus

scissors (Fig. 8.17). The internal jugular vein in the neck is double ligated and cut or closed with vascular clips (Fig. 8.18). The vein is elevated superiorly, with care being taken not to injure the related lower cranial nerves (Figs. 8.19 and 8.20). In cases in which the 11th nerve passes laterally, the vein has to be pulled under the nerve

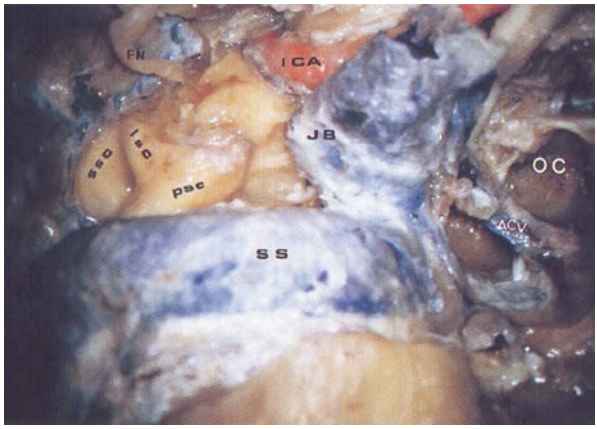

Fig. 8.19 The transtubercular transcondylar extension. *ACV* anterior condylar vein, *FN* facial nerve, *ICA* internal carotid artery, *JB* jugular bulb, *LSC* lateral semicircular canal, *OC* occipital condyle, *psc* posterior semicircular canal, *SS* sigmoid sinus, *ssc* superior semicircular canal

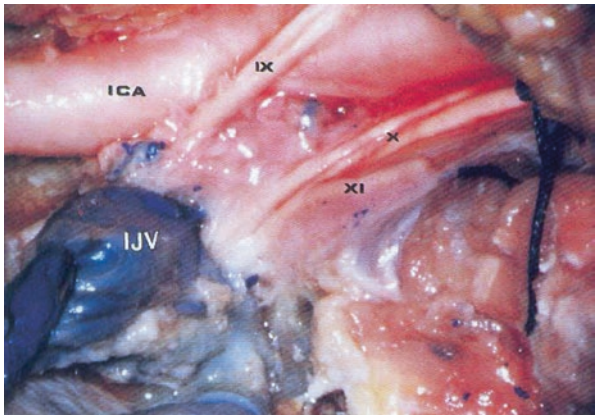

Fig. 8.20 The lower cranial nerves on the medial wall of the jugular bulb. *ICA* internal carotid artery, *IJV* internal jugular vein, *IX* glossopharyngeal nerve, *X* vagus nerve, *XI* accessory nerve

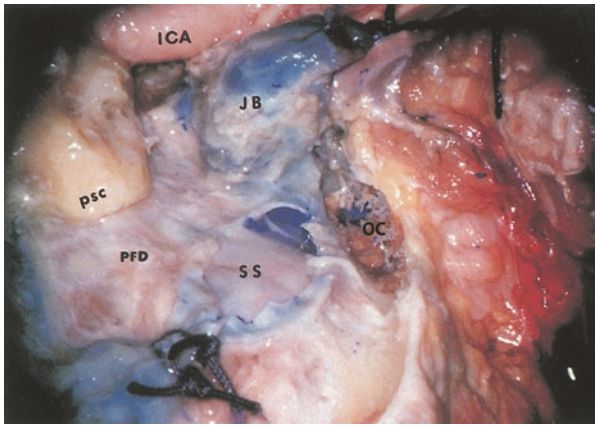

Fig. 8.21 Drilling of the occipital condyle posterior to the jugular bulb. *ICA* internal carotid artery, *PFD* posterior fossa dura, *SS* sigmoid sinus, *JB* jugular bulb, *psc* posterior semicircular canal, *OC* occipital condyle

carefully to prevent it from being damaged. If necessary (as in the case of TJPs), the lateral wall of the sigmoid sinus can be removed (Fig. 8.21). Removal continues down to the level of the jugular bulb. The lateral wall of the jugular bulb is opened. Bleeding usually occurs from the apertures of the inferior petrosal sinus and the condylar

emissary vein. This is controlled by Surgicel packing (Fig. 8.22). If there is limited intradural extension, the dura is opened without injury to the endolymphatic sac (Fig. 8.23). Figures 8.24, 8.25, and 8.26 show the view after the dura of the posterior fossa has been opened. At the end of the procedure, the Eustachian tube (Fig. 8.27) is

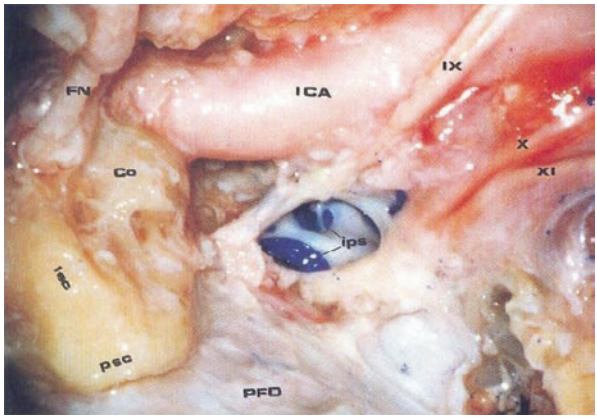

Fig. 8.22 The inferior petrosal sinus opens into the medial wall of the jugular bulb and is seen after excision of the bulb. *Co* cochlea, *FN* facial nerve, *ICA* internal carotid artery, *IPS* inferior petrosal sinus, *LSC* lateral semicircular canal, *PFD* posterior fossa dura, *psc* posterior semicircular canal, *IX* glossopharyngeal nerve, *X* vagus nerve, *XI* accessory nerve

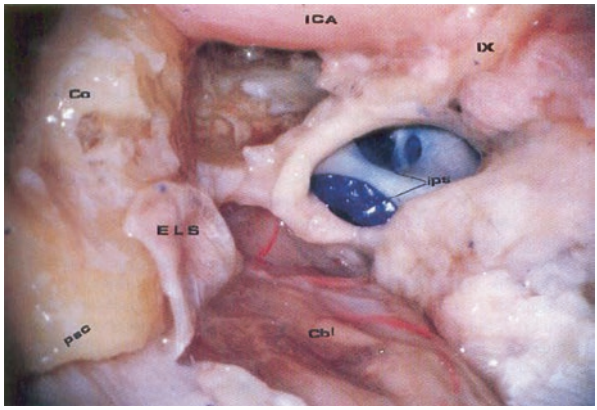

Fig. 8.23 The posterior fossa dura is opened. *Cbl* cerebellum, *Co* cochlea, *ELS* endolymphatic sac, *ICA* internal carotid artery, *IPS* inferior petrosal sinus, *psc* posterior semicircular canal, *IX* glossopharyngeal nerve

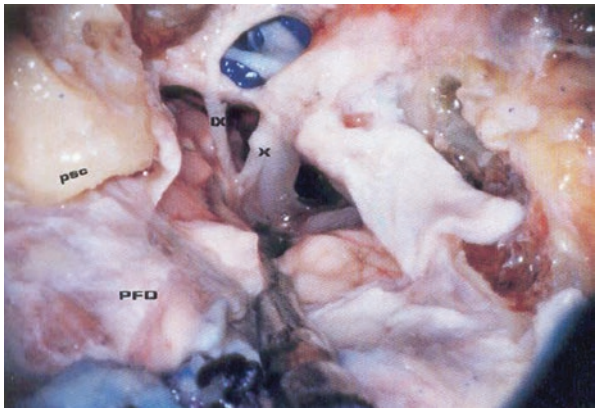

Fig. 8.24 The glossopharyngeal and vagus nerves are well identified in the cerebellomedullary cistern before entering the jugular foramen. *PFD* posterior fossa dura, *psc* posterior semicircular canal, *IX* glossopharyngeal nerve, *X* vagus nerve

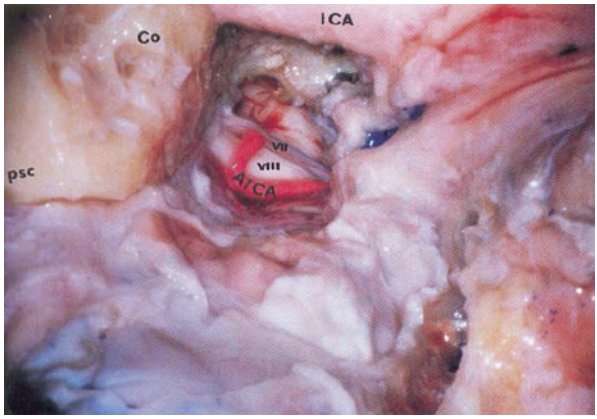

Fig. 8.25 The facial and vestibulocochlear nerves and the anterior inferior cerebellar artery are visible. *AICA* anterior inferior cerebellar artery, *Co* cochlea, *ICA* internal carotid artery, *psc* posterior semicircular canal, *VII* facial nerve, *VIII* vestibulocochlear nerve

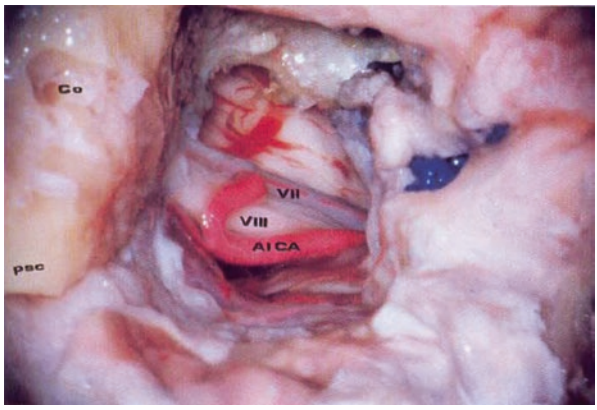

Fig. 8.26 A closer view shows the anterior inferior cerebellar artery passing between the seventh and eighth nerves. *AICA* anterior inferior cerebellar artery, *Co* cochlea, *psc* posterior semicircular canal, *VII* facial nerve, *VIII* vestibulocochlear nerve

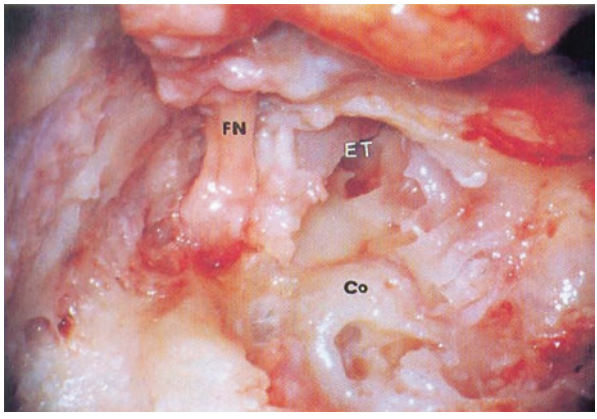

Fig. 8.27 Relationship of the re-routed facial nerve to the cochlea and the Eustachian tube. *Co* cochlea, *ET* Eustachian tube, *FN* facial nerve

closed by a piece of muscle. The dural opening is closed by a muscle plug or with only abdominal fat. We never use a rotated temporalis muscle (as suggested by Fisch) in order to avoid aesthetic problems, but the sternocleidomastoid muscle and the digastric muscle are sutured together, and the temporalis muscle is left in its place.

Extensions of the ITFA Type A Approach

Based on the IFTA approach, various extensions can be added depending upon the extent of the pathology. The standard extension we use is a transcondylar-transtubercular extension for C2–C4 tumors (Fig. 8.28). This allows additional posteroinferior and medial access to the jugular fossa, widening the exposure, thus facilitating venous and neural control. The widened angle also affords better access to the petrous apex, medial to the carotid artery. Very rarely a far lateral is employed with full exposure of the vertebral artery (Fig. 8.29). The use of a translabyrinthine extension is occasionally required for otic capsule involvement. A modified transcochlear approach is uncommonly required to access petrous apex, clival involvement, and infratemporal fossa involvement.

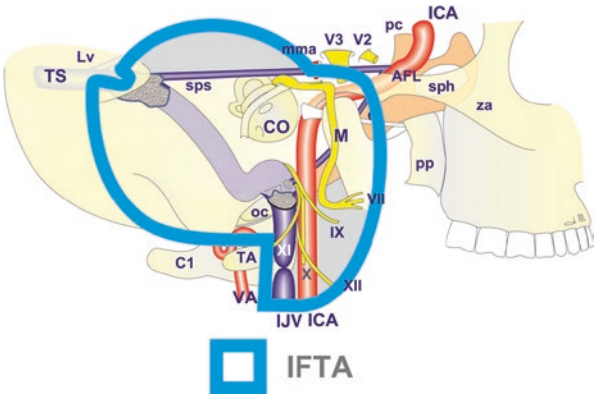

Fig. 8.28 Transcondylar-transtubercular extension improves postero-inferolateral and medial exposure

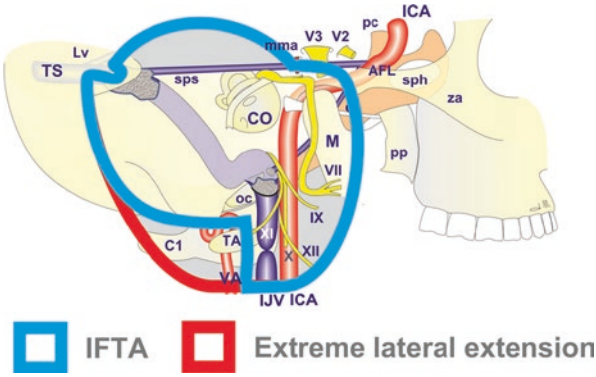

Fig. 8.29 Far-lateral approach further extends postero-inferolateral exposure

Transcondylar-Transtubercular Extension of the ITFA Type A

The classic infratemporal fossa approach type A of Fisch permits only superior and anterior exposure of the jugular bulb and is indicated for class C1 and certain C2 tumors. For larger tumor such as class C2, C3, and C4 tumors involving the lower cranial nerves, a transcondylar-transtubercular extension is required in addition to the classic infratemporal fossa approach type A. This extension facilitates inferomedial access to the jugular bulb above the lateral mass of the atlas and occipital condyle (Figs. 8.30 and 8.31).

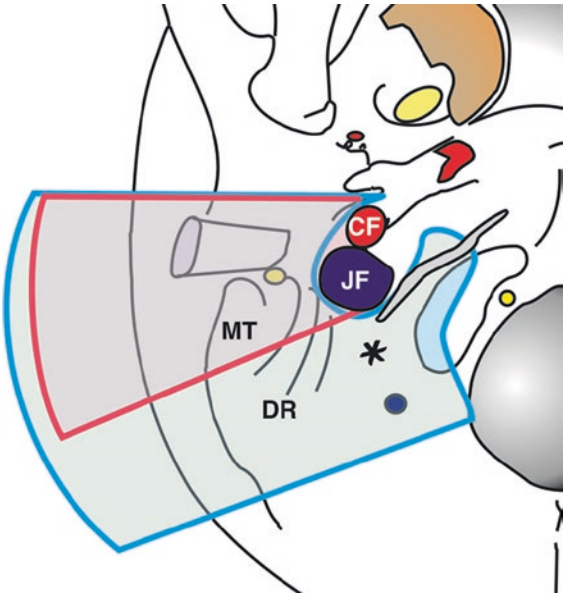

Fig. 8.30 Comparison of class IFTA and IFTA with transcondylar-transtubercular extension. *Red line zone*: classic infratemporal fossa approach type A. *Blue line zone*: infratemporal fossa approach type A with transcondylar-transtubercular extension. *CF* carotid foramen, *MT* mastoid tip, *DR* digastric ridge, *JF* jugular foramen

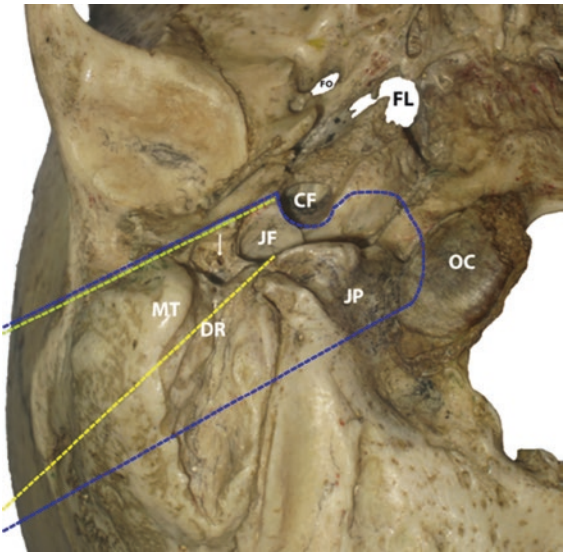

Fig. 8.31 Inferior view of skull base, comparison of classic ITFA by Fisch, and modified ITFA with transcondylar-transtubercular extension. In addition to removal of bone in classic ITFA by Fisch, drilling of the jugular process of the occipital bone and even some of the occipital condyle facilitates control of the area of the jugular bulb. *Yellow dash line*: classic ITFA by Fisch. *Blue dash line*: modified ITFA with transcondylar-transtubercular extension. *FO* foramen ovale, *FL* foramen lacerum, *CF* carotid foramen, *JF* jugular foramen, *JP* jugular process of the occipital bone, *MT* mastoid tip, *DR* digastric ridge, *OC* occipital condyle

Steps of ITFA Type A with Transtubercular-Transcondylar Extension

As described in the previous pages, the ITFA type A approach is performed. The transcondylar-transtubercular approach begins with the identification of the splenius capitis muscles. The posterior fossa dura is uncovered toward the occipital skull base in order to start drilling of the jugular process and occipital condyle. The drilling of the jugular process is commenced followed by the identification and drilling of the occipital condyle superior to the atlanto-occipital joint posteromedial to the jugular bulb (Figs. 8.32 and 8.33). The hypoglossal canal is then identified between the jugular tubercle and occipital condyle above the vertebral artery, if indicated (Figs. 8.34, 8.35, 8.36, 8.37, 8.38, and 8.39).

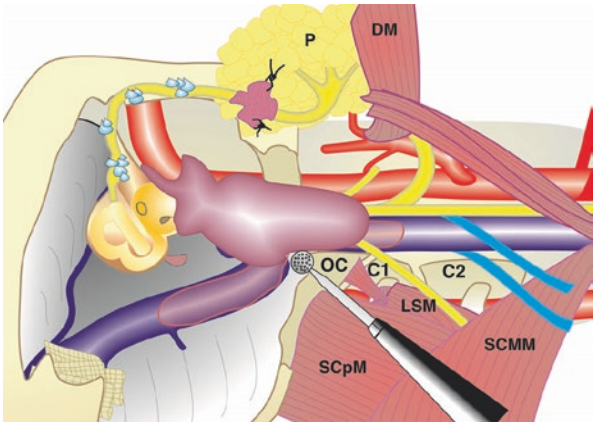

Fig. 8.32 The styloid process is completely removed. In order to fully expose posterior and medial aspects of the tumor, a transcondylar-transtubercular extension is performed. For this, the jugular process and occipital condyle (OC) of the occipital bone are drilled out. *C1* atlas, *C2* axis, *DM* posterior belly of the digastric muscle, *LSM* levator scapulae muscle, *P* parotid gland, *SCMM* sternocleidomastoid muscle, *SpCM* splenius capitis muscle

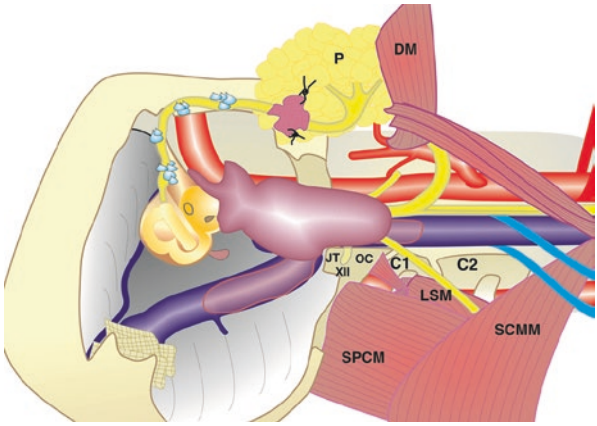

Fig. 8.33 After removal of the jugular process, the jugular tubercle (JT) and hypoglossal nerve (XII) are identified. *C1* atlas, *C2* axis, *DM* posterior belly of the digastric muscle, *LSM* levator scapulae muscle, *OC* occipital condyle, *P* parotid gland, *SCMM* sternocleidomastoid muscle, *SpCM* splenius capitis muscle

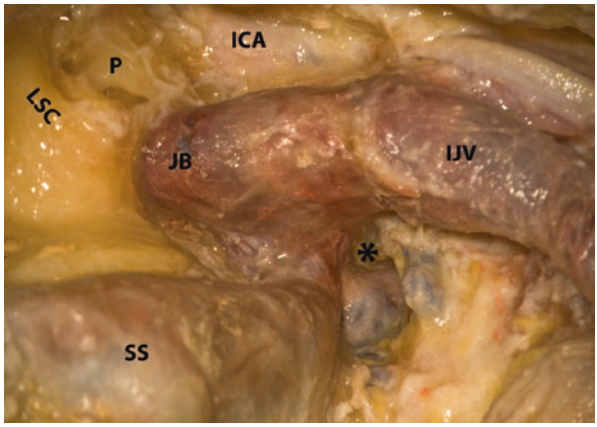

Fig. 8.34 The jugular process and the portion of the occipital condyle have been drilled out. The left occipital condyle is identified below the jugular bulb and posterior to the internal jugular vein. *ICA* internal carotid artery, *P* promontory, *LSC* lateral semicircular canal, *JB* jugular bulb, *IJV* internal jugular vein, *SS* sigmoid sinus. *Occipital condyle

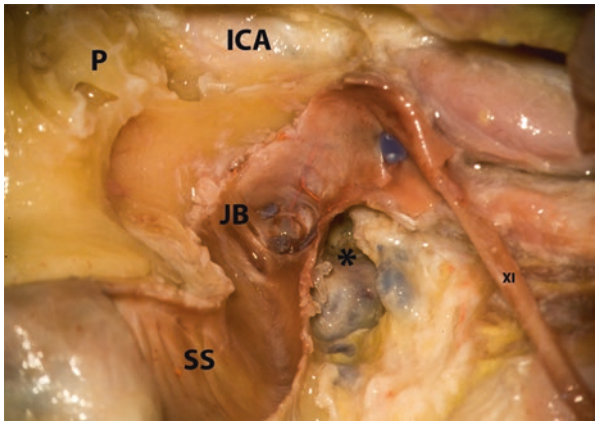

Fig. 8.35 The lateral aspect of the jugular bulb, sigmoid sinus, and internal jugular vein has been removed. On the medial wall of the jugular bulb, the inferior petrosal sinus is identified. The opening of the posterior condylar vein is seen. *ICA* internal carotid artery, *P* promontory, *JB* jugular bulb, *SS* sigmoid sinus.*Occipital condyle

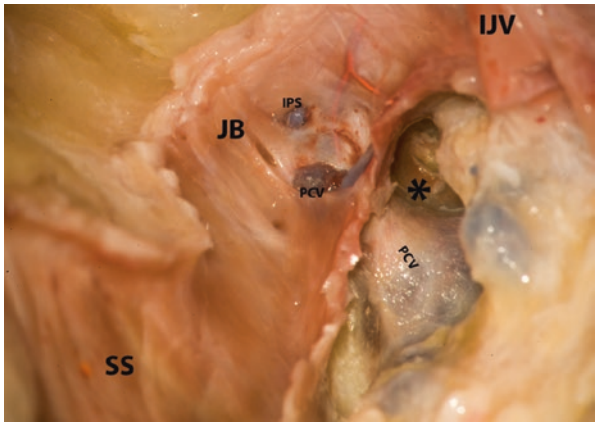

Fig. 8.36 The inferior petrosal sinus and the posterior condylar veins open into the medial wall of the jugular bulb. *IPS* inferior petrosal sinus, *IJV* internal jugular vein, *PCV* posterior condylar vein, *JV* jugular vein. *Occipital condyle

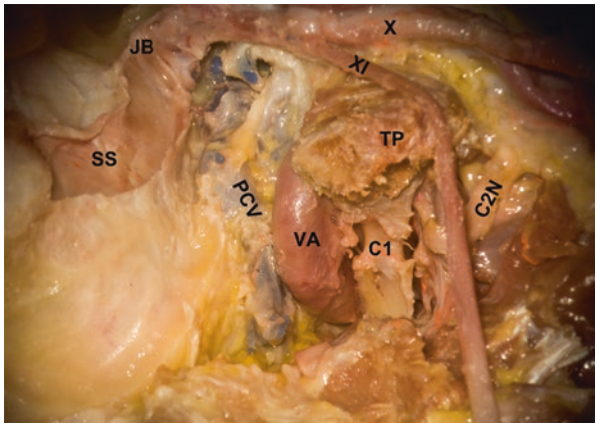

Fig. 8.37 Note the relationship among the sigmoid sinus, jugular bulb, posterior condylar vein, vertebral artery, and lower cranial nerves. *IPS* inferior petrosal sinus, *JB* jugular bulb, *PCV* posterior condylar vein, *JV* jugular vein, *VA* vertebral artery, *TP* transverse process of C1, *C1* the first cervical vertebra, *C2N* the second cervical vertebra, *X* vagus nerve, *XI* spinal accessory nerve. *Occipital condyle

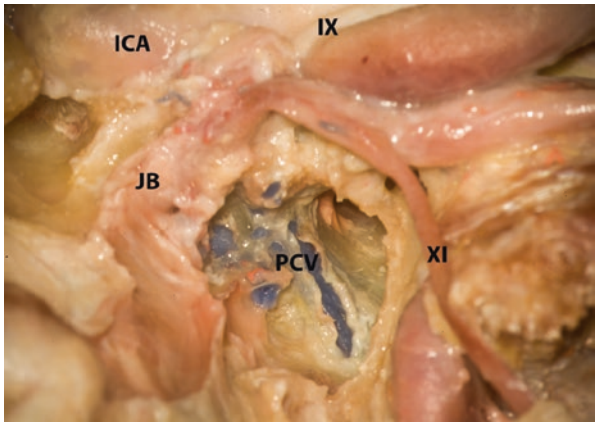

Fig. 8.38 The posterior condylar vein crossing the occipital condyle is noted. *IX* glossopharyngeal nerve, *XI* spinal accessory nerve, *ICA* internal carotid artery, *JB* jugular bulb, *PCV* posterior condylar vein

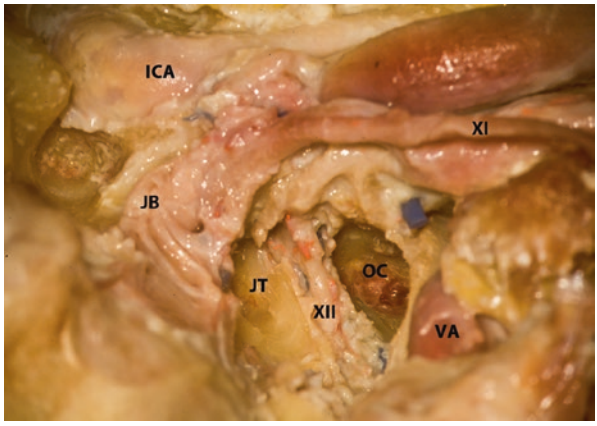

Fig. 8.39 After removal of the posterior condylar vein and further removal of the occipital condyle (OC), the hypoglossal nerve (XII) is noted. *XI* spinal accessory nerve, *ICA* internal carotid artery, *JB* jugular bulb, *JT* jugular tubercle, *VA* vertebral artery

The tumor removal is commenced at this point. The IJV is closed with vascular clips. The IJV is mobilized up to the jugular fossa by mobilizing it away from the spinal accessory nerve. The tumor is peeled away from the dura of the posterior cranial fossa. The infiltrated bone of the fallopian canal and tympanic bone is then drilled out. The tumor is debulked from the jugular bulb area. The infiltrated infralabyrinthine cells are drilled out. The sigmoid sinus is opened to expose the tumor within. The IJV is opened to expose the distal end of the tumor. The inferior petrosal sinus is packed with Surgicel®. The tumor is then separated from the lower cranial nerves. The ICA is identified after extensive drilling of the bone of the vertical portion of the carotid canal, and the tumor around is coagulated with bipolar coagulation. The tumor is gently separated from the wall of the ICA. Further drilling of all the suspect bones of infralabyrinthine and apical cells is carried out until complete removal is accomplished. If required, the internal carotid artery is partially mobilized, and the infiltrated clivus is drilled out. The posterior fossa dura is not opened, and the intradural portion of the tumor is left behind to be removed in a second stage. The closure of the Eustachian tube, cavity obliteration, and watertight closure of the subcutaneous and cutaneous tissue are carried out as with the conventional ITFA type A.

Considerations in the Management of Complex TJPs

Complex TJPs are a challenge to even the most experienced skull base team. The following issues need to be taken into consideration while managing such complex cases.

Very large size—As TJPs grow, they extend either into the carotid canal and the petrous apex or into the intradural space through the medial wall of the jugular bulb and thereby involving the LCNs. A large size obviously brings into play the other factors mentioned above that complicate the presentation of TJPs discussed below. Fisch class C3 and C4 tumors are generally considered as large tumors. Of the 245 TJPs treated at our center, we managed 35 patients with tumors considered to be of a large size, of which 27 were Fisch C3, 5 were C4, and 3 were De2. As a rule, ITFA-A is used for C2 tumors, and ITFA-A or ITFA-A combined with ITFA-B can be used for C3/C4 tumors. If the tumor involves the clivus, occipital condyle, or foramen magnum, additional procedures such as MTCA or ELTCA are necessary and were performed at our center.

Large intradural extension (IDE)—Although some authors prefer a single-staged surgery [11], we feel that if an extensive area of dura is involved by tumor, a planned second-stage resection can be considered. We managed a total of 45 patients with IDE: 25 with Fisch Di1, 18 Di2, and 2 Di3. In 14 of them, a staged surgery was performed. The advantage of a staged surgery is that a clear plane of dissection would have been established between the tumor and the brain stem due to the devascularization of the tumor at the first-stage surgery and subsequent shrinkage of the intradural mass (Fig. 8.40a–d). Another consideration is that in tumors involving

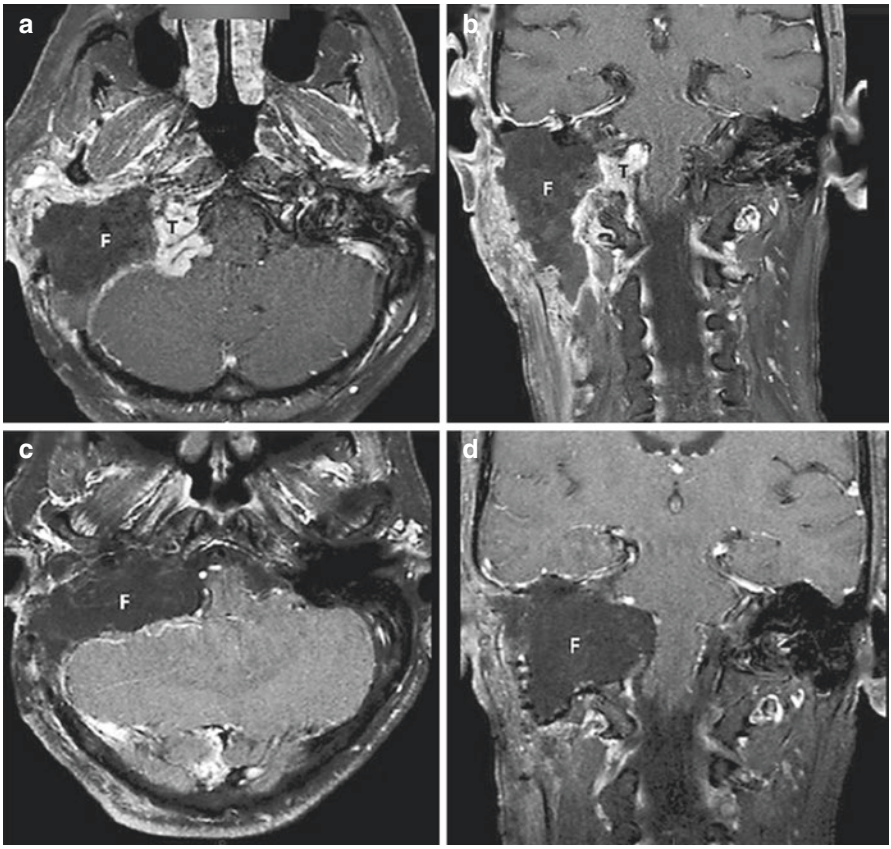

Fig. 8.40 (**a**, **b**) MRI, axial, and coronal views after the first-stage surgery. The residual intradural tumor is noted. The surgical defect is filled with abdominal fat. *T* intradural tumor, *f* fat. (**c**, **d**) MRI, axial, and coronal views after the second-stage surgery. After the surgery, there is no residual tumor

LCNs, their sacrifice could cause severe aspiration with continuous cough. The resulting increase in intracranial pressure could give rise to CSF leaks [38]. To also prevent any such postoperative CSF leaks, we prefer a staged surgery for tumors with more than 2 cm IDE. At the second stage, the approach is determined by the location and size of the residual tumor and the patient's hearing function. Although the petro-occipital trans-sigmoid approach is preferred in most cases, a MTCA or an ELTCA may also be used.

Extension to the foramen magnum, clivus, or the cavernous sinus—For tumors extending to the foramen magnum and lower clivus, MTCA type D or the ELTCA may be used [5]. In order to prevent tumor recurrence, any part of the clival bone suspected of being infiltrated must be drilled out until healthy bone appears. We had 13 patients: 2 with tumor involvement of the cavernous sinus, 3 of foramen magnum, and 8 of the clivus. In two of them, the tumor involved the cavernous sinus, and they were intentionally left intact to avoid compromising cranial nerves III, IV,

and VI and maintain ocular mobility. After surgery, stereotactic radiotherapy was carried out in both patients. We had three cases involving the foramen magnum, and total removal was difficult to achieve in one of them due to persistent bleeding.

Involvement of the ICA—TJPs frequently involve the ICA due to their close anatomical proximity [39]. When indicated, the tumor must be dissected from the arterial wall. This can be achieved by subperiosteal (or supra-adventitial) dissection of the ICA in the carotid canal (horizontal portion) or subadventitial dissection in the vertical portion [40]. When the artery is completely surrounded by a tumor resulting in severe stenosis on arteriography, manipulation without proper endovascular intervention may give rise to severe bleeding, incomplete removal, or a cerebral vascular accident [41]. Permanent balloon occlusion is performed when the ICA is infiltrated by the tumor and the collateral blood flow is sufficient. But in cases with insufficient collateral blood flow, we routinely use intraluminal stenting (Figs. 8.41a–d and 8.42). Stenting of the cervical and petrous segments of ICA was introduced as a preoperative management protocol by the Gruppo Otologico in the clinical and surgical management of complex HNPs since the early 2003 as a method to avoid preoperative closure of the ICA or high-risk bypass procedures and to protect and preserve integrity of the artery during surgery, mainly in cases in which the collateral flow through the circle of Willis is deemed insufficient [42–44]. 21 preoperative ICA stenting procedures were performed at our center on 19 patients. Stenting of the ICA allows reinforcement of the artery, reducing the risk of intraoperative injury of its wall while performing a more aggressive carotid dissection in the subadventitial plane. The presence of the stent allows the safe mobilization of the artery if necessary. This new technique can allow reappraisal of selected cases previously suited only for subtotal resection. To the best of our knowledge, the literature contains only one case of stenting of the intratemporal segment of the ICA for the management of TJPs [11].

A single ICA on the lesion side—As mentioned above, management of the ICA is essential for total tumor removal. For a case with a single carotid artery on the lesion side, possible management options are "wait and scan," partial resection followed by radiotherapy, or total removal subsequent to the preoperative reinforcement with stents [43]. In a patient with a single carotid artery on the lesion side, bypass surgery can cause severe cerebral ischemic damage. Therefore, the stent insertion may be the best option. We have so far treated two patients with a single ICA without any adverse consequences.

Vertebral artery involvement—Although involvement of the VA by TJPs is extremely uncommon, with a total of 11 cases reported worldwide, of which 8 cases belong to our series, it represents the pinnacle of difficulty in management of TJPs. 7/8 patients underwent surgery and the results are summarized. In two patients, preoperative occlusion was performed. In one of our articles [1], we have presented the radiological and surgical findings of VA involvement by TJPs to emphasize the importance of VA assessment and propose the addition of the "V" category to the existing Fisch classification. Angiography of the vertebrobasilar system should always be included in the assessment of TJPs planned for surgery. This is to detect anastomotic connections between the external carotid and the VA that

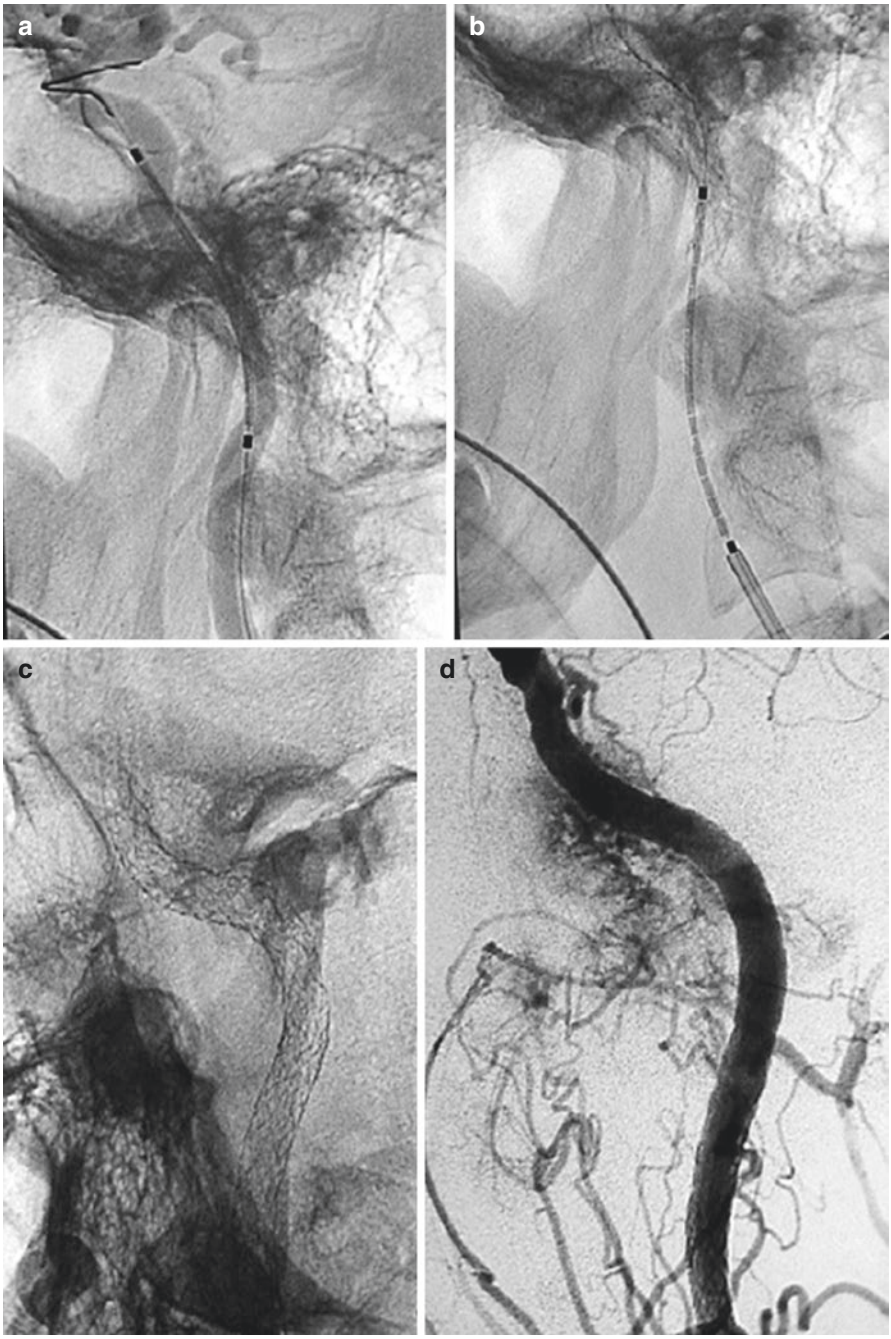

Fig. 8.41 (**a**, **b**) Insertion of the stents in the petrous and cervical portions of the internal carotid artery (ICA). (**c**) Digital x-ray in oblique projection showing the stents fully deployed in the petrous and cervical segments of the ICA. (**d**) Digital subtraction angiography of the ICA after stenting showing resolution of the stenosis

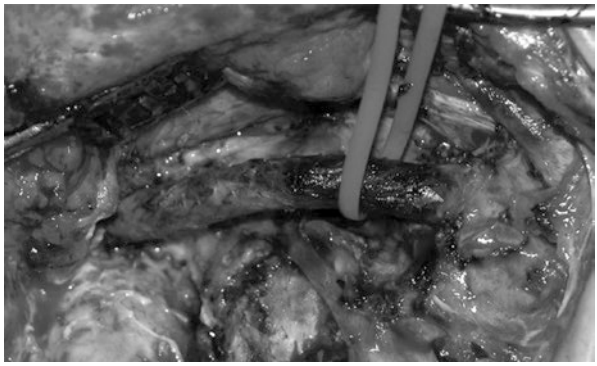

Fig. 8.42 The view of the internal carotid artery. Tumor removal has been completed. Dissection has been carried out down to the stent in an almost bloodless field

are potentially dangerous during embolization, such as between branches of the ascending pharyngeal, deep cervical, ascending cervical, and occipital arteries with the VA [45], as well as to adequately assess direct involvement of the VA. For the surgical strategy, involvement of the V3 segment requires the addition of an extreme lateral extension to the standard ITFA, in order to ensure its adequate exposure. The V4 segment involvement is inevitably accompanied by a large IDE. In such cases, we prefer a two-stage surgery (Fig. 8.43a–f).

Dominant or unilateral sigmoid sinus on the lesion side—The SS obliteration and the jugular vein often need to be ligated during resection of TJPs. However, ligation SS of the dominant or the presence of unilateral SS on the lesion side may cause intracranial hypertension and venous congestion leading to swelling of the brain [5]. Therefore, preoperative evaluation of venous drainage of the brain is essential, especially of the ipsilateral mastoid emissary vein or the condylar vein. If their diameters are larger than normal, they should be preserved during surgery. In cases where the collateral venous drainage cannot be preserved or when the patient has no sufficient collateral venous drainage, a more conservative treatment plan such as partial resection with preservation of the SS, gamma knife surgery, or a "wait and scan" approach is recommended.

Bilateral or multiple head and neck paragangliomas—In the management of bilateral TJPs, the possibility of bilateral deficits of important LCNs looms large, and hence neural preservation is very important to achieve a good quality of life for the patient postoperatively. We had 11 patients with multiple HNPs. According to our management protocol, in patients with LCN deficits on the side of the larger tumor, it is removed first, and then the smaller tumor is either followed up or irradiated. On the contrary, if the patients have LCN deficits on the side of the smaller tumor, it is removed first, and then the larger tumor is followed up with MRI. During follow-up, if the larger tumor shows evidence of growth, it may be partially removed with the preservation of LCN function or irradiated. In patients with no LCN deficit, the "wait and scan" approach is first applied. However, if the tumor shows growth, radiotherapy or subtotal removal

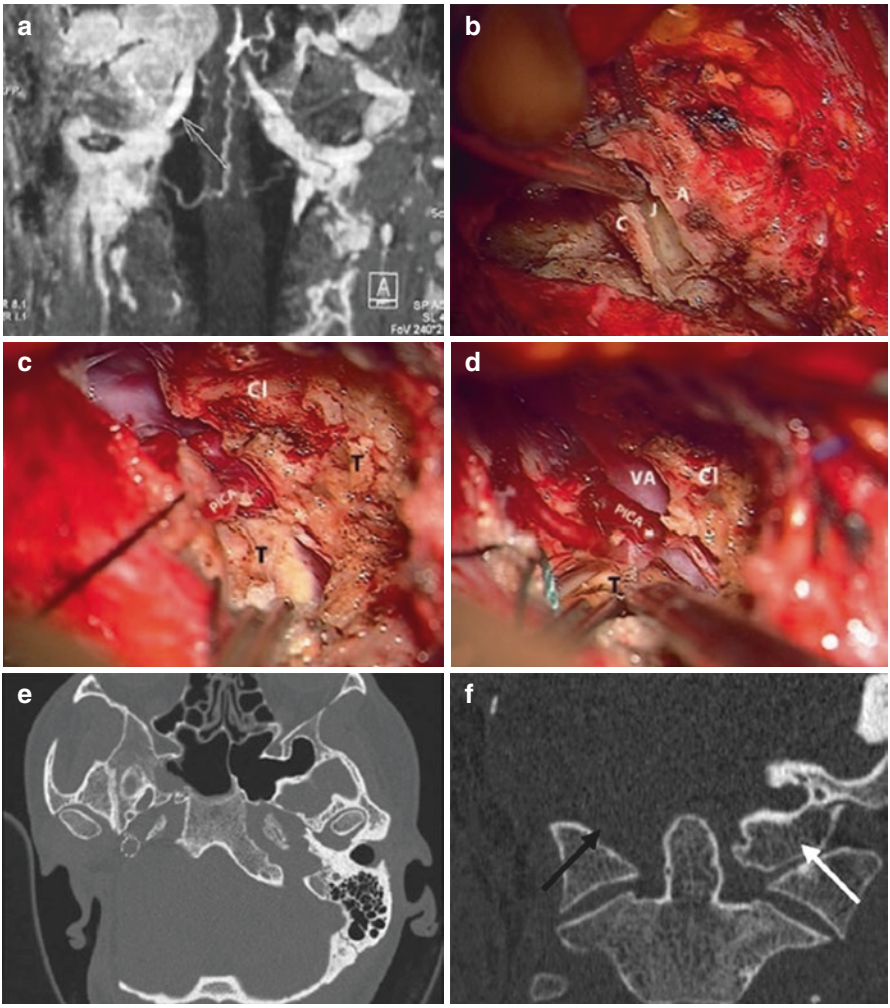

Fig. 8.43 (**a**) A class C4Di2Vi tumor. MRI coronal image showing the tumor attached to the VA. (**b–f**) Surgical sequences of extreme lateral transcondylar approach. (**b**) The transverse process of the atlas (A) is drilled out, and the atlanto-occipital joint (J) is removed. *C* condyle. (**c**) The tumor (T) is attached to the vertebral and posterior inferior cerebellar arteries infiltrating the clival (Cl) bone, which is partially drilled out. (**d**) The tumor is separated from the PICA. (**e**) CT scan. Axial view showing the stent in the ICA and the extent of bone removal. (**f**) CT scan coronal view showing absence of the surgically removed occipital condyle (*black arrow*) compared to non-operated side (*white arrow*)

of the tumor with LCN preservation is performed first. Subsequently, if the tumor continues to grow despite radiotherapy or surgical removal, the other remaining modalities can be applied.

Recurrence after previous surgery, radiotherapy, or stereotactic radiosurgery—Any revision surgery is a challenge as there are no normal tissue planes and surgical

landmarks. Previous surgery or radiation increases the risk of CSF leak and damage to the LCNs and FN [5, 41]. The carotid canal is the most common site for recurrence in TJPs, and previous dissection increases the risk of injury to the ICA. In such cases, the preoperative management of the ICA by permanent balloon occlusion or stenting is especially important. An ITFA-A with FN rerouting should be performed in all cases with the appropriate extension and extensive bone removal. In our opinion, there is no place for a conservative approach for the FN and external auditory canal in revision surgery. In our present series, 13 cases had undergone previous treatment.

Hints

- Routinely drilling out the jugular process and jugular tubercle improves access in all TJPs.
- Care is taken to fully uncover the geniculate ganglion. Sharp bone left at this level might injure the anteriorly transposed nerve.
- During anterior rerouting of the FN, a Beaver knife is used to cut the sharp attachments of the mastoid segment of the FN.
- A soft tissue cuff is left around the nerve at the level of the stylomastoid foramen. This tissue affords protection for the nerve during transposition. It also helps to maintain vascularity of the nerve.
- Removing the large intradural part of the tumor would necessitate a larger dural opening and therefore a higher risk of postoperative cerebrospinal fluid leakage. In such cases, a second-stage operation is needed to remove the intradural component of the tumor.
- There is no need to displace the vertebral artery during drilling of the occipital condyle. This procedure permits better control of the posteroinferior spread of the tumor.
- Drilling out of the one-third lateral part of the occipital condyle permits complete visualization of inferior aspect of the jugular bulb.
- In some cases, the occipital condyle is infiltrated by the tumor. The partial removal of the occipital condyle improves a postero-inferolateral and medial exposure reducing the possibility of recurrences.
- TJPs usually infiltrate the jugular bulb and insinuate into the openings of the inferior petrosal sinus. Such fingerlike tumor projections should be removed, and bleeding is controlled with Surgicel packing. However, overzealous packing should be avoided as it might cause excessive swelling with resultant paralysis of the intimately related lower cranial nerves due to compression.
- Preservation of the medial wall of the jugular bulb is necessary to save lower cranial nerve function if there is no tumor infiltration.
- The cochlea may be involved by TJP in spite of normal preoperative hearing. In these cases, total tumor removal necessitates its removal.

- In cases of class C3–C4 tumors with risk of carotid blowout or previously irradiated cases, we can utilize definitive balloon occlusion instead of a preoperative stenting of the ICA.
- Subtotal removal is indicated in tumor that extends to the cavernous sinus to avoid neurologic deficits. In these cases, the patient is sent for radiotherapy if growth is demonstrated at follow-up.
- Preservation of the branches of the external carotid artery would allow for the possibility of tumor embolization prior to any planned second-stage surgery.

Pitfalls

- Before anterior transposition is performed, the FN has to be liberated in the parotid gland. This provides an extra length of free nerve and prevents it from being stretched during the transposition.
- Direct suction over the FN is avoided. A Brackmann suction tip is used instead. Cottonoids can also be used to avoid direct trauma from the suction tip.
- Care should be taken while applying the Fisch infratemporal retractor so as not to injure the FN. We do not use the Fisch retractor anymore, but a self-retaining retractor.
- While removing the base of the styloid process, the utmost care has to be taken not to injure the internal carotid artery lying immediately deep to it.
- The internal carotid artery is surrounded by a dense fibroperiosteal layer at its entrance in the skull base. The glossopharyngeal nerve lies deep to this layer and is slightly adherent to its undersurface. Care has to be taken not to injure the nerve while dissecting tumors at this level. In large TJPs, however, the nerve has been usually infiltrated, and it is therefore sacrificed.
- Care is taken not to injure the hypoglossal nerve which traverses the condyle at a more anterior level. In about 50% of cases, the accessory nerve passes anterolateral to the internal jugular vein in the neck. After ligating the vein, care is taken to not injure the nerve during elevation of the vein. We currently preserve the medial wall of the internal jugular vein and jugular bulb if not infiltrated, which afford protection for the closely related lower cranial nerves.
- With paragangliomas, all cancellous bone should be removed if suspected. The Haversian system of this bone is usually invaded by the tumor and is a frequent cause for recurrence. Drilling should continue until sound bone is reached. This is especially important in the area lying between the basal turn of the cochlea and the internal carotid artery. The bone from the petrous apex lying medial to the internal carotid artery should also be drilled if suspected.
- There is no need to use the transposition of the temporalis muscle for obliteration of dead space.
- Anterior displacement of the mandible is not required.

Conclusion

An infratemporal fossa approach type A with transcondylar-transtubercular extension is required for C2–C4 tumors. 70% of patients recover to House-Brackmann grade I or II following anterior rerouting of the FN. Hence, permanent anterior rerouting of the FN offers definite advantages in C2–C4 TJPs, and a mild FN palsy is a small price to pay to achieve total tumor clearance in large tumors. An unprotected ICA should never be placed at risk during dissection. This risk is avoided with intraluminal stent of the ICA. Safe subadventitial dissection of the ICA involvement is possible with the use of an intra-arterial stent. Staged procedures are mandatory when the intradural extension is larger than 2 cm. Lower cranial nerve palsies are common after paraganglioma surgery. Young patients compensate well, but the elderly can experience significant morbidity. The recurrence rates are about 5–10% despite aggressive surgery even in highly experienced skull base units.

Careful consideration of the complicating factors and thorough preoperative evaluation and intervention can decrease surgical morbidity in TJPs with a high probability of gross total removal. The application of the abovementioned advanced management techniques will definitely improve prognostic results of this subset of tumors.

Representative Case 1 with Detailed Description and Illustration of Surgical Steps of ITFA, Type A

A 33-year-old lady presented with dysphonia and left shoulder weakness. A year back, she was indicated for surgery at another center. During preoperative embolization, she suffered a cerebrovascular accident due to connection between an unidentified branch of the ECA and the vertebral artery. On otoscopy, a retrotympanic reddish mass was noted (Fig. 8.44). Audiogram showed normal hearing. Cranial nerve examination revealed a normal facial nerve function but complete palsy of the IX and X cranial nerves with weakness of the XI and XII cranial nerves. CT revealed tumor in the jugular fossa with infiltration of the bone surrounding the IAC extending toward the genu (Fig. 8.45a). There was no tumor surrounding the horizontal portion of the ICA (Fig. 8.45b). MRI showing tumor extending into the hypoglossal canal. MRI showed confirmed the diagnosis of a C2De1 TJP (Fig. 8.46).

A single-stage IFTA with preoperative embolization was planned. A wide postauricular incision is made with extension down to the neck (Fig. 8.47). The postauricular flap is raised superficial to the superficial layer of the temporalis fascia, in a subcuticular plane (Fig. 8.48). This becomes more difficult toward the mastoid tip, and a subcutaneous fat dissection ensures adequate thickness. This plane of dissection allows the use of the temporoparietal fascia (superficial layer of the temporalis fascia), which can be used as a vascularized pedicled flap in reconstruction. The standard incision is carried a little deeper, however, with preservation of the temporalis muscle fascia and periosteum over the mastoid tip. This layer is maintained into the neck superficial to the superficial layer of the deep cervical fascia over the sternocleidomastoid muscle. This important step preserves a continuous substantial layer to ensure watertight closure. The canal is then transected lateral to

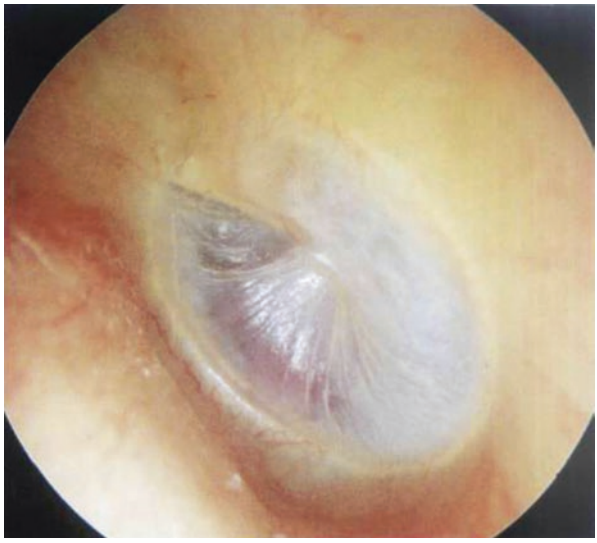

Fig. 8.44 Note the reddish retrotympanic mass in the anteroinferior portion of the tympanic membrane

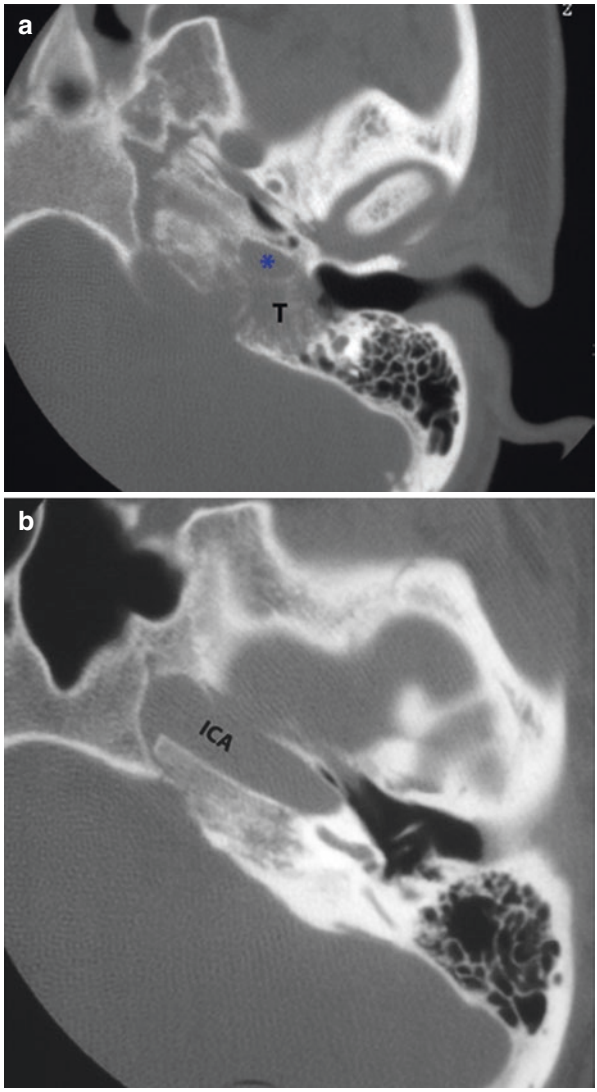

Fig. 8.45 (**a**) Asterisk: IAC, *T* tumor. (**b**) The horizontal segment of the internal carotid artery appears free of tumor. *ICA* internal carotid artery

the bony cartilaginous junction (Fig. 8.49). This allows rapid identification of the cartilage and thus the correct plane of dissection, in addition to providing robust skin with which to form the blind sac closure (Fig. 8.50). An anteriorly based periosteal flap is classically used to reinforce this closure, sutured medially to the remnant cartilage of the EAC. Alternatively, the anterior cartilage can be preserved which then provides an ideal material with which to reinforce the blind sac closure (Figs. 8.51 and 8.52).

The neck dissection is commenced. An incision in the superficial layer of deep cervical fascia is made along the anterior border of the SCMM, with identification

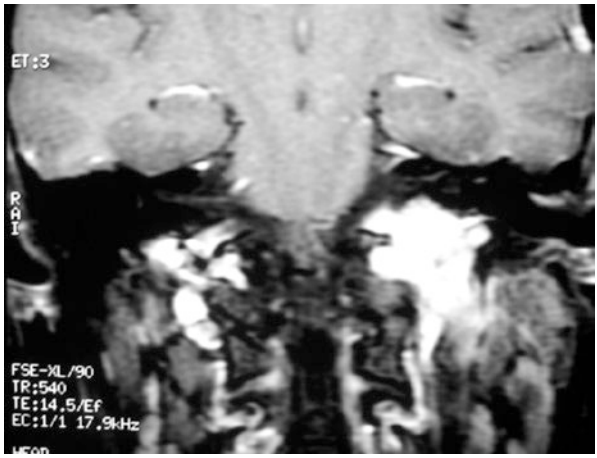

Fig. 8.46 Coronal T1 contrast enhanced MRI showing tumor extending into the hypoglossal canal

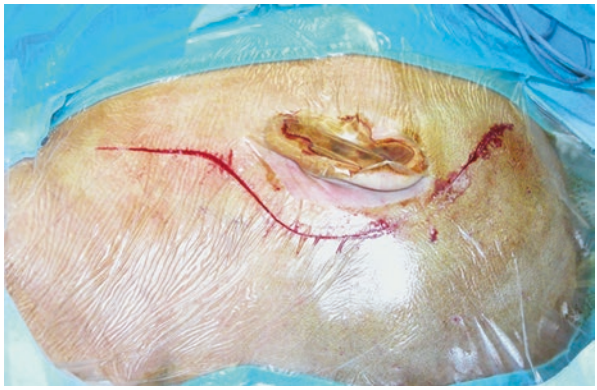

Fig. 8.47 Cranio-temporo-cervical incision

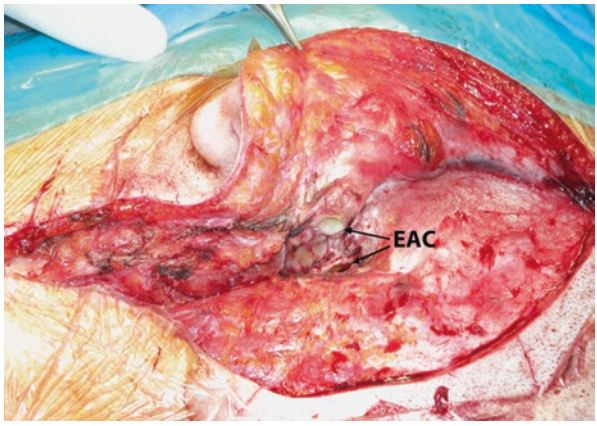

Fig. 8.48 The flap is raised superficial to the superficial layer of the temporalis fascia. *EAC* external auditory canal

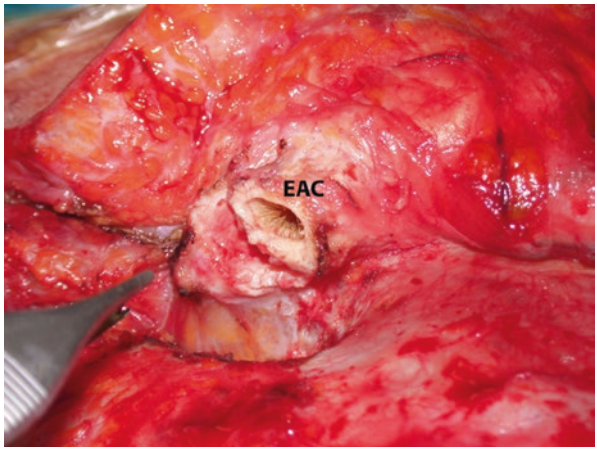

Fig. 8.49 EAC is transected just lateral to the bony cartilaginous junction. *EAC* external auditory canal

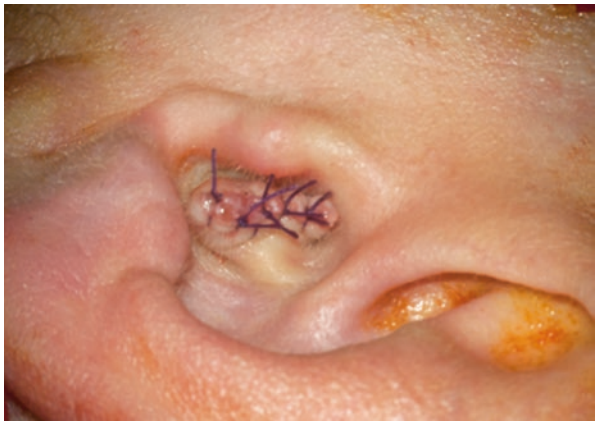

Fig. 8.50 Skin is everted and closed with sutures

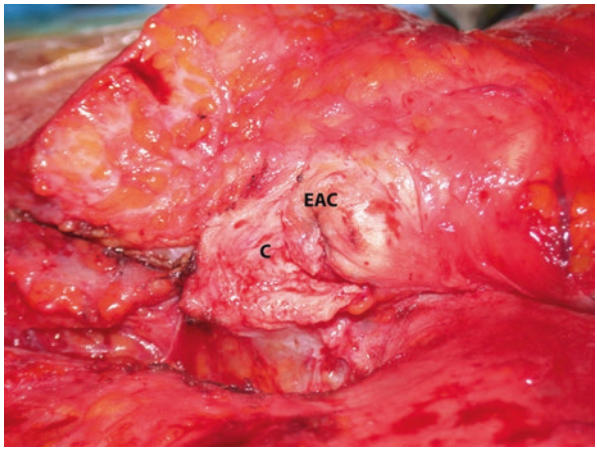

Fig. 8.51 Note that the inferior angle of cartilage represents the "tragal pointer." *C* cartilage, *EAC* everted external auditory canal

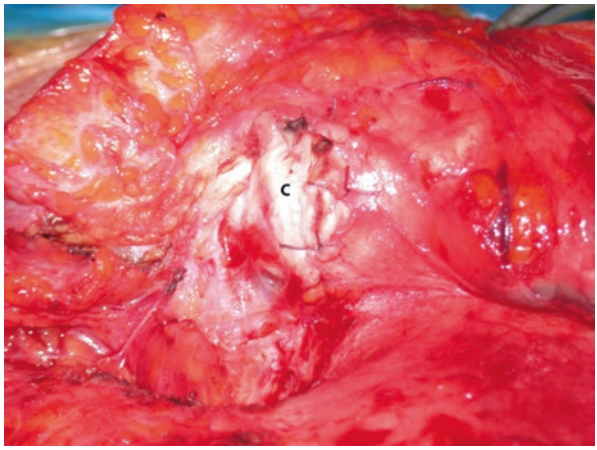

Fig. 8.52 The cartilage (C) is then folded and sutured in place

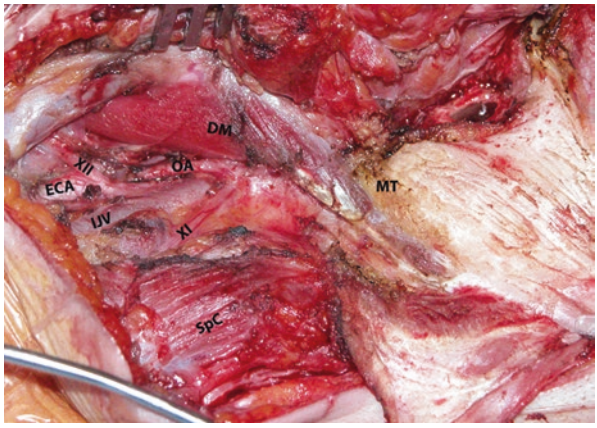

Fig. 8.53 The SCMM has been dissected from the mastoid tip and sutured to the skin edge. The digastric muscle can now be seen inserting into the digastric groove, medial to the mastoid tip. *ECA* external carotid artery, *DM* digastric muscle, *SpCM* splenius capitis muscle, *MT* mastoid tip, *OA* occipital artery, *IJV* internal jugular vein, *XI* spinal accessory nerve, *XII* hypoglossal nerve

of the digastric muscle, and the neurovascular bundle in the neck (Fig. 8.53). A T-shaped incision is made in the musculofascial layer with a supplementary rectangular-shaped flap created superior to the bony canal to assist in watertight closure. This is designed due to tissue loss as a result of the blind sac closure. Performing the blind sac closure at this stage also assists in anterior access. The extratemporal FN is then identified and exposed at the bifurcation. The exit at the stylomastoid foramen is closely related to the digastric muscle. It is also 6–8 mm anteromedial to the inferior aspect of the tympanomastoid suture line (Fig. 8.54). With the transection of the EAC and anterior retraction of the auricle, the facial nerve appears to be in a more superficial plane than when identifying the nerve via a preauricular incision. Once the facial nerve has been definitively identified, the posterior belly of the digastric muscle is cut using a monopolar diathermy. The transected muscle is retracted anteriorly, further enhancing exposure (Fig. 8.55). Medial to this are the muscles attached to the styloid process beginning with the stylohyoid. Ligation of the facial vein is required to adequately access the carotid

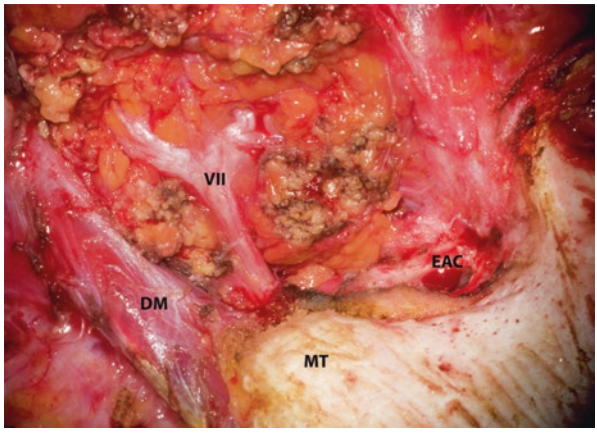

Fig. 8.54 The FN is identified at its exit from the stylomastoid foramen. *EAC* external auditory canal, *DM* digastric muscle, *VII* facial nerve, *MT* mastoid tip

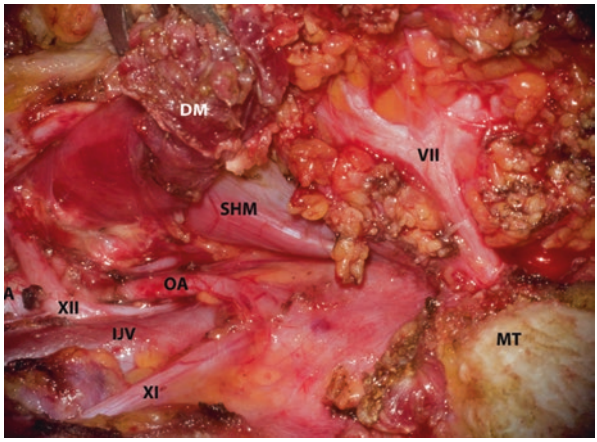

Fig. 8.55 The digastric muscle has been detached with monopolar diathermy. *MT* mastoid tip, *VII* facial nerve, *DM* posterior belly of digastric muscle, *OA* occipital artery, *IJV* internal jugular vein, *XI* spinal accessory nerve, *XII* hypoglossal nerve, *SHM* stylohyoid muscle, *ECA* external carotid artery

sheath. The occipital artery is then identified and ligated. The lateral process of C1 is palpated as a landmark to identify the internal jugular vein and the point at which the XI passes laterally to it in 80–85% of cases. The vagus, spinal accessory, and hypoglossal nerves and the ICA, ECA, and occipital artery are identified and vascular loops passed around the IJV and the ICA (Fig. 8.56). A level II neck dissection is performed in order to sample the lymph nodes for the possibility of metastatic disease.

A wide mastoidectomy is then performed, with care to remove all skin of the EAC. The posterior canal wall, tympanic membrane, malleus, and incus are removed. Care is taken not to leave any bit of squamous material behind (Fig. 8.57). The superstructure of the stapes is then removed using neurosurgical scissors (Fig. 8.58). The crura of the stapes are transected to avoid trauma to the inner ear while dissecting the FN during anterior rerouting. This is essential to avoid sensorineural hearing loss during anterior rerouting of the FN due to footplate displacement.

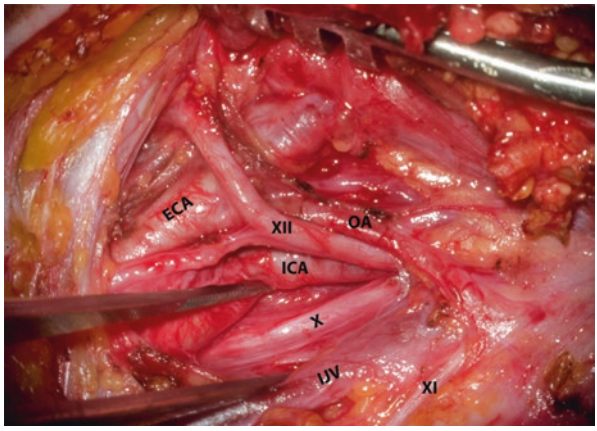

Fig. 8.56 The major neurovasculature in the upper neck is identified. *OA* occipital artery, *X* vagus nerve, *XI* spinal accessory nerve, *XII* hypoglossal nerve, *ECA* external carotid artery, *ICA* internal carotid artery, *IJV* internal jugular vein

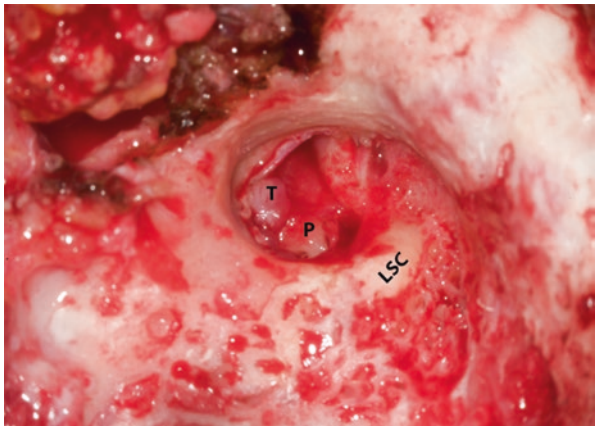

Fig. 8.57 Wide canal wall down mastoidectomy is performed. *T* tumor, *P* promontory, *LSC* lateral semicircular canal

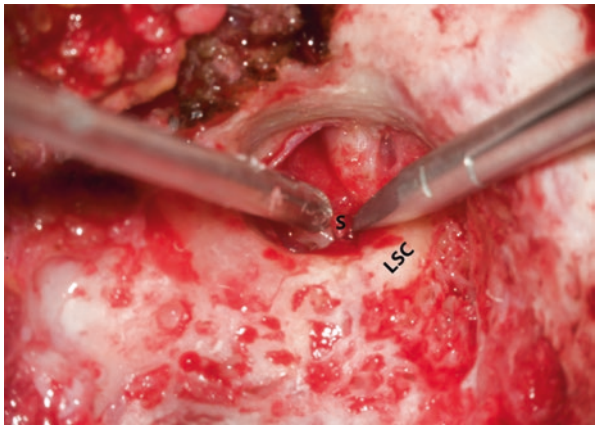

Fig. 8.58 The superstructure of the stapes is removed. *S* stapes, *LSC* lateral semiciruclar canal

In order to ensure a clear and bloodless field during FN rerouting, the middle ear component of the tumor is always debulked and packed with Surgicel if necessary (Fig. 8.59). This is the only component of tumor that is dissected prior to wide exposure of all margins. The vertical segment of the FN is skeletonized (Fig. 8.60). This is facilitated by drilling the retrofacial air cells and the tympanic bone anterior to the FN. The FN is completely exposed in the fallopian canal bed (Fig. 8.61).

The FN is then decompressed and displaced anteriorly. It is carefully separated from the fallopian canal with Beaver knife (Fig. 8.62). The nerve is allocated a new groove drilled into the anterosuperior wall of the external auditory canal and secured with fibrin glue (Fig. 8.63). Another groove for the terminal portion is created in the parotid gland. Displacement of the FN represents the key point of the surgery because it allows unobstructed control of the jugular fossa and the vertical carotid canal. The most important steps to perform a good anterior rerouting include complete bony decompression of the geniculate ganglion area and sharp dissection of

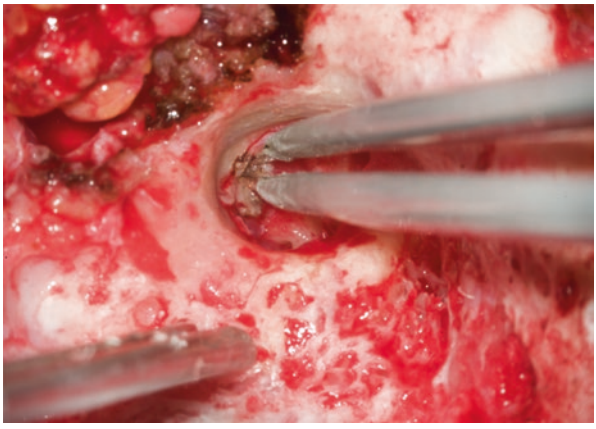

Fig. 8.59 The middle ear component of the tumor is debulked first

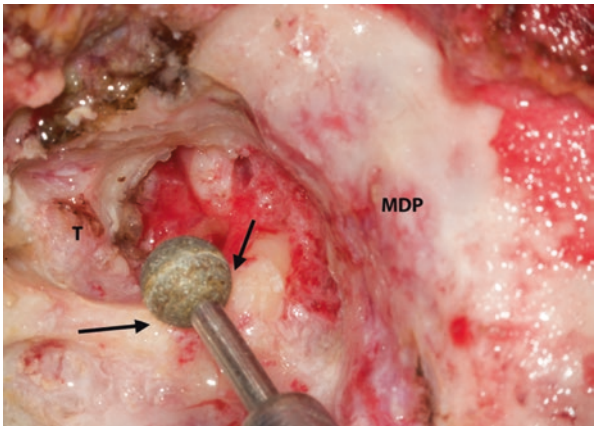

Fig. 8.60 Drill parallel to FN (arrows). Add arrow. *MDP* middle cranial fossa dural plate, *T* tumor

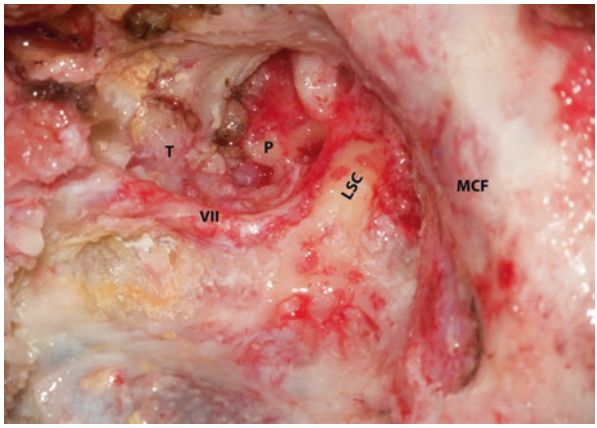

Fig. 8.61 Note the extensive infiltration of the tympanic bone (TB) by tumor. *MCF* middle cranial fossa, *T* tumor, *LSC* lateral semiciruclar canal, *P* promontory

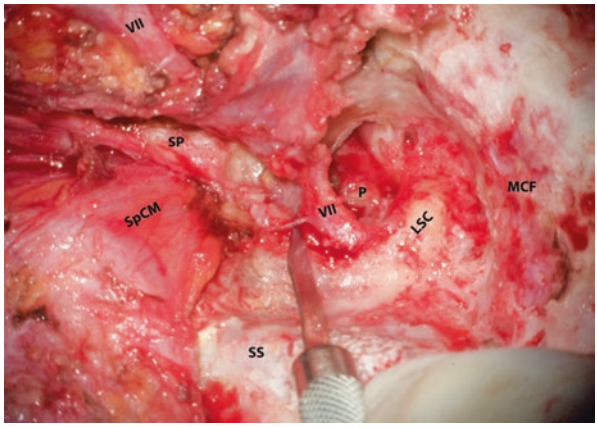

Fig. 8.62 The dense connective tissue at the level of styloid mastoid foramen is freed and the nerve freed from the canal using a Beaver knife. *LSC* lateral semicircular canal, *MCF* middle cranial fossa, *SpCM* splenius capitis muscle, *SS* sigmoid sinus, *VII* facial nerve, *SP* styloid process

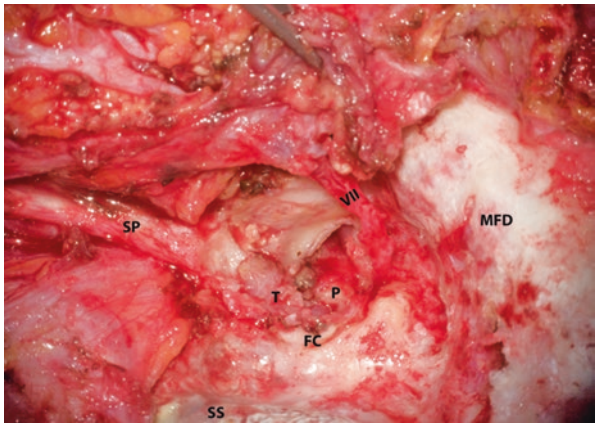

Fig. 8.63 Anterior rerouting is complete. *MFD* middle fossa dura, *SP* styloid process, *SS* sigmoid sinus, *VII* facial nerve, *T* tumor, *FC* fallopian canal, *P* promontory

the nerve from the fallopian canal. An important step in the dissection of the upper neck is the removal of the styloid process and the muscles attached to it (Fig. 8.64). The muscle attachments are detached and the styloid process transected, mindful of the medially placed ICA. The bone posterior to the internal jugular vein is drilled out followed by drilling of the occipital condyle (Fig. 8.65).

Complete removal of the anterior wall of the EAC is rarely required for C1 and C2 tumors, avoiding the use of any retractors. When required, retraction without dislocation of the temporomandibular joint (TMJ) is performed using a standard self-retaining retractor (Fig. 8.66). In rare cases the head of the mandible is mobilized, which is facilitated by the opening of the TMJ and removal of the interarticular disk. The Fisch infratemporal fossa retractor is then placed. Drilling is continued by removing the bone posteroinferiorly which represents the bone of the jugular tubercle of the occipital bone and the posteromedial third of the occipital condyle (Fig. 8.67). Drilling around the occipital condyle, the posterior condylar emissary vein is identified posteriorly. This is controlled with bipolar and/or Surgicel packing.

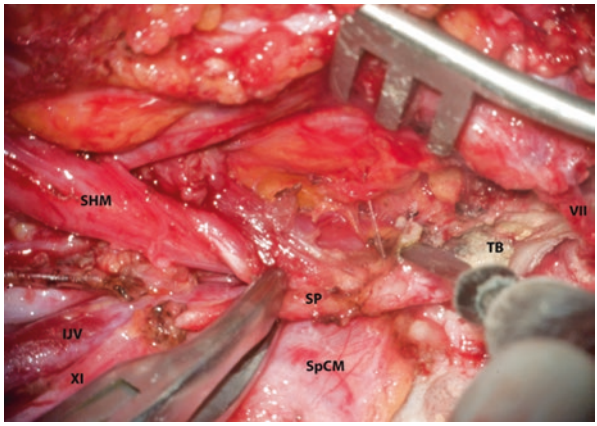

Fig. 8.64 The styloid process is further detached from the soft tissue with the monopolar diathermy. *VII* facial nerve, *TB* temporal bone, *SP* styloid process, *SpCM* splenius capitis muscle, *SHM* stylohyoid muscle, *IJV* internal jugular vein, *XI* spinal accessory nerve

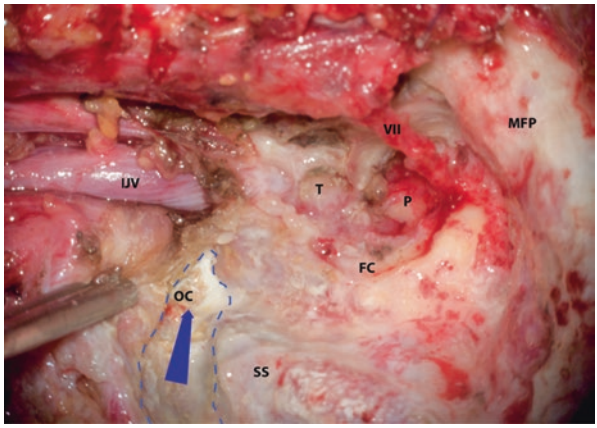

Fig. 8.65 Direction of bone removal is indicated by blue arrows. *P* promontory, *MFP* middle fossa plate, *SS* sigmoid sinus, *VII* facial nerve, *OC* occipital condyle

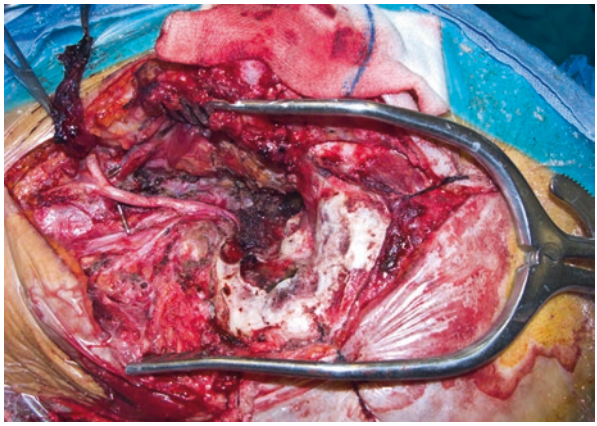

Fig. 8.66 Self-retaining retractor

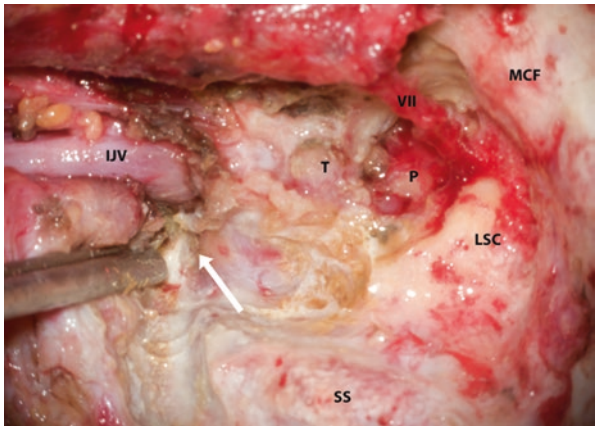

Fig. 8.67 Drilling of the jugular tubercle is completed. *IJV* internal jugular vein, *T* tumor, *P* promontory, *MCF* middle cranial fossa, *LSC* lateral semicircular canal, *VII* facial nerve, *arrow* direction to the occipital condyle

The occipital condyle contains cancellous bone with the hypoglossal canal running in a posteromedial to an anterolateral direction.

Transcondylar extension: Further extradural bone removal extends anteromedially to the jugular bulb, superior to the hypoglossal canal, which represents the jugular tubercle. This is situated approximately 5 mm above the intracranial opening of the hypoglossal canal [30] over which the IX, X, and XI nerves cross intradurally before entering the jugular fossa. This area of bone removal allows additional exposure to tumor margins from posterior to inferior and medial directions. The bipolar is then used to devascularize the tumor, minimizing the degree of bleeding from the subsequent resection. Bony dissection can be made significantly more difficult by the presence of extensive bony infiltration, resulting in continuous bleeding. The use of bipolar diathermy, diamond bur, bone wax, and judicious packing with Surgicel allows dissection to proceed. The sigmoid sinus is closed just before its junction with the transverse sinus using extraluminal packing

method (Fig. 8.68). This is facilitated by preservation of a bony shell over the proximal sigmoid sinus. The extraluminal compression prevents the blocking of the transverse sinus. If necessary the sigmoid can be slit and Surgicel packing reinforced intraluminally also. Closure of the IJV is delayed until after sigmoid closure in order to maintain venous outflow. The previously placed ties around the IJV are tied and the vein is ligated (Fig. 8.69). The vein is opened and tumor exposed (Fig. 8.70).

The final stage of surgery involves the definitive management of carotid artery involvement. Identification of the correct plane of dissection around the ICA is best performed inferiorly where the artery has a rather tough periadventitial and periosteal tissue (Fig. 8.71). A plane of cleavage is established between tumor and the carotid artery by blunt dissection, and the tumor is carefully dissected away (Figs. 8.72, 8.73, 8.74, and 8.75). The bone medial to the carotid genu is drilled to ensure removal of all infiltrated bone and to optimize superior control of the tumor

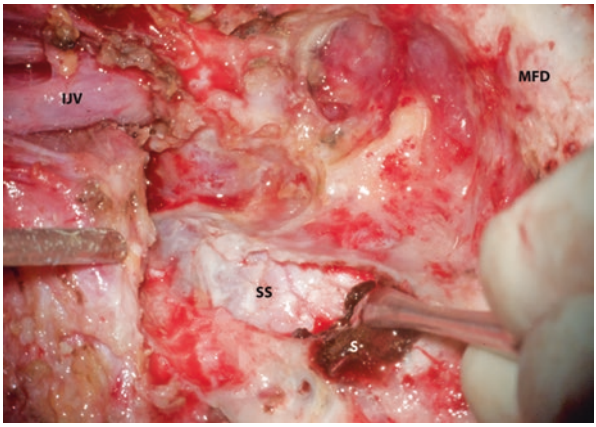

Fig. 8.68 Packing the sigmoid sinus. *MCD* middle cranial fossa dura, *SS* sigmoid sinus, *IJV* internal jugular vein

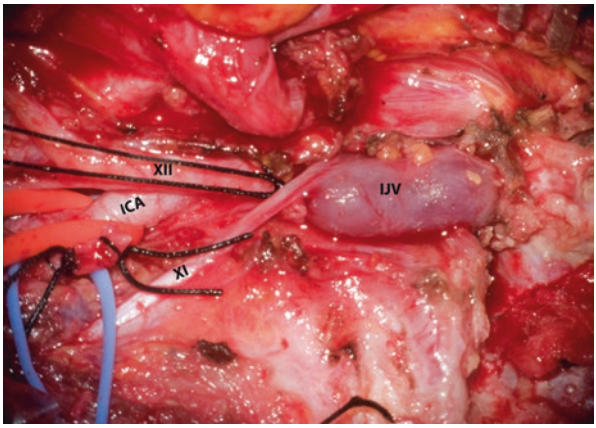

Fig. 8.69 The internal jugular vein is then double ligated and transected. This is performed following sigmoid closure to minimize venous congestion of the tumor. *MCD* middle cranial fossa dura, *SS* sigmoid sinus, *IJV* internal jugular vein

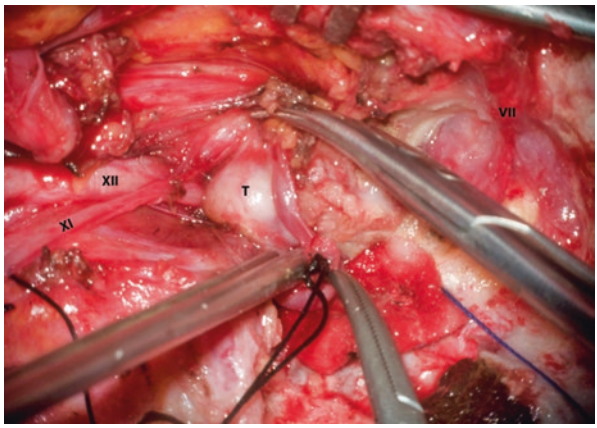

Fig. 8.70 The jugular bulb is opened to expose the tumor. *T* tumor, *XI* spinal accessory nerve, *XII* hypoglossal nerve, *VII* facial nerve

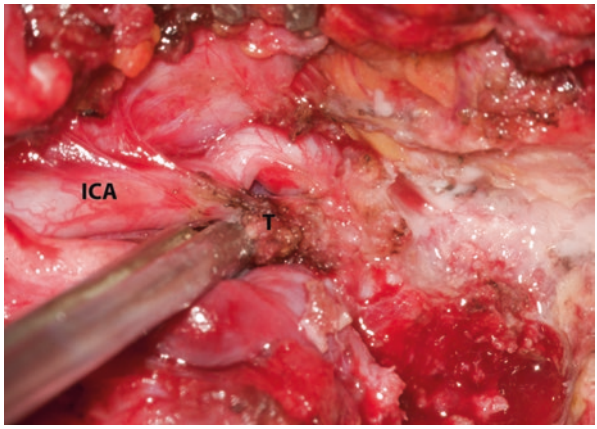

Fig. 8.71 Tumor adherent to this tissue is being dissected. There is no involvement of the ICA adventitia. *T* tumor, *ICA* internal carotid artery

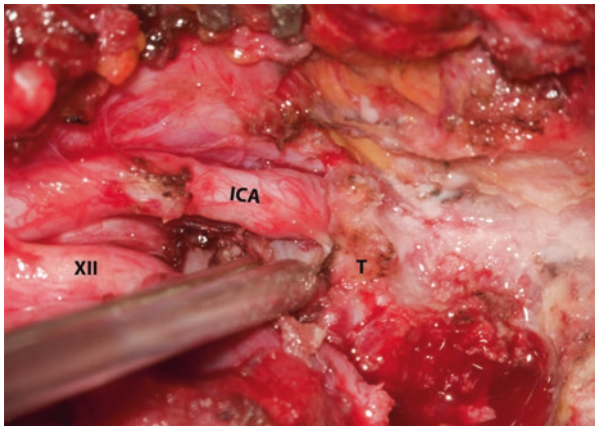

Fig. 8.72 The carotid artery has been freed up to its carotid canal. Note the periosteal layer retracted by the suction irrigator. Also note that all this dissection is performed under microscopic control. *ICA* internal carotid artery, *XII* hypoglossal nerve, *T* tumor

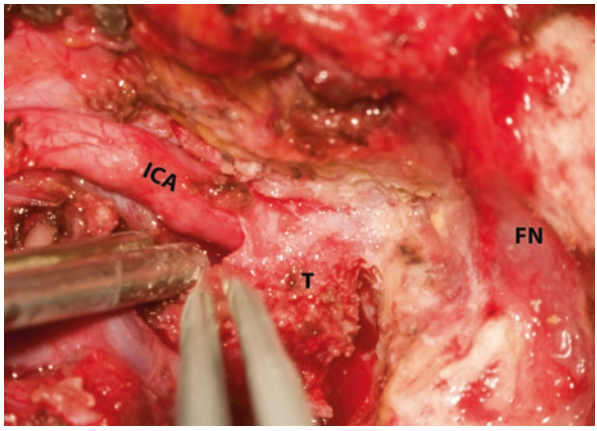

Fig. 8.73 Following further bone removal around the carotid artery, dissection is continued in a subperiosteal plane. *FN* facial nerve, *T* tumor, *ICA* internal carotid artery, *XII* hypoglossal nerve

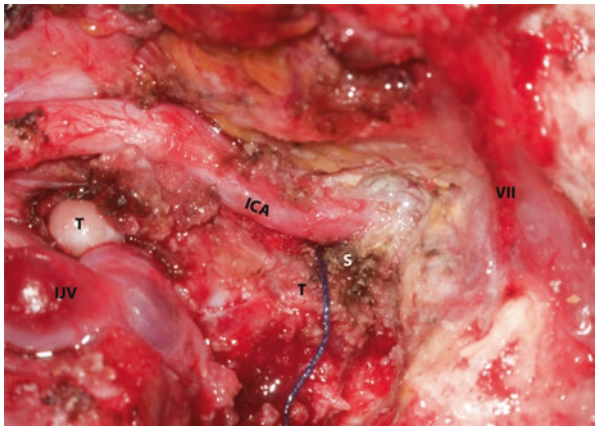

Fig. 8.74 Tumor can now be seen extending from the jugular fossa area anteromedially. A merocel patty has been placed medial to the ICA. The bone lateral and medial to the ICA has been further drilled to the level of the genu, which will allow gentle mobilization of the artery. *VII* facial nerve, *T* tumor, *ICA* internal carotid artery, *IJV* internal jugular vein, *S* Surgicel

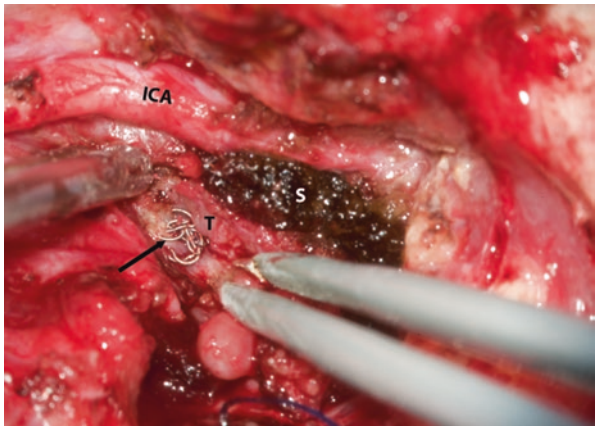

Fig. 8.75 The coils used to embolize the tumor can be seen. Note the fibrous consistency of the tumor. *ICA* internal carotid artery, *arrow* coils, *T* tumor, *S* Surgicel

margins (Fig. 8.76). The sigmoid sinus and the jugular bulb are then opened to identify the last bit of tumor attachment. The openings of the inferior petrosal sinus are identified and packed with Surgicel (Fig. 8.77). The critical point is represented by the invasion of the medial wall of the jugular bulb; in the presence of such infiltration, radical surgery requires removal of the entire bulb, with inevitable sacrifice of the lower cranial nerves. On the contrary, if the medial wall of the bulb can be preserved, the neural function can be preserved too. This technique is also referred to as intrabulbar dissection. Prior identification of the lower cranial nerves in the uninvolved neck further aids in preservation of these nerves. Care must be taken when packing branches of the inferior petrosal sinus. These can be multiplied and usually enter between the IX and X and XI nerves. If the medial wall of the jugular bulb is involved by the tumor, this is removed, but this step also puts in risk any functional lower cranial nerves (Figs. 8.78, 8.79, and 8.80). Hemostasis is achieved

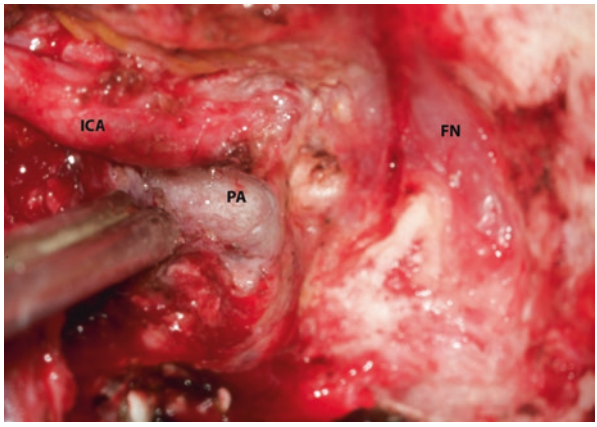

Fig. 8.76 The bone medial to the carotid genu is drilled to ensure removal of all infiltrated bone and to optimize superior control of the tumor margins. *ICA* internal carotid artery, *PA* petrous apex, *FN* facial nerve

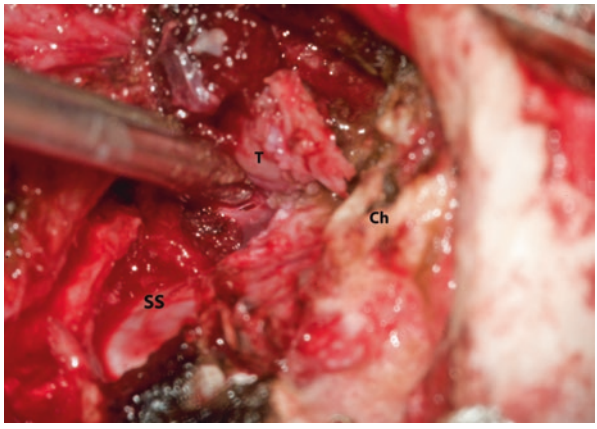

Fig. 8.77 The last bit of tumor is elevated from the medial wall of the jugular bulb. The openings of the inferior petrosal sinuses can be visualized. *T* tumor, *Co* cochlea, *SS* sigmoid sinus (medial wall)

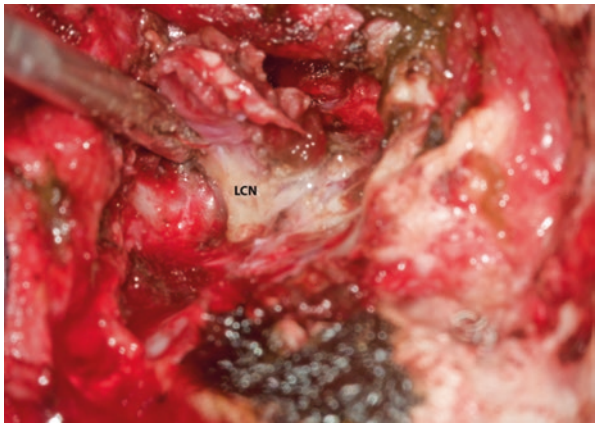

Fig. 8.78 The X and XI cranial nerves can now been seen entering the jugular fossa. Tumor has infiltrated these nerves, explaining preoperative dysfunction. *LCN* lower cranial nerves

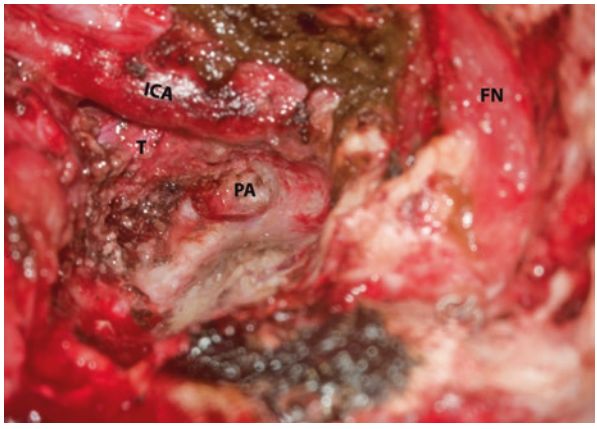

Fig. 8.79 It is important to reiterate that the degree of bony invasion is often difficult to assess even intraoperatively. *ICA* internal carotid artery, *PA* petrous apex, *FN* facial nerve, *T* tumor

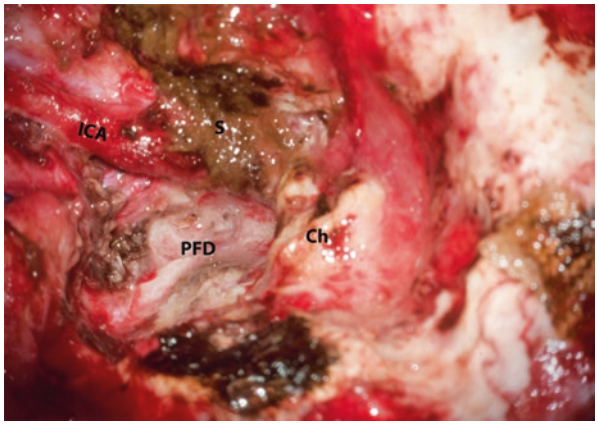

Fig. 8.80 The tumor was removed, with transection of the infiltrated nerves. Further bone removal of the lower clivus is performed to ensure complete removal of infiltrated bone. *ICA* internal carotid artery, *Co* cochlea, *S* Surgicel, *PFD* posterior fossa dura

using bipolar coagulation and Surgicel packing. The Eustachian tube is closed with periosteum plug. The cavity is obliterated with abdominal fat. The dead space is filled with abdominal fat. The skin is closed with sutures in a watertight fashion (Figs. 8.81 and 8.82).

This patient suffered postoperative paralysis of the IX, X, XI, XII, and lower cranial nerves, but she achieved very good contralateral compensation after rehabilitation. The FN function was grade III and the patient had normal bone conduction. The genetic study was negative for hereditary genetic traits (Figs. 8.83 and 8.84).

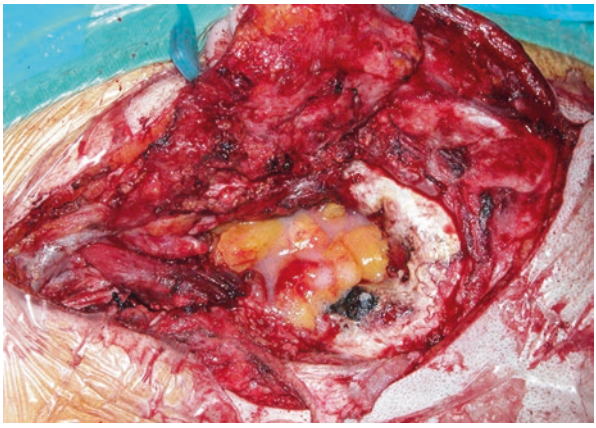

Fig. 8.81 Cavity obliteration with abdominal fat

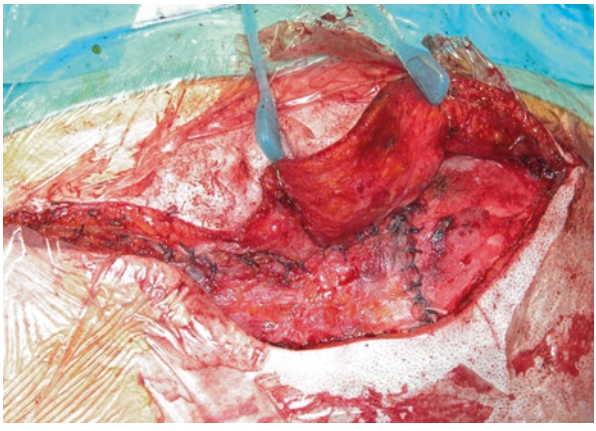

Fig. 8.82 Meticulous closure of the musculofascial flaps

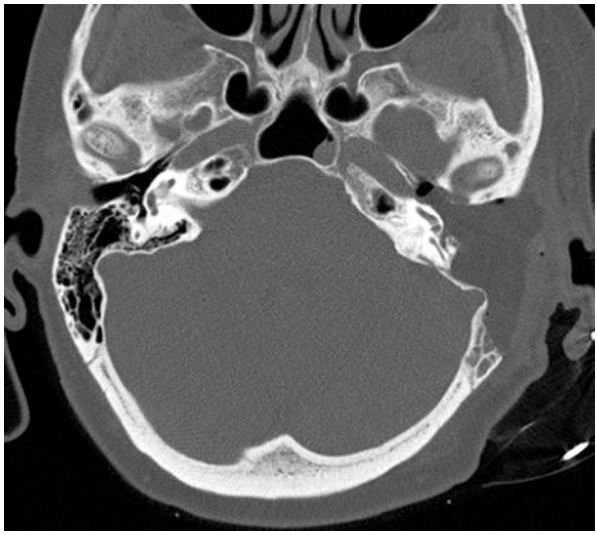

Fig. 8.83 Postoperatively CT scan shows the extent of bone removal

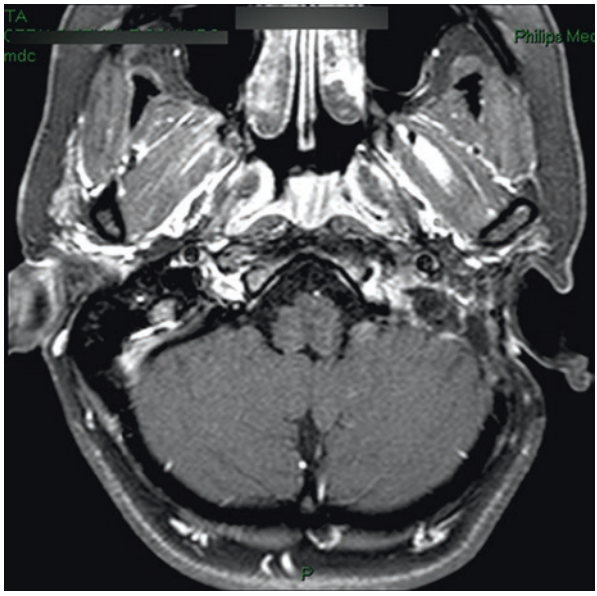

Fig. 8.84 Postoperatively MRI shows complete tumor clearance

Representative Case 2 with Detailed Description and Illustration of Surgical Steps

Two-stage removal in a case of a complex paraganglioma of the skull base with a class C3Di2 TJP and a stage I vagal paraganglioma after permanent balloon occlusion of the internal carotid artery.

Complex paragangliomas include extensive tumors; tumors with large intradural extension; tumors involving the cavernous sinus, ICA, or vertebral artery; and previously operated or irradiated tumors (Fig. 8.85). Also included are tumors with a single carotid artery, dominant or unilateral sigmoid sinus on the side of the lesion, or bilateral or multiple tumors. It is difficult to decide on the treatment for these tumors, and accurate preoperative surgical planning is mandatory. Here we present one such case.

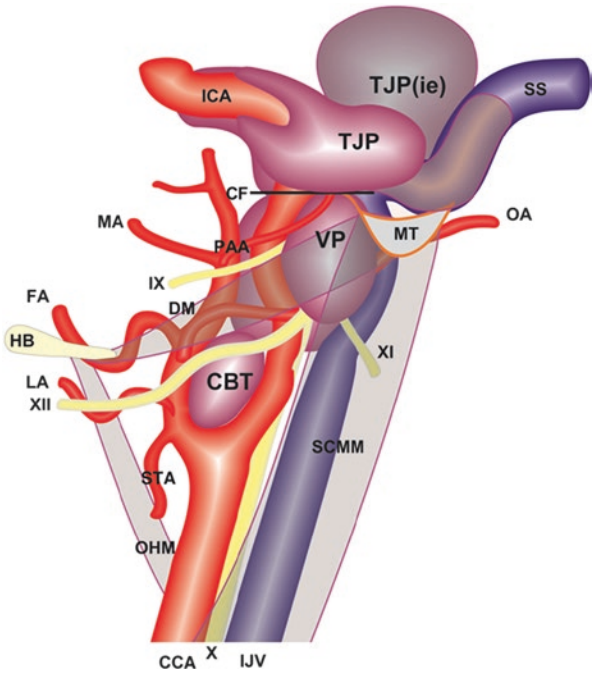

Fig. 8.85 Illustration for complex tympanojugular paragangliomas. *TJP* tympanojugular paraganglioma, *TJP (ie)* intradural or extradural TJP, *CF* carotid foramen, *VP* vagal paraganglioma, *CBT* carotid body tumor, *OHM* omohyoid muscle, *CCA* common carotid artery, *IJV* internal jugular vein, *ICA* internal carotid artery, *HB* hyoid bone, *PAA* posterior auricular artery, *MT* mastoid tip, *OA* occipital artery, *IX* glossopharyngeal nerve, *X* vagus nerve, *XI* spinal accessory nerve, *XII* hypoglossal nerve, *MA* maxillary artery, *DM* posterior belly of the digastric muscle, *FA* facial artery, *LA* lingual artery, *SCMM* sternocleidomastoid muscle

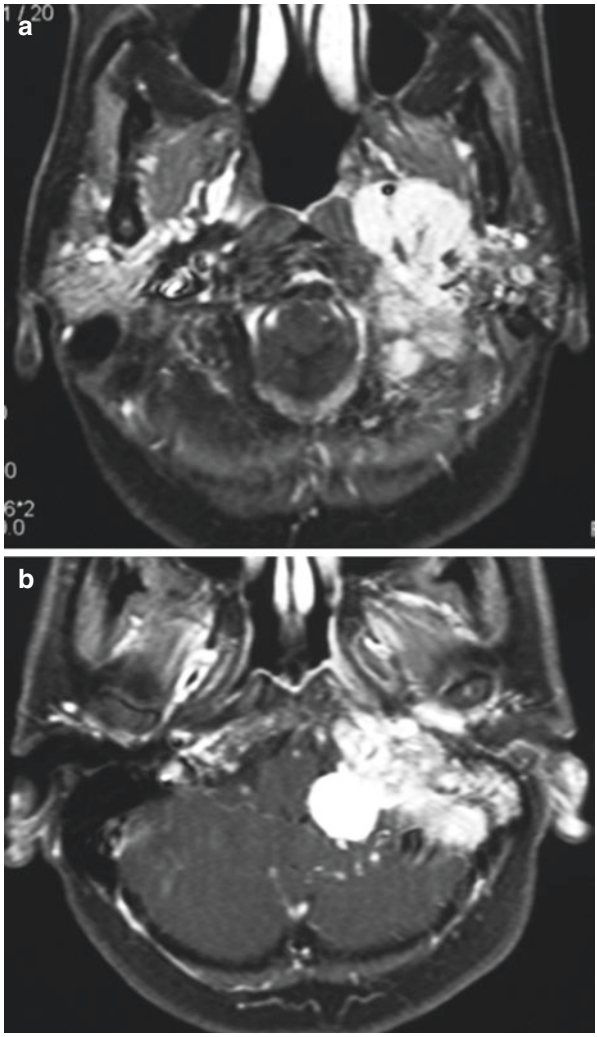

Fig. 8.86 Preoperative MRI showing an extensive jugular fossa mass with (**a**) infratemporal fossa and (**b**) jugular fossa and intradural involvement

A 52-year-old lady presented with a 3–4-year history of dysphonia, progressive hearing loss, and pulsatile tinnitus. She had no family history. Otoscopy revealed a keratin-covered mass occupying the medial compartment of the external auditory canal. She showed paralysis of vagus and hypoglossal nerve and had a dead ear. Axial T1-enhanced MRI scans revealed a large hypervascular mass occupying the post-styloid parapharyngeal space with complete encasement of the carotid artery (Fig. 8.86). At a higher level, a large intradural component was seen extending through the medial aspect of the jugular fossa with dural infiltration along the entire posterior face of the petrous bone. MRA showed an absence of the left ICA, but

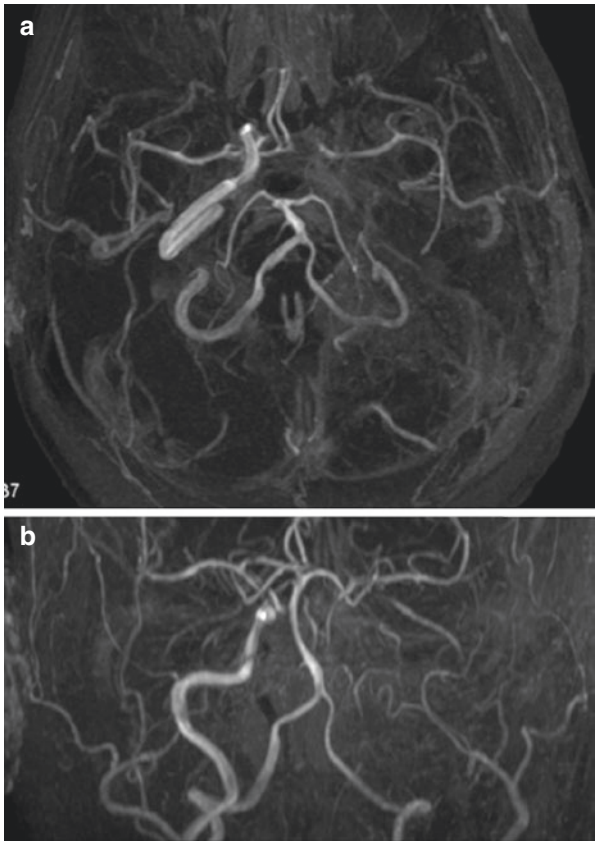

Fig. 8.87 (**a**, **b**) MRA showing the absence of the left ICA, but adequate collateral supply through the circle of Willis

adequate collateral supply through the circle of Willis (Fig. 8.87). Angiography confirmed the likelihood of two lesions (Fig. 8.88a, b). In summary, the preoperative findings were a stage I of large vagal paraganglioma and a C3Di2 TJP (Figs. 8.89 and 8.90). Due to the circumferential involvement of the ICA both in its cervical and intratemporal segments, the patient was assessed for permanent balloon occlusion followed by a two-staged resection.

The blind sac closure, neck dissection, and exposure of the extratemporal segment of the FN were carried out as described before. The important neurovasculature in the neck was identified. Tumor in the middle ear was extensively diathermized to control bleeding prior to rerouting of the FN. The FN was mobilized and rerouted anteriorly. The styloid process was cut along with the attached muscles and ligaments to optimize ICA exposure. The sigmoid sinus was extraluminally packed and the IJV was ligated in the neck. Further drilling of the bone was done posteroinferi-

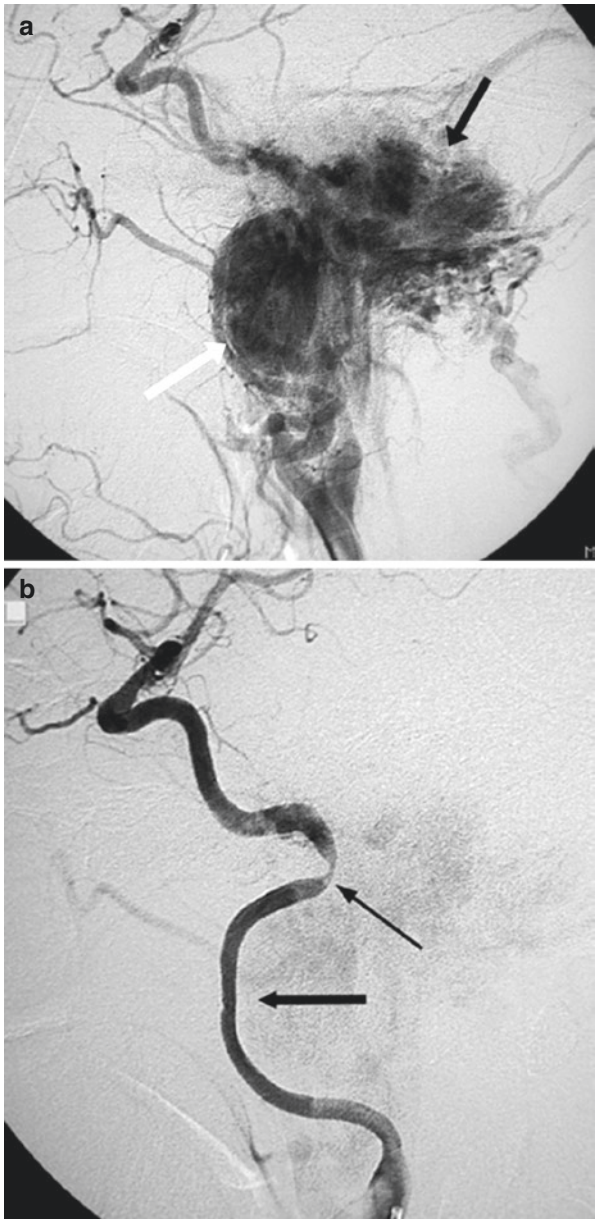

Fig. 8.88 (**a**) The ovoid mass represents a large vagal paraganglioma (*white arrow*), with the poorly defined tumor blush posterosuperiorly representing a jugular paraganglioma (*black arrow*). Tumor can be seen involving the horizontal segment of the ICA. (**b**) Angiogram of a case of a vagal paragangliomas combined with a tympanojugular paraganglioma (*lateral view*). The right internal carotid artery shows evidence of stenosis (*thin arrow*) and displacement (*thick arrow*) due to the vagal paraganglioma

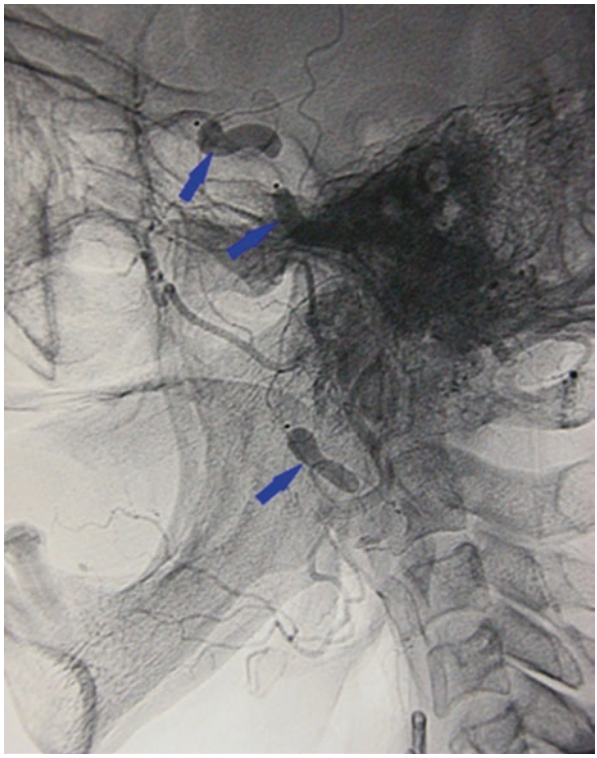

Fig. 8.89 Preoperative permanent balloon occlusion. The proximal and distal balloons (*arrows*) can be seen in place prior to deployment

orly to the sigmoid and bulb, and tumor was seen to be extending toward the occipital condyle (Fig. 8.91). The feeding artery (the ascending pharyngeal artery) and the occluded ICA were ligated with vascular clips (Fig. 8.92). The ICA was found to be completely encircled and infiltrated by the tumor. Extensive bone removal was performed around the horizontal segment of the ICA to the foramen lacerum to expose the horizontal and vertical portions of the petrous ICA (Fig. 8.93). The ICA was resected at the level of the foramen lacerum (Fig. 8.94). The vagal paraganglioma was then approached and excised in toto with the involved ICA and the lower cranial nerves X, XI, and XII (Figs. 8.95 and 8.96). Postoperatively the patient developed an additional XI cranial nerve palsy. The FN was HB grade III within 3 months after surgery. Postoperative imaging showed complete excision of the extradural part of the tumor with the intradural component left in situ (Fig. 8.97a, b).

In the second stage after 6 months, a translabyrinthine-transclival approach was employed to remove the intradural component of the tumor. A large postauricular C-shaped skin incision was performed. An inferiorly based U-shaped musculoperi-

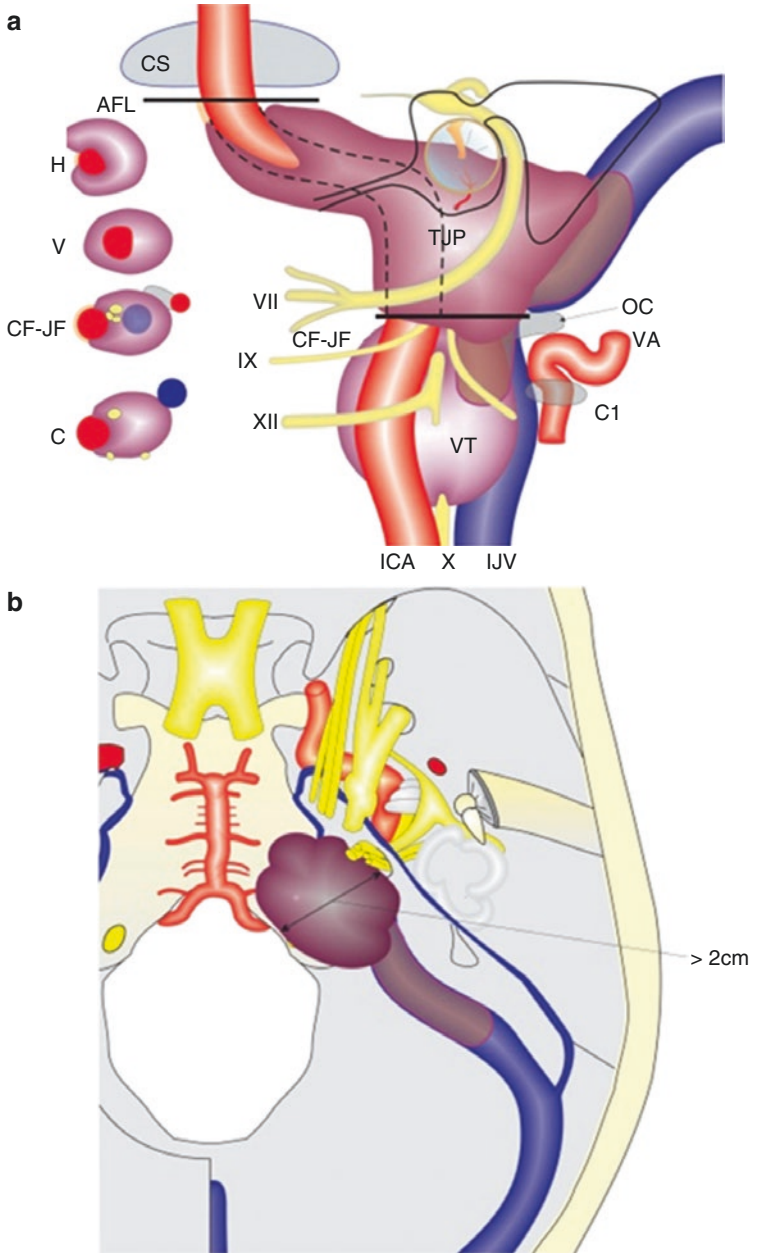

Fig. 8.90 Illustrative diagram of the lesion. (**a**) Class C3Di2 TJP on the left side. (**b**) Intradural component

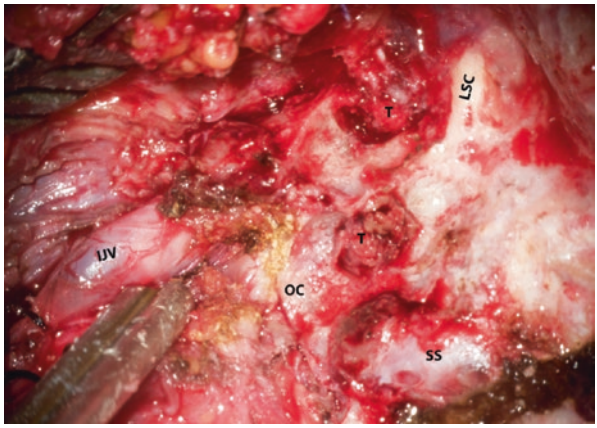

Fig. 8.91 Note the wide exposure of the extended jugular fossa area due to anterior rerouting of the FN and excision of the styloid process. *IJV* internal jugular vein (ligated), *T* tumor, *OC* occipital condyle, *LSC* lateral semicircular canal, *SS* sigmoid sinus

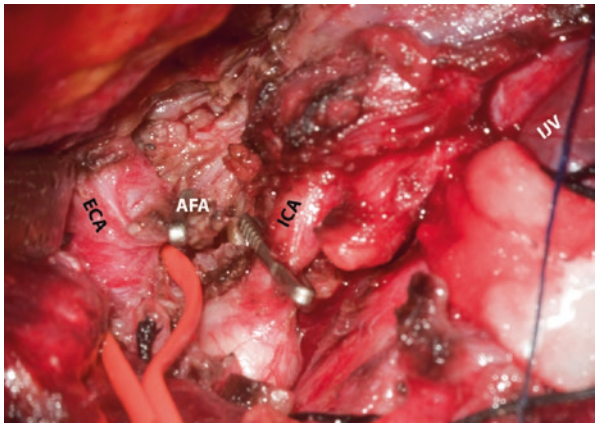

Fig. 8.92 A vascular clip has been used to close the balloon-occluded ICA. *ICA* internal carotid artery, *ECA* external carotid artery, *AFA* ascending pharyngeal artery

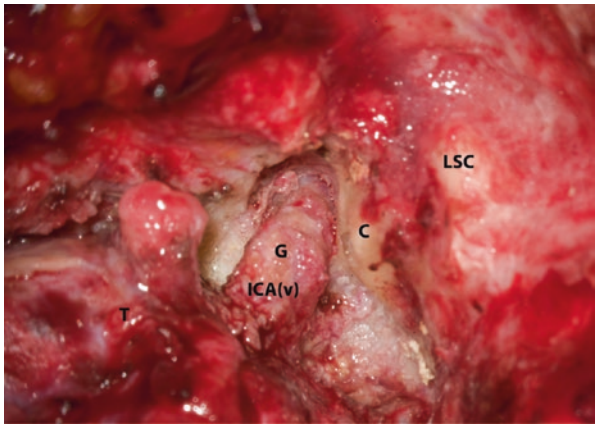

Fig. 8.93 The vertical and horizontal portion of the ICA is skeletonized. Note the relationship of the cochlea to the ICA. *ICA(V)* vertical segment of the ICA, *G* carotid genu, *Co* cochlea, *LSC* lateral semicircular canal, *T* tumor

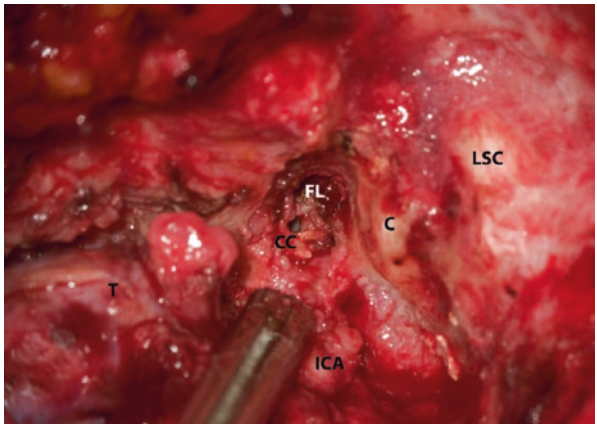

Fig. 8.94 The ICA has been transected at the level of the foramen lacerum, with the cell of the petrous apex now visible. The medial bony carotid canal was seen. The essentially bloodless dissection is a testament to the permanent balloon occlusion of the ICA. Superior control of the tumor has now been attained. *T* tumor, *FL* foramen lacerum, *CC* carotid canal, *LSC* lateral semicircular canal, *Co* cochlea

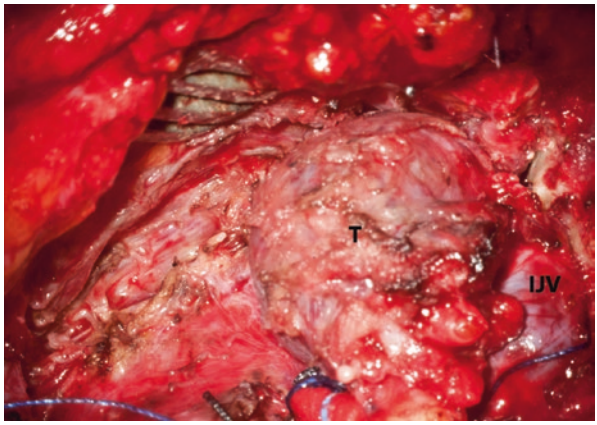

Fig. 8.95 The vagal paraganglioma is now addressed. The ICA is within this large tumor mass. *IJV* internal jugular vein

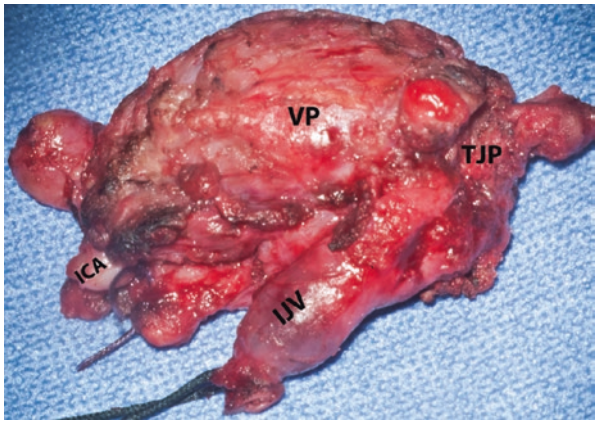

Fig. 8.96 The removed tumor, with IJV and ICA embedded. *ICA* internal carotid artery, *IJV* internal jugular vein, *VP* vagal paraganglioma, *TJP* tympanojugular paraganglioma

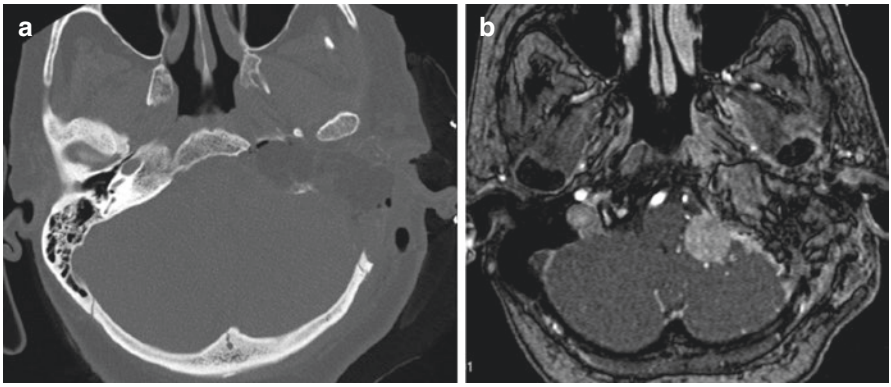

Fig. 8.97 Post-op imaging shows. (**a**) CT illustrating that the entire petrous apex surrounding the ICA has been removed. (**b**) Enhanced axial T1 MRI revealing complete removal of the extradural component, with the residual intradural tumor and extensive dural enhancement seen

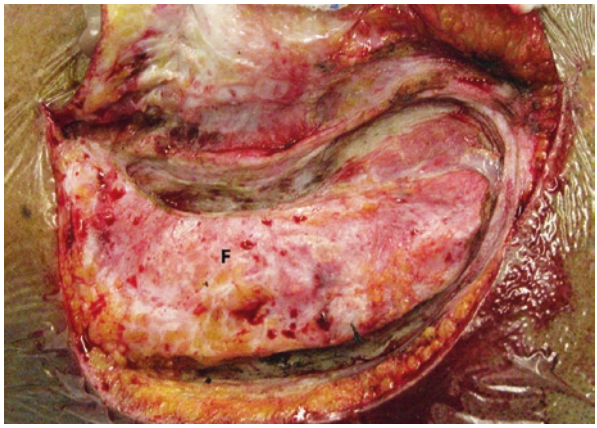

Fig. 8.98 A large postauricular C-shaped skin incision was performed. An inferiorly based U-shaped musculoperiosteal flap (F) is used in this approach

osteal flap (F) is used in this approach (Fig. 8.98). The previously dissected mastoid cavity was exposed, with care being taken not to damage the rerouted FN (Fig. 8.99). The middle and posterior fossa dura are uncovered, with the labyrinthine block providing a ready landmark (Fig. 8.100). The labyrinthectomy was completed, and the IAC was skeletonized (Fig. 8.101). The posterior fossa dura lateral to the porus acusticus was widely opened (Fig. 8.102). The tumor was seen extending to involve the acousticofacial bundle. The tumor was coagulated on all surfaces using a bipolar and shrinked. It is then dissected carefully from the anterior inferior cerebellar artery, the brain stem, the FN, and the lower cranial nerves (Figs. 8.103, 8.104, 8.105, 8.106, and 8.107). The closure of the musculoperiosteal flap was performed with abdominal fat having been placed through the dural defect into the intradural space (Fig. 8.108). Postoperative MRI showed complete tumor clearance (Fig. 8.109a, b).

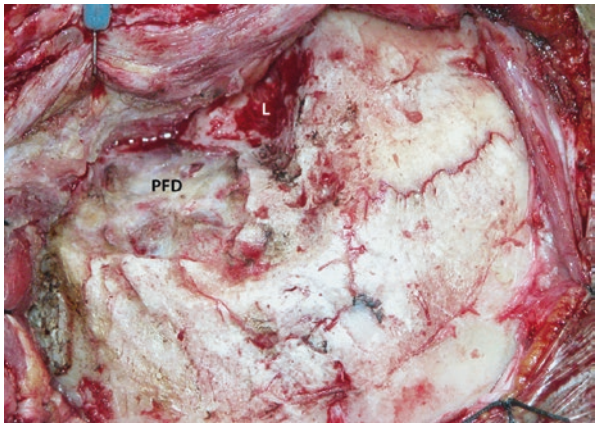

Fig. 8.99 Care must be taken to avoid injury to the anteriorly rerouted FN during the soft tissue approach. *PFD* posterior fossa dura, *L* labyrinth

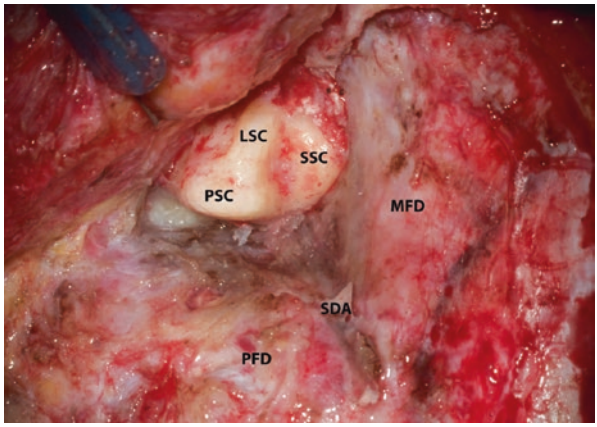

Fig. 8.100 Note that the sigmoid sinus was sacrificed at the previous surgery. *LSC* lateral semicircular canal, *PSC* posterior semicircular canal, *ssc* superior semicircular canal, *MFD* middle fossa dura, *PFD* posterior fossa dura, *SDA* sinodural angle

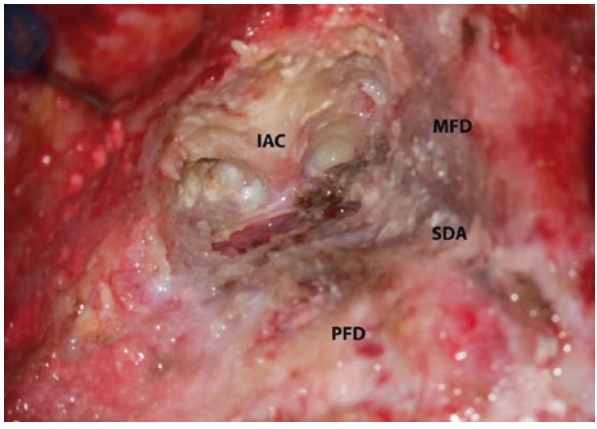

Fig. 8.101 The labyrinthectomy has been completed, and IAC is skeletonized. *IAC* internal auditory canal, *MFD* middle fossa dura, *PFD* posterior fossa dura, *SDA* sinodural angle

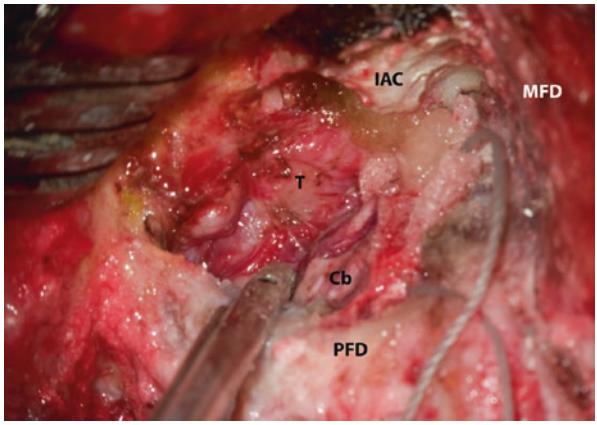

Fig. 8.102 The wide dural resection has been performed, with exposure of the large intradural tumor. *IAC* internal auditory canal, *T* tumor, *Cbl* cerebellum, *MFD* middle fossa dura, *PFD* posterior fossa dura

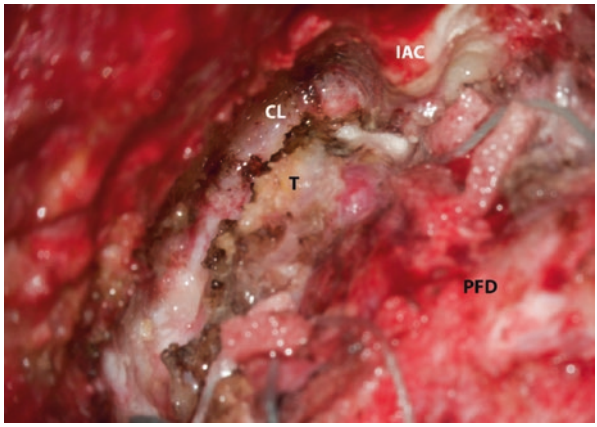

Fig. 8.103 The clivus anterior to the tumor was drilled until the normal cancellous bone has been exposed. *IAC* internal auditory canal, *T* tumor, *CL* clivus, *PFD* posterior fossa dura

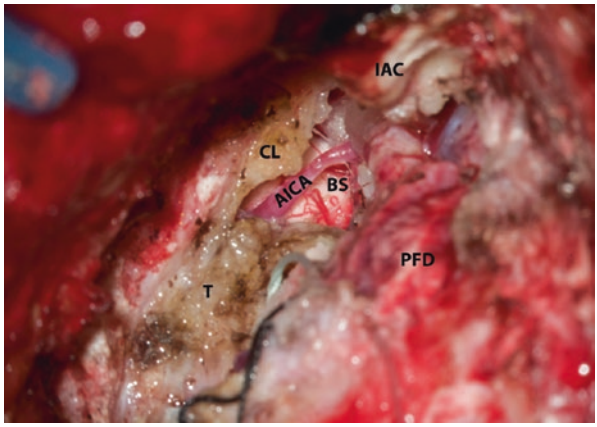

Fig. 8.104 Removal of tumor has been performed from a superior direction. Note the gradual dissection of tumor from the anterior inferior cerebellar artery. *IAC* internal auditory canal, *T* tumor, *CL* clivus, *AICA* anterior inferior cerebellar artery, *BS* brain stem, *PFD* posterior fossa dura

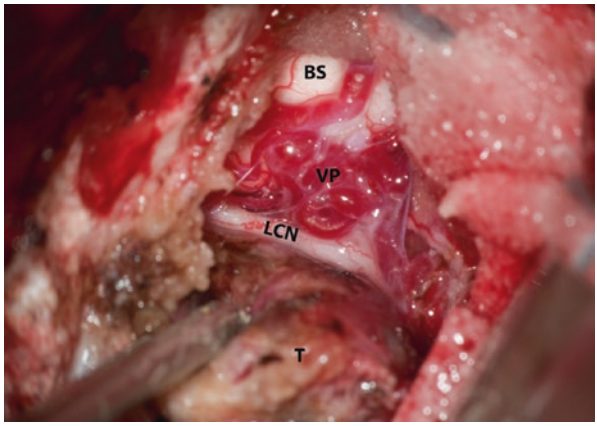

Fig. 8.105 The debulked tumor is gradually peeled from the brain stem and vasculature. The extensive vascularization can be appreciated. *T* tumor, *BS* brain stem, *VP* venous plexus of the tumor, *LCN* lower cranial nerve IX

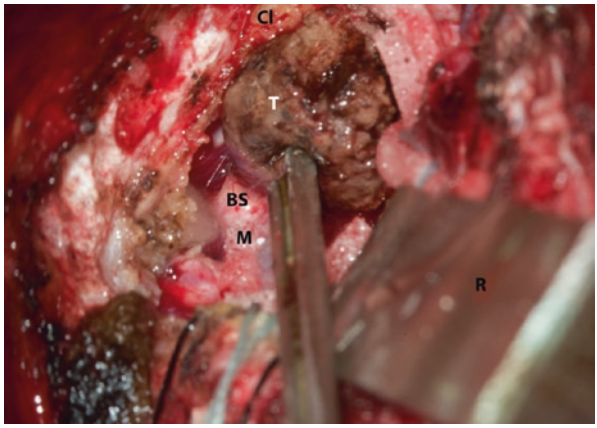

Fig. 8.106 The inferior pole of the tumor (T) is now approached. Note the extensive devascularization of the tumor by surface bipolarization. A merocel (M) patty is introduced between the tumor and brain stem. *R* cerebellar retractor, *CL* clivus, *T* tumor, *BS* brain stem, *M* merocel

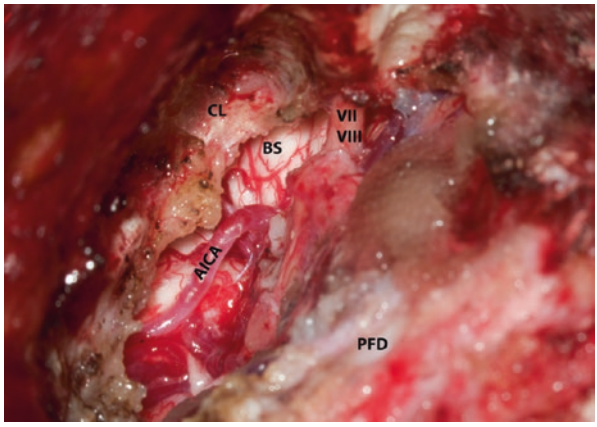

Fig. 8.107 The tumor has now been completely removed, with the VII or VIII complex seen superiorly. *CL* clivus, *BS* brain stem, *AICA* anterior inferior cerebellar artery, *PFD* posterior fossa dura

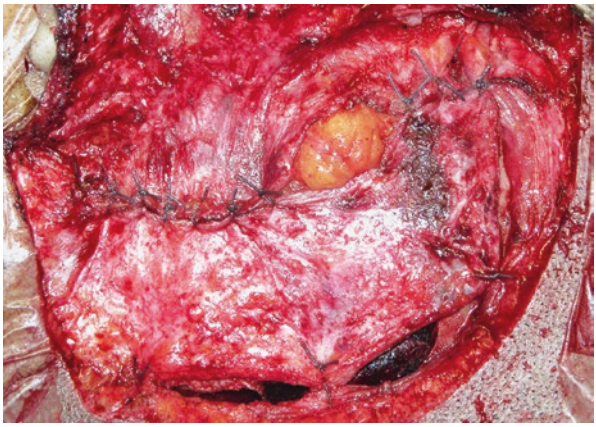

Fig. 8.108 A watertight closure is ensured

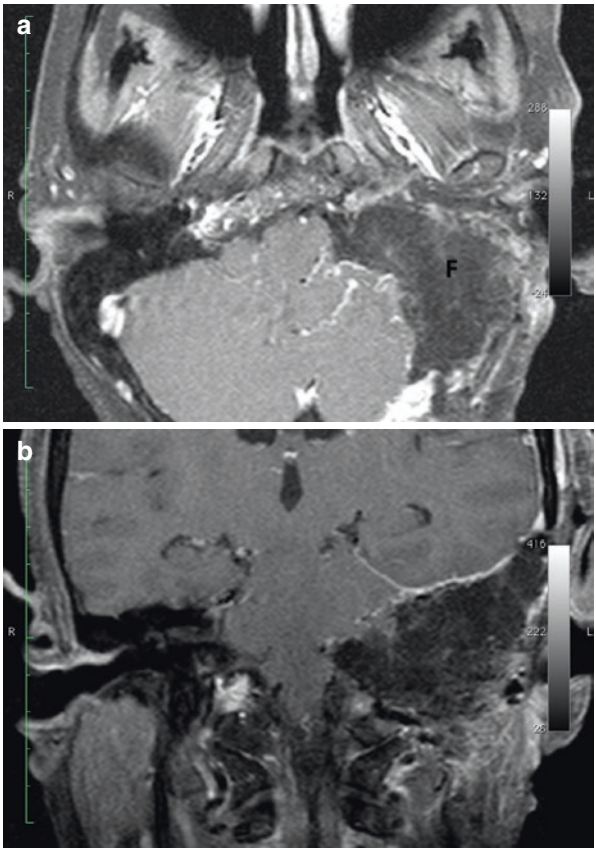

Fig. 8.109 (**a**) Gd-enhanced MRI axial view with fat suppression after surgery shows that there is no residual tumor. (**b**) MRI, coronal view. Total tumor removal is completed. *F* abdominal fat

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Chapter 9
Management of Internal Carotid Artery in Skull Base Paraganglioma Surgery

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Introduction

The surgical management of skull base paragangliomas is particularly challenging as a result of their complex anatomical location, the local major neurovascular structures, and the proximity of intracranial structures. The internal carotid artery (ICA) is often involved by tympanojugular paragangliomas (TJPs) in its upper cervical and petrous portions [1]. Similarly carotid body paraganglioma and the vagal paragangliomas are also intimately related to the ICA. Early attempts to resect tumors involving the ICA were associated with high rates of morbidity and mortality [2]. However, today, significant reduction in morbidity has been achieved in the surgical management of this subset of tumors due to advances in preoperative interventional neuroradiology and refinements in skull base microsurgery [3]. To avoid intraoperative morbidity and mortality from vascular compromise, various modalities of management of the cervical and intratemporal ICA have been described. These modalities include cervical-to-petrous ICA saphenous vein bypass grafting [4], permanent balloon occlusion (PBO) [5, 6], and intravascular reinforcement with stenting [7–12].

Skull base paragangliomas require an accurate preoperative neurovascular evaluation taking into consideration the degree of ICA involvement, the anatomical

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and functional integrity of the Circle of Willis, previous surgery or radiotherapy, and the patient's age and the general condition of the patient [3, 10, 13–15]. Patients can be considered as having a high risk of intraoperative ICA injury if (1) encasement of the ICA reaches more than half (i.e., 180–360°) of the arterial circumference, (2) there is evidence of stenosis or irregularity of vessel walls, (3) patients with a past history of radiotherapy or surgery around the ICA, and in cases of (4) multiple ipsilateral lesions, (5) single ipsilateral ICA, or (6) recurrent disease medial to the petrous ICA [16, 17]. A significant proportion of the mortality in TJP surgery, reported in earlier series, was due to injury of the artery and as a consequence of resection of the ICA [2]. ICA manipulation can be extremely dangerous resulting in spasm, thrombosis, rupture, massive stroke, and even death [3, 18]. To minimize such risks, PBO of the ICA in TJP surgery was first employed by Andrews et al. [5] and Zane et al. [19] in order to facilitate radical tumor removal and enable safe mobilization of the carotid. While PBO of the ICA allows safe removal of the lesion, this procedure cannot be used in cases of inadequate collateral circulation and is not inherently risk-free.

We have developed the application of preoperative stenting of the ICA in the management of TJPs since 2003 to avoid preoperative closure or bypass procedures and to protect and preserve integrity of the ICA during surgery [3, 11]. Preoperative stent insertion also allows an aggressive ICA dissection with significant reduction of the surgical risks [3, 10, 12]. In class C3 and C4 tumors, major encasement of the ICA is usually found at the inferomedial wall of the horizontal petrous segment. Curative treatment necessitates aggressive removal of the bone in the region of the carotid canal and dissection of the arterial wall in class C3 and C4 tumors. We have noted that most of the recurrences were localized to the area around and medial to the petrous ICA [8]. Preoperative endovascular intervention in the form of intra-arterial stents in the cervical and petrous (vertical and horizontal) segments of the ICA allows total tumor clearance in these areas without compromising the artery. In our experience of over 30 cases, the stenting of ICA has transformed the therapeutic management in cases of advanced TJPs, leaving very few or no TJPs inoperable.

Preoperative Assessment of the ICA

The aims of preoperative assessment are to (1) determine the degree and extent of involvement of the artery by the tumor and (2) determine the efficacy of the collateral circulation in maintaining the perfusion of the areas that would be affected by the manipulation or sacrifice of the artery. The investigations used for this purpose include high-resolution CT scan, MRI, magnetic resonance angiography (MRA), and digital subtraction angiography. Narrowing and irregularities of the arterial lumen are strongly suggestive of infiltration of the ICA wall. To determine the efficacy of the collateral circulation, four vessels angiography with manual cross compression test, xenon-enhanced computed tomography cerebral blood flow, single-photon emission computed tomography, and carotid stump pressure management are used.

The indications for preoperative endovascular intervention of the ICA are:

(1) Encasement of the distal cervical and petrosal 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 petrosal segments of the ICA as determined by angiography
(3) All class C3 and C4 TJPs, vagal and carotid body paragangliomas
(4) Extensive blood supply from ICA branches as seen on angiography
(5) Previous surgery with ICA manipulation and/or previous radiotherapy

In these situations, the options include preoperative PBO, external-internal carotid artery bypass followed by PBO or reinforcement with intra-arterial stents. In this chapter, we will briefly discuss PBO and stenting of the ICA.

Preoperative Endovascular Management of the ICA

Permanent Balloon Occlusion

A balloon occlusion test (BOT) is performed if there is good cross-filling from at least one of the two communicating systems. A PBO would be undertaken if the patient tolerated the BOT and angiographic data demonstrated good cross-flow.

The BOT-PBO procedure is performed under local anesthesia with mild sedation and systemic heparinization. A bilateral femoral approach is employed in which an 8F guiding catheter is inserted into one femoral artery and positioned in the ICA to be occluded. The contralateral femoral artery puncture is used for the angiographic evaluation. To permanently occlude the ICA, a GVB 16 balloon mounted on a CIF catheter (Minyvasis, Gennevilliers, France) is used. The first balloon is usually placed into the cavernous segment of the ICA just proximal to the origin of the ophthalmic artery and two more balloons at the carotid foramen and in the neck just distal to the bifurcation (Figs. 9.1, 9.2, and 9.3). After balloon inflation, occlusion of the ICA is confirmed angiographically by injection of contrast into the guiding

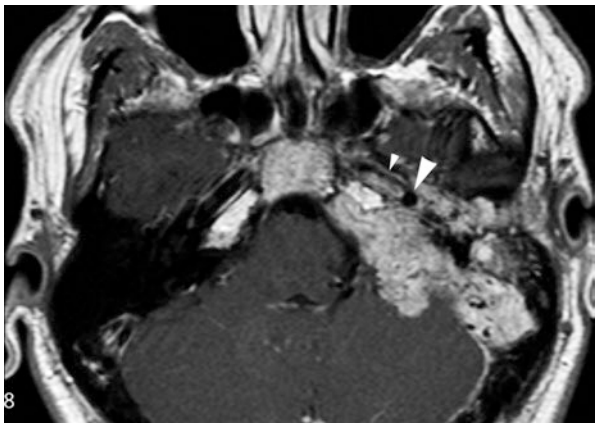

Fig. 9.1 MRI with gadolinium (axial view) of a case of right C3 TJP at the level of the horizontal segment (*small arrow head*) of the internal carotid artery. Note the encasement of the vertical segment (*big arrow head*) of the artery

catheter, followed by confirmatory angiography to establish that adequate cross-flow is achieved, with special attention to the symmetry of the arterial, capillary, and venous phases on either side (Figs. 9.4 and 9.5). The patient's physical and

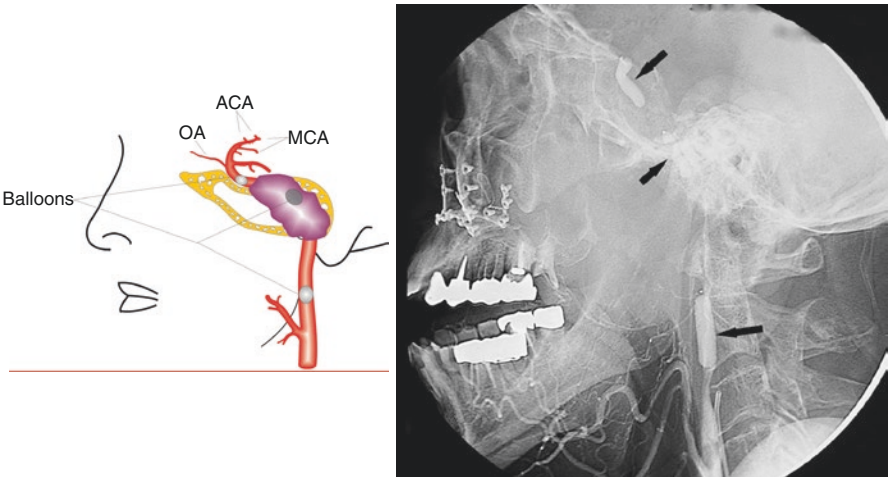

Fig. 9.2 Angiogram showing the balloons (*three arrows*). *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *OA* ophthalmic artery

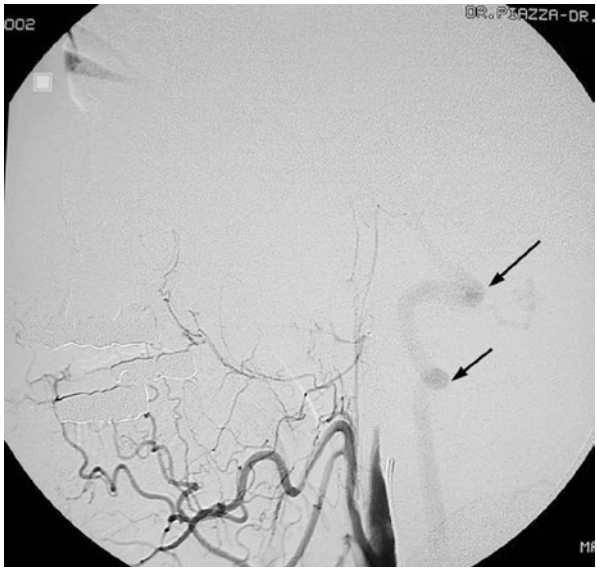

Fig. 9.3 Angiogram showing complete occlusion of the artery after placement of the balloons. The distal branches of the external carotid artery are not seen as they were closed in a previous surgery. The shadow of the vertebral artery can be appreciated (*two arrows*)

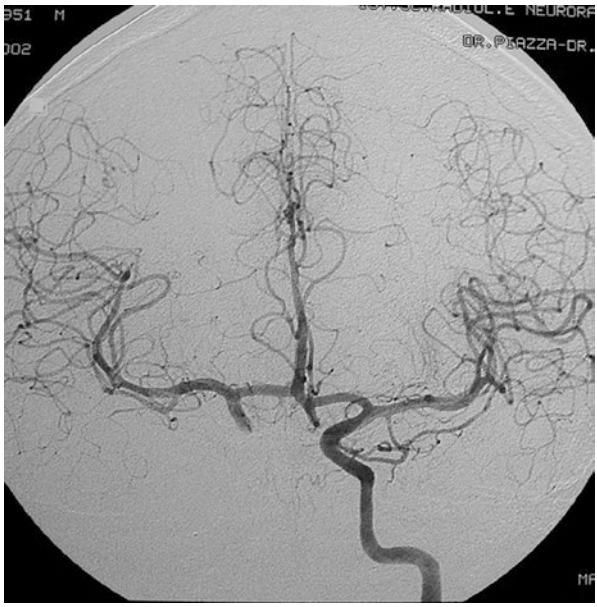

Fig. 9.4 Angiography (arterial phase) of a patient with injection of the left internal carotid artery after manual cross compression test of the right internal carotid artery showing patency of the anterior communicating and perfect symmetry of the arterial and venous phases of the two cerebral hemispheres

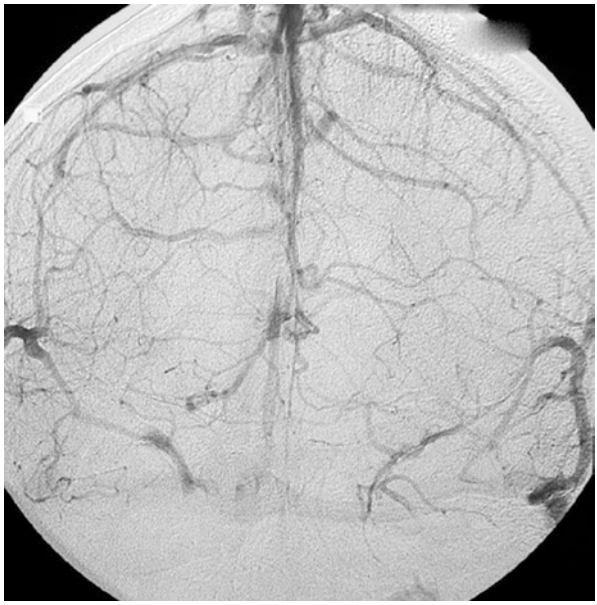

Fig. 9.5 Venous phase angiography of same patient as Fig. 13.41

mental status is then monitored for 20 min. The first balloon is then detached. If balloon occlusion is not tolerated, the balloon is deflated immediately. In most cases this is apparent very quickly, in the first few minutes after carotid occlusion. If asymmetry (>1 s) in the capillary and venous phases of the angiogram is identified, angiography is repeated a few minutes later. If this asymmetry does not correct, the balloon is deflated and alternatives must be considered. After PBO, the patient is monitored for 24 h in an intensive care unit. Surgery is scheduled only after 3–4 weeks.

Intra-arterial Stenting

The introduction of preoperative reinforcement of the ICA with stents is a significant advancement in the surgical management of patients who are at risk of damage to the ICA. Stent insertion reinforces the artery and allows more aggressive carotid dissection while reducing the possibility of intraoperative injury to the ICA. To reduce the risk of thromboembolic complications, antiplatelet therapy is commenced 5 days before the stent insertion using a combination of clopidogrel (75 mg/day) and aspirin (100 mg/day). This therapeutic regimen is administrated for 1–3 months after stenting and then reduced to single-drug treatment with aspirin only. Antiplatelet agents are stopped and low molecular weight heparin (LMWH) commenced 5 days before surgery. Antiplatelet agents are introduced 2 days after surgery and LMWH is stopped 3 days after surgery. The patient then is placed on lifelong antiplatelet therapy (Fig. 9.6).

Reinforcement with stents is performed under general anesthesia as a separate procedure following diagnostic angiography. Three different types of self-expanding nitinol stents are used: Xpert Stent System (Abbott Laboratories Vascular Enterprises, Dublin, Ireland), Neuroform 3 (Boston Scientific, Fremont, CA), and LEO (Balt Extrusion, Montmorency, France). We consider the Xpert stent the most suitable for reinforcement of both the cervical and intratemporal portions of the ICA because of its diameter (4 or 5 mm) and length (20, 30, or 40 mm). To reduce the possibility of injuring the ICA at the stent-tumor border, at least 10 mm of tumor-free vessel wall must be reinforced with the stent, both proximally and distally. To achieve this, it is necessary to insert up to two or even three stents. Each stent is carefully selected and tailored to the individual patient. It is difficult to negotiate the stent between the vertical and horizontal portions of the carotid canal and in arteries that are coiled or kinked in the neck, and great care must be taken while this is being performed. In such situations, softer and more flexible stents must be chosen, to reduce the risk of dissection of the ICA. If a stent placement is technically impossible, a PBO is the next option.

The timing of reinforcement with stents also plays an important role; an interval of at least 4–6 weeks is advocated between stenting and surgery. This allows the

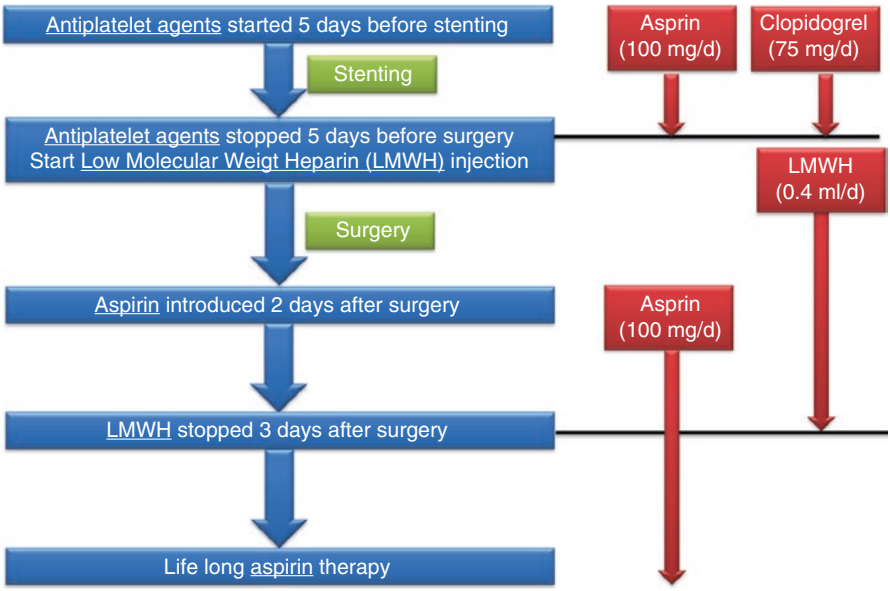

Fig. 9.6 Medication schedule associated with stenting into the internal carotid artery

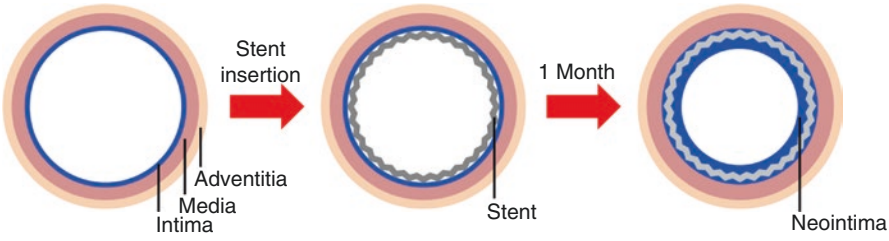

Fig. 9.7 Changes of anatomy of the internal carotid artery after stent insertion

formation of a stabilized neointimal lining (Fig. 9.7) on the luminal surface of the stent. In the presence of significant blood supply from the ICA, a bare stent is ineffective in reducing the vascular supply to the tumor. In such situations, the use of PBO, preoperative embolization with particles during temporary balloon occlusion of the ICA, and insertion of covered stents are possible alternative solutions. Present literature suggests that covered stents have several theoretical disadvantages, increased thrombogenicity, rigidity, and greater difficulty in positioning at arterial angles, when compared to bare stents.

One month after the stent insertion, the neointimal layer is developed and subsequent subadventitial dissection can be safely performed.

Intraoperative Management of the ICA

Intraoperatively, the ICA may require the following types of intervention, depending on degree of involvement: (1) decompression with or without partial mobilization of the artery, (2) subperiosteal dissection, (3) subadventitial dissection, (4) subadventitial dissection with stent coverage, and (5) arterial resection (after preoperative PBO).

Simple decompression—This technique is employed when the tumor is around the ICA but not adherent to the artery (i.e., Fisch class C1 TJPs). Decompression of the ICA is performed after identifying it medial to the Eustachian tube by drilling out the tympanic bone. A large diamond burr is used parallel to the course of the artery. Drilling is advanced both laterally and medially to the artery. By removing the bone anterior to the ICA, the artery can be displaced laterally or medially by manipulating it with the tip of the suction tube while drilling is being performed. If additional drilling around the ICA is required, a vessel loop is wrapped around the artery to enable a wider range and better control.

Subperiosteal dissection—This technique is indicated when the tumor involves the periosteum of the carotid canal without reaching the adventitia. In this technique, a plane of dissection is developed between the adventitia of the ICA and the periosteum of the carotid canal [20]. This is relatively easier and safer in the vertical petrous segment, as the ICA is thicker and more accessible when compared to the horizontal segment. The dissection of the tumor is started at the cervical level, from an uninvolved extratemporal segment of the ICA, where a good plane of dissection is easily identified. The bone of the carotid canal around the ICA from its entrance into the temporal bone is drilled out along with the tumor infiltrating the bone and periosteum. Gentle displacement of the ICA, from its entrance in the skull base to at least the genu of the horizontal segment, is required if the tumor has extended anterior to the artery. There could be areas where the tumor may extend into the adventitia of the artery, and subadventitial dissection may be required.

Subadventitial dissection—This technique is applied to tumors that infiltrate the adventitia without reaching the muscular layer (media) of the ICA. Subadventitial dissection consists of separating the adventitia from the muscular layer. The wall of the ICA at the level of the vertical segment is 1.5–2.0 mm thick with the adventitia being approximately 1 mm thick. The adventitia is absent at the horizontal portion [21]. Therefore, subadventitial dissection can only be executed at the vertical portion. The intraoperative risk of a vascular injury is especially high in irradiated or previously operated cases. Small lacerations to the arterial wall, or any avulsion of the caroticotympanic branches, can often be controlled with judicious use of the bipolar cautery. For small to medium defects, direct suture repair is recommended. Double-armed vascular sutures are used while temporary occlusion is applied. Care to evert the edges of the artery while suturing is important to avoid stenosis. The postoperative risks of subadventitial dissection include weakening of the vessel leading to subsequent blowout or to dilatation and delayed aneurysm formation.

Dissection and Resection Following Permanent Balloon Occlusion

Following balloon occlusion of the artery, dissection is started from cervically upward. It is ligated immediately proximal to the proximal balloon using a large vascular clip, followed by en bloc resection of the artery with the surrounding tumor. Care must be taken to identify the distal segment of the occluded artery and perform transection here, to avoid excess traction on the cavernous sinus segment during final tumor removal (Fig. 9.8).

In rare cases with failed tumor embolization due to high flow of tumor blood supply, permanent balloon occlusion can be performed even in cases with stent insertion (Fig. 9.9).

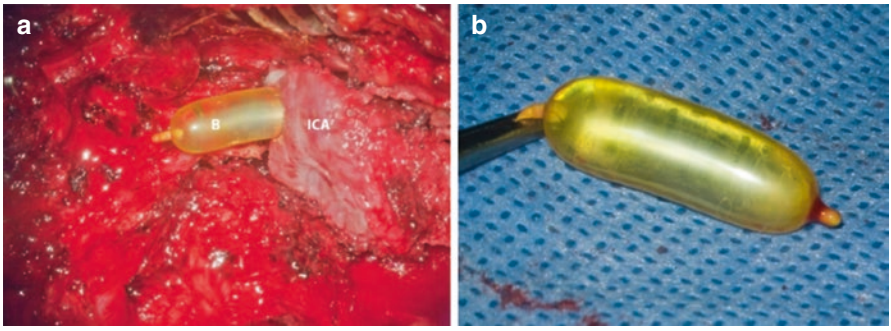

Fig. 9.8 (**a**) Latex balloon inserted into the internal carotid artery. (**b**) The harvested balloon

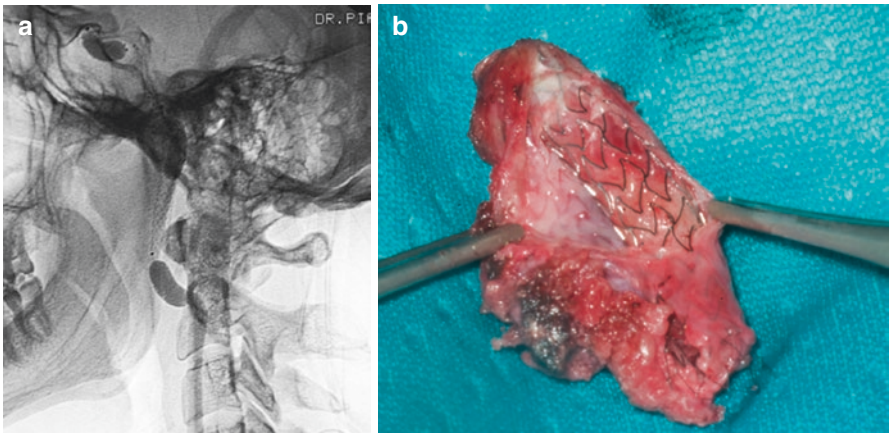

Fig. 9.9 (**a**) Angiography, lateral view. Three balloons are seen in the course of the internal carotid artery. (**b**) The stent is seen in the harvested internal carotid artery

Intraoperative Internal Carotid Artery Injury

Prevention of injury to the ICA must be achieved at all costs. However, on rare occasions, a vascular injury may be encountered [22, 23]. In such case, the presence of proximal and distal control allows temporary occlusion, while a primary repair is carried out. A primary principle in such a situation is to achieve adequate visualization. Temporary compression or occlusion is achieved quickly by using previously placed control tapes. A variety of atraumatic vascular clips can also be used. Back-bleeding is a reassuring sign indicating some degree of collateral flow and allowing repair to be carried out in a timely fashion. Once the controls are achieved proximally and distally, small lacerations to the arterial wall or avulsion of the caroticotympanic branches can often be controlled with judicious use of the bipolar. Fine tips are used to approximate the edges in the longitudinal direction of the laceration. A low energy pulse is applied, and the forceps are advanced, and the process is repeated until the laceration is sealed. The occlusion is partially and then fully released to ensure closure. A layer of Surgicel® is placed over the repair and reinforced with fibrin glue. For small to medium defects, direct suture repair is recommended. Double armed vascular sutures are used while temporary occlusion is applied. Care to evert the edges is important as to avoid significant stenosis. Patch grafting and bypass using saphenous vein are options in extreme situations. In case of a stented ICA, the greatest risk is potential injury is at the transition point of the stented and non-stented artery. It is imperative to use minimal traction at this point. Facilities for rapid transfer of the patient to the neuroradiology suite once temporary control is gained are essential, with the options of emergency balloon occlusion or covered stent placement [24]. Apart from repair of the artery, important resuscitation principles must also be adhered to. Judicious volume replacement, estimation of blood loss, and consideration of component therapy were made. Following repair, normotension and adequate circulating volume must be maintained to ensure adequate repair and maintain neuroprotection. Any injury to the internal carotid artery or subadventitial dissection must be followed up radiographically due to the risk of pseudo-aneurysm formation.

Vasospasm of the ICA can also occur while manipulating the ICA. The etiology can be multifactorial but includes mechanical trauma, thermal changes, desiccation, and prolonged exposure to blood [25]. Therefore, irrigation with warmed saline and a gentle technique are essential to minimize this risk. It has been reported that younger patients are more prone to this complication due to increased vascular tonicity and reactivity [25, 26]. If the surgeon notices any segmental reduction in the ICA, manipulation must stop, and papaverine is placed onto the artery. The surgeon must wait till normotension or mild hypertension is achieved.

Representative Cases

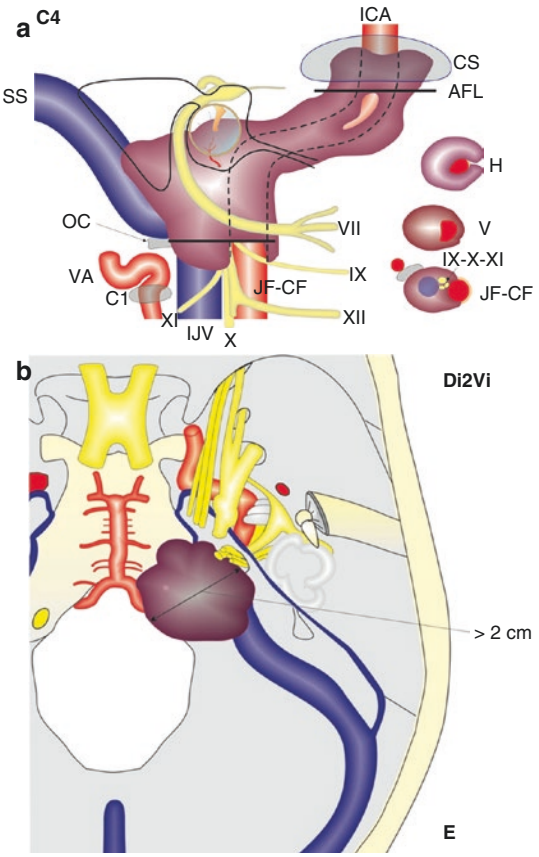

Fig. 9.10 (**a**, **b**) A class **C4Di2Vi** (right side) was operated in two stages. In the second stage, the remnant of the tumor that involved the ICA was excised and is shown here in pictorial steps. Angiography revealed inadequacy of the collateral circulation. A stent was placed in the artery preoperatively. *SS* Sigmoid Sinus, *OC* Occipital Condyle, *VA* Vertebral artery, *C1* C1 vertebra, *XI* XI cranial nerve, *IJV* Internal Jugular Vein, *JF-CF* Jugular foramen - cartid foramen, *XII* XII cranial nerve, *IX* IX cranial nerve, *VII* VII cranial nerve, *ICA* Internal carotid artery, *CS* Cavernous segment, *AFL* anterior foramen lacerum, *H* Horizontal carotid, *V* Vertical carotid

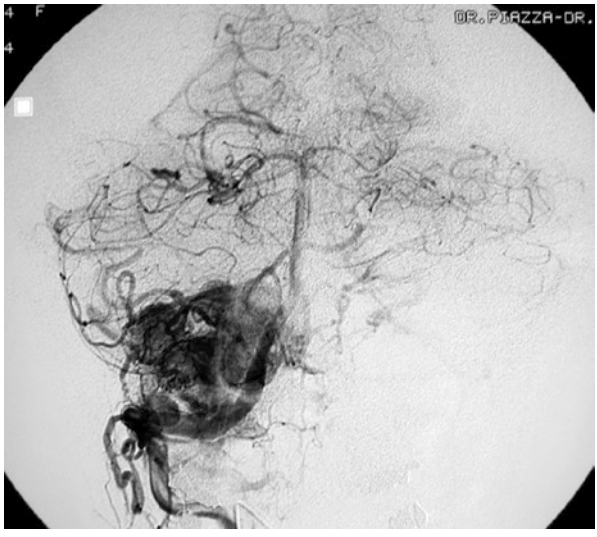

Fig. 9.11 Angiogram of the case shows the tumor blush and the massive involvement of the internal carotid artery

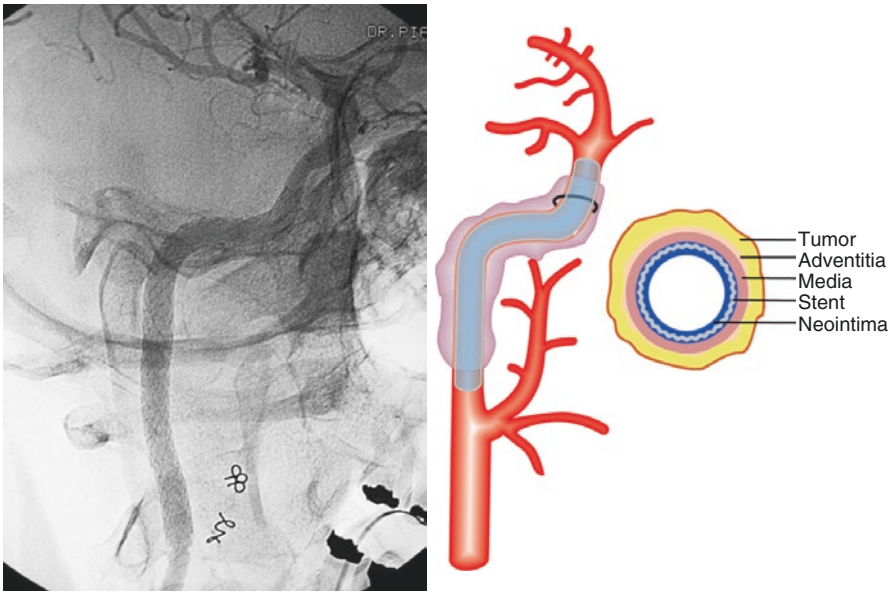

Fig. 9.12 Angiogram, lateral view, showing the stent inside the internal carotid artery

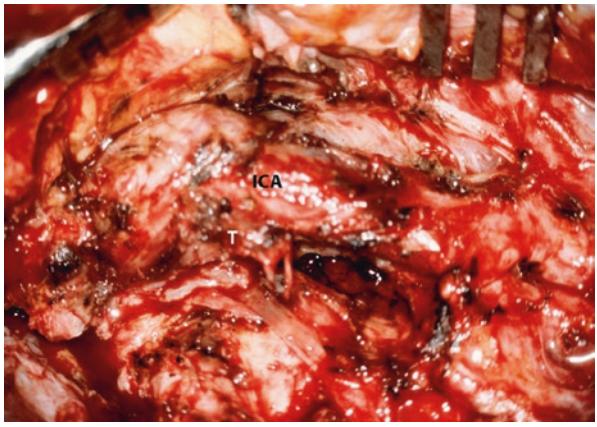

Fig. 9.13 Intraoperative view showing the internal carotid artery completely encased by the tumor. *ICA* internal carotid artery, *T* tumor

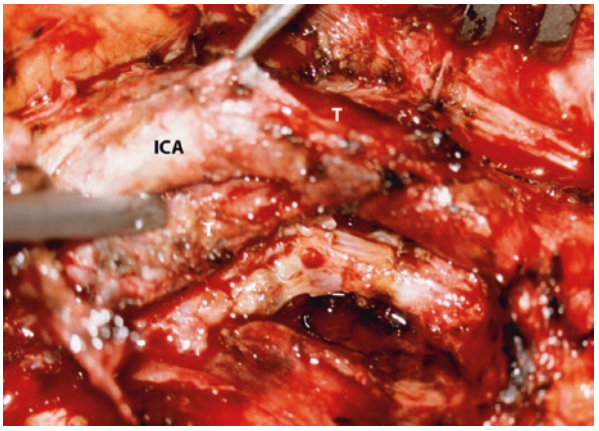

Fig. 9.14 Establishment of the plane of cleavage. *ICA* internal carotid artery, *T* tumor

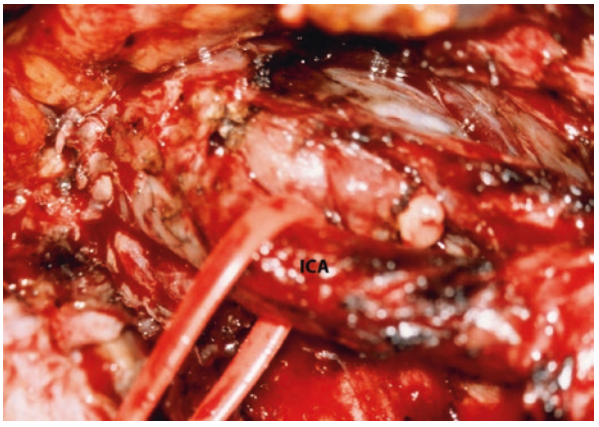

Fig. 9.15 The artery (posteriorly displaced by an umbilical tape) has been partially dissected from the tumor. Note that the tumor is anteriorly placed. *ICA* internal carotid artery, *T* tumor

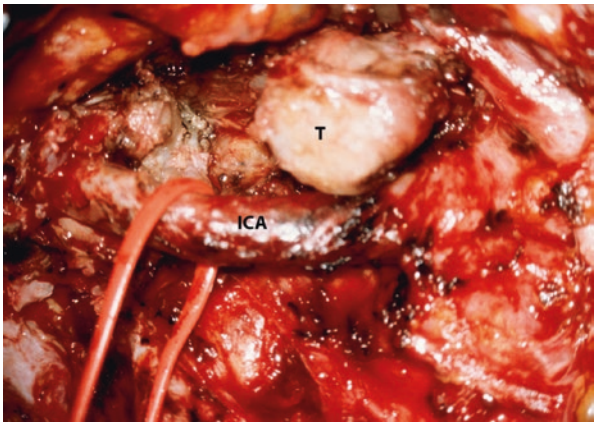

Fig. 9.16 Further dissection of the tumor. The internal carotid artery (ICA) is posteriorly displaced, *T* tumor

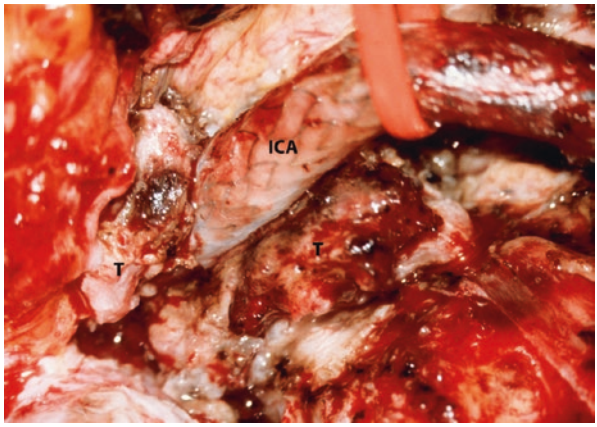

Fig. 9.17 Here the ICA has been anteriorly displaced. Note that the stent appears clearly through the thinned arterial wall. *ICA* internal carotid artery, *T* tumor

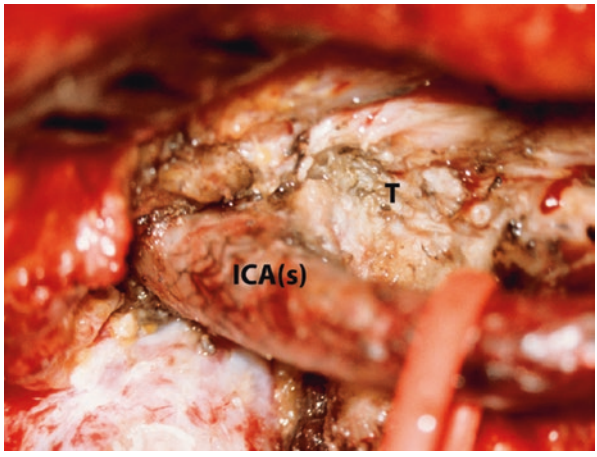

Fig. 9.18 The horizontal segment of the ICA was made free from the tumor (T). Note that the tumor extended to the foramen lacerum

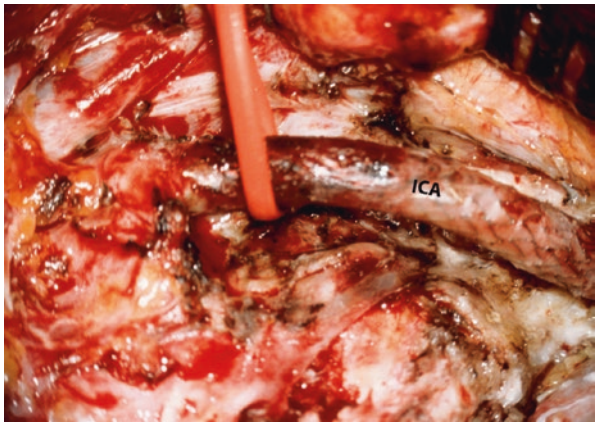

Fig. 9.19 Final view at the last procedure. Most of the internal carotid artery in the petrous bone had been freed from the tumor. Note the bloodless surgical field and the reinforcement of the internal carotid artery with a stent. To avoid postoperative cerebrospinal leak, the recurrent intradural lesion was left in place and removed in another stage (see Case 3 in Chap. 17)

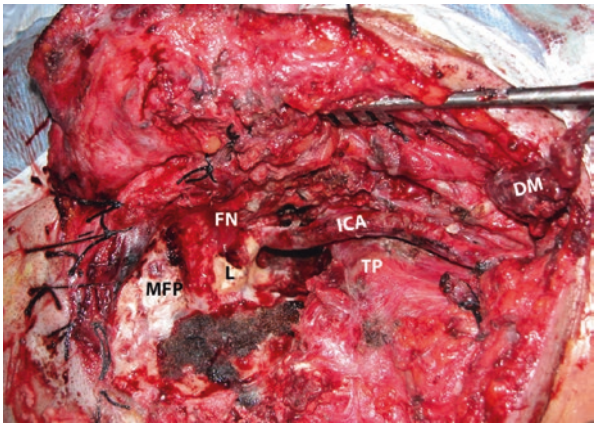

Fig. 9.20 Note the fully exposed internal carotid artery after complete tumor removal. *DM* posterior belly of the digastric muscle, *FN* facial nerve, *ICA* internal carotid artery, *L* labyrinth, *MFP* middle fossa plate, *TP* transverse process of the atlas

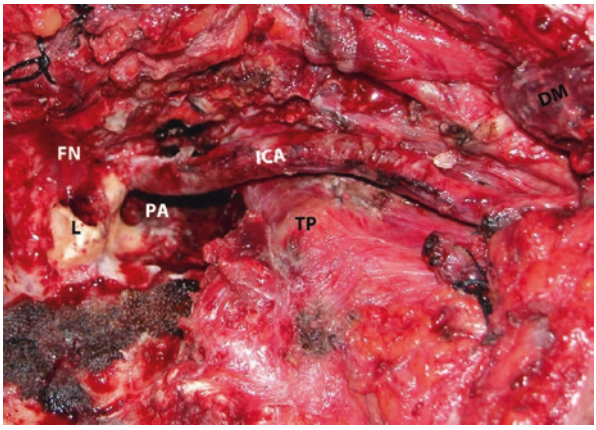

Fig. 9.21 Higher magnified view. *DM* posterior belly of the digastric muscle, *FN* facial nerve, *ICA* internal carotid artery, *L* labyrinth, *PA* petrous apex, *TP* transverse process of the atlas

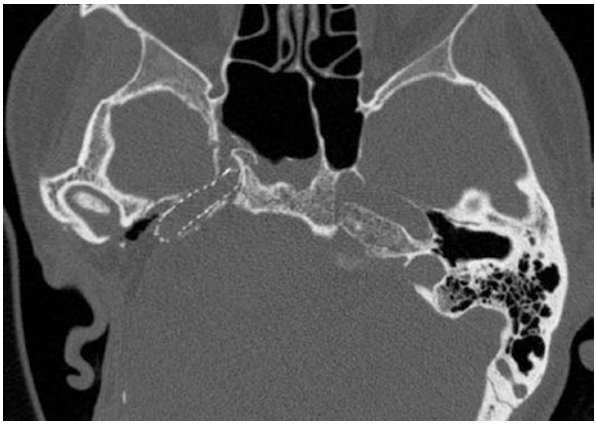

Fig. 9.22 CT scan, axial view showing the stent inserted into horizontal portion of the internal carotid artery

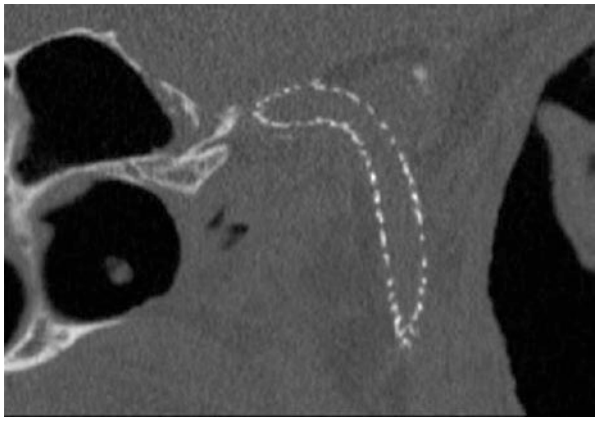

Fig. 9.23 CT scan, axial view showing the stent inserted into vertical portion of the internal carotid artery

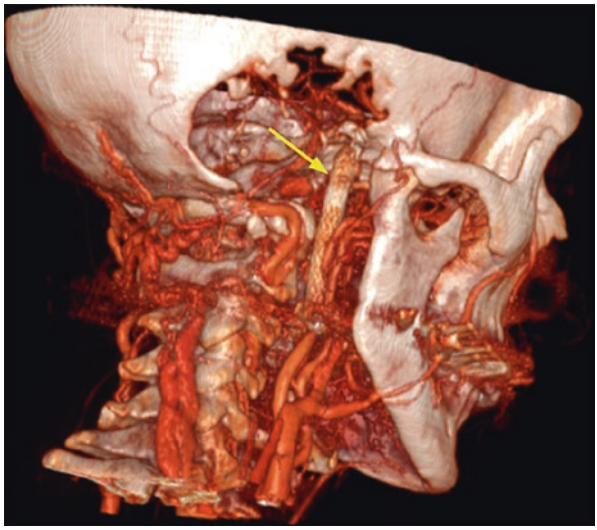

Fig. 9.24 Color 3D angioCT: view from below. Note the large bone removal and the stented artery (*arrow*)

Hints and Pitfalls

- A preoperative assessment of the ICA is of paramount importance.
- Determine the degree and extent of involvement of the artery by tumor with CT, MRI, MRA, and digital subtraction angiography.
- Determine the efficacy of collateral circulation.
- Do not use a PBO if the angiographic phase has a delay of more than 1 s.
- Use intraluminal stents when possible. It avoids closure of the ICA and facilitates subadventitial dissection of the tumor.
- It is advisable to wait 4–5 weeks after stenting before operating on these patients.
- Start dissection of the tumor inferiorly at a point not invaded by the tumor

- Exposure of the cervical segment of the ICA is an essential step in the management of these tumors.
- Gentle displacement of the vertical segment of the artery is often required in order to remove tumor extending to the medial and anterior portion to the artery.
- Dissection of the tumor must be accomplished parallel to the artery.
- Dissection of the occluded ICA is started at the cervical level.
- The ICA is closed proximal to the preoperative balloon using a large vascular clip.
- Avoid traction of the cavernous sinus segment during final tumor removal.

Conclusion

ICA involvement is no longer considered a limiting factor in TJP surgery, but requires an accurate preoperative neuroimaging evaluation of the extent of ICA invasion by the tumor and appropriate perioperative management. Decompression of the ICA and subperiosteal dissection are relatively simple surgical procedures that can be employed in cases where the adventitia of the ICA is free of involvement. Preoperative endovascular intervention in the form of intra-arterial stents in the cervical and petrous segments of the ICA has transformed the therapeutic management in cases of advanced TJPs. Stenting of the ICA avoids the need for potentially troublesome maneuvers like PBO, bypass procedures, and arterial repair or reconstruction. PBO is currently limited to those patients in which stent placement is technically impossible or in patients with tumors that derive significant blood supply from the ICA. No major perioperative complications, related either to preoperative stenting or intraoperative surgical management of the ICA, have been reported to date in our series of patients.

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Chapter 10
Subtotal Resection of Jugular Paragangliomas

John R. Sims, Alex D. Sweeney, Matthew L. Carlson, George B. Wanna, and James L. Netterville

Introduction

Historically, the mainstay of treatment for jugular paraganglioma has been gross total resection. While this strategy has led to relatively low recurrence rates [1–5], it has often been pursued at the expense of cranial nerve function. This trade-off was especially true for larger tumors extending through the pars nervosa of the jugular foramen and those with intracranial extension. Bacciu et al. [6] recently reviewed 122 patients with Fisch class C and D jugular paraganglioma and found that 54% of patients developed one or more new cranial nerve deficits after surgery with gross total resection being achieved in 86% of cases. Similarly, the Vanderbilt Otology Group's review of 202 patients with jugular paragangliomas found a 60% rate of new cranial nerve injuries after performing gross total resection in 90% of cases [2, 7].

The impact of cranial nerve sacrifice should be a major consideration in the treatment algorithm of jugular paragangliomas. The nerves at highest risk are cranial nerves IX, X, and XI due to their intimate relationship with the jugular bulb;

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however, cranial nerves VII and XII can also be involved in advanced stage tumors. With unilateral paralysis of any one of these nerves, patients can struggle significantly with speech and swallowing function. While certain deficits can be rehabilitated, this process often requires an additional surgical procedure, and overall function may never reach a near-normal state, especially when multiple cranial nerves are injured or in patients of advanced age [8].

As more is discovered about the natural history of these benign tumors and as data regarding tumor control and functional outcomes with stereotactic radiosurgery develop, at most centers treatment paradigms have shifted toward more conservative approaches in certain patient populations in an effort to avoid the morbidity associated with cranial nerve injuries. One such approach that is increasing in utilization for large tumors where cranial nerve function is relatively intact is subtotal resection. In this chapter, we focus on this treatment strategy and define appropriate clinical scenarios for employing it.

Natural History of Jugular Paragangliomas

An understanding of the natural history of jugular paragangliomas is necessary when considering different treatment options available. These tumors are histologically benign yet locally invasive. While patients most commonly present with pulsatile tinnitus and hearing loss, advanced lesions may present with cranial neuropathies involving VII, IX, X, XI, and XII, brain stem compression, and hydrocephalus. The primary goal of any treatment is to obtain tumor control, alleviate reversible symptoms, and prevent more severe late complications. Therefore, it is key to have a good understanding of the biological behavior of these tumors and how quickly these complications may develop.

Jansen et al. [9] at Leiden University in the Netherlands was the first group to specifically examine the natural history of jugular paragangliomas. Their study included 11 jugulotympanic paragangliomas that were observed with a mean follow-up of 3.8 years. They found that only 55% of patients exhibited radiologic growth over the study period at a rate of 0.8 mm/year. The cases in this series were relatively small (average tumor volume 0.8 cm^3), and no delineation was made between jugular and tympanic paragangliomas.

Prasad et al. [10] examined 23 cases with Fisch class C and D jugular paragangliomas who had follow-up for greater than 3 years. Only 35% of these tumors showed any progression with the remaining 65% either remaining stable or regressing. New lower cranial nerve deficits were seen in 30% of patients, though one patient experienced worsening of a preexisting cranial nerve palsy. Facial nerve status remained stable for all 23 patients. They concluded that a wait-and-scan approach should be considered in elderly patients with class C and D jugular paragangliomas.

More recently, Carlson et al. [11] reviewed 15 patients with jugular paragangliomas that were observed over a median follow-up of 4.8 years. In the 12 patients with serial imaging, 42% had radiologic progression with a growth rate of 0.8 mm/year.

However, similar to Prasad et al. [10], they found higher rates of radiologic progression in patients with longer follow-up and therefore cautioned against observing younger patients who would be expected to live with their disease for several decades. A detailed discussion regarding the natural history of jugular paraganglioma is beyond the scope of this chapter and is reviewed in greater depth elsewhere in this book.

Indications for Surgery

Historically, surgical resection has been the primary treatment for jugular paragangliomas. However, in the past two decades, advances in radiation therapy have led to decreased complications and promising tumor control rates in patients treated with primary radiosurgery [1]. A 2011 meta-analysis [1] looking at 869 patients with jugular paragangliomas found pooled estimates of control rates after stereotactic radiosurgery (SRS) were 95% vs. 86% for gross total resection. They also found lower rates of lower cranial nerve injury in patients who underwent primary SRS versus gross total resection.

Despite the growing body of literature supporting SRS as an initial treatment modality for jugular paragangliomas, there are several scenarios where primary surgery should be strongly considered: small resectable tumors in young patients, tumors with aggressive behavior concerning for malignancy, secreting tumors where the benefits of radiotherapy are not well elucidated, and tumors with large intracranial extension and brain stem compression (Fig. 10.1).

Types of Subtotal Resection

In general, three forms of subtotal resection have been described and will be discussed further in this chapter: limited resection of only the middle ear portion of the tumor for audiological symptom improvement, resection of the intracranial portion of the tumor to relieve brain stem compression, and aggressive resection of all tumor except for that which is intimately involved with the carotid artery or functional cranial nerves.

Resection of the Middle Ear Component

Many jugular paragangliomas are indolent and can be observed for several years without risk of rapid growth. With this finding in mind, some authors [12, 13] have reviewed the role of limited surgery with the primary goal of symptom relief (Fig. 10.2). Cosetti et al. [12] treated three patients over the age of 70 with a limited

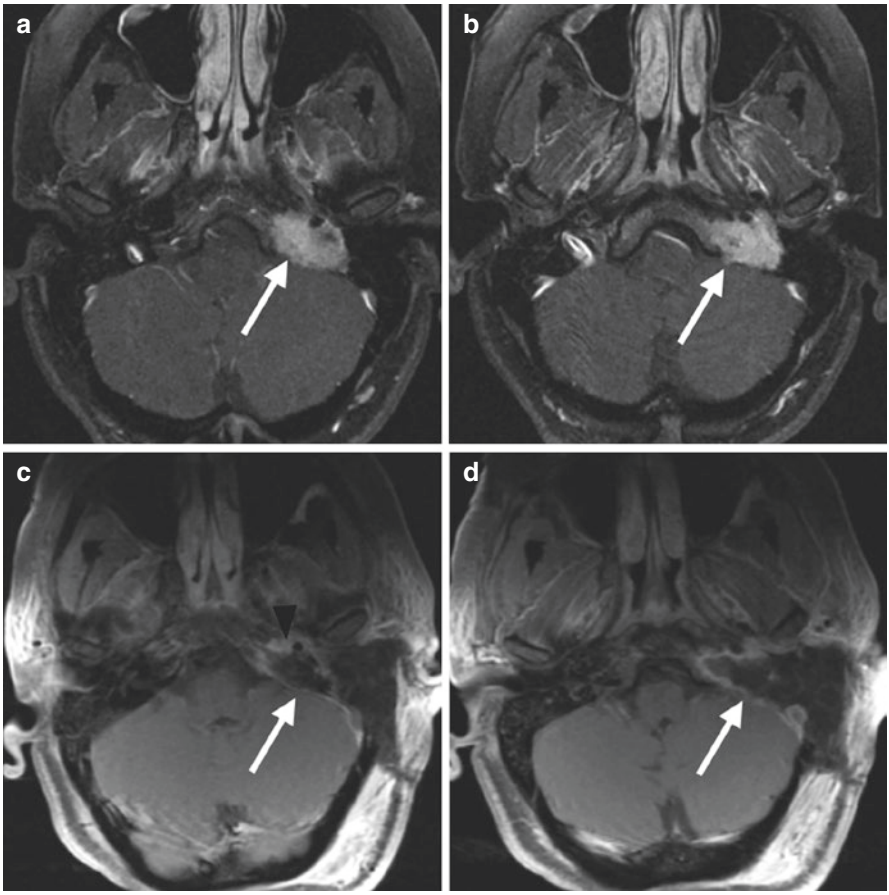

Fig. 10.1 38-year-old woman with a large jugular paraganglioma, intact lower cranial nerves, and excess dopamine and norepinephrine secretion resulting in arrhythmia (**a**, **b**). She underwent an aggressive subtotal resection with minimal residual disease left at the medial wall of the jugular bulb and internal carotid artery. She had normalized catecholamine levels and intact lower cranial nerves postoperatively (**c**, **d**)

resection that primarily addressed the middle ear component of tumors. All three patients had immediate relief of their pulsatile tinnitus after surgery, improved hearing, and no new cranial nerve deficits. One of these patients had radiologic progression 6 years after surgery, and this was treated with radiation therapy. Willen et al. [13] described similar subtotal resections in five patients over the age of 60 with Fisch class C3 tumors or greater; however, all patients in their series also underwent postoperative radiosurgery to the residual tumor. All patients had relief of their pulsatile tinnitus and stable or improved hearing. They reported no new lower cranial nerve deficits as a result of their treatment, and no tumors had grown after a mean of 19 months of follow-up. It should be noted that in the elderly population, subtotal

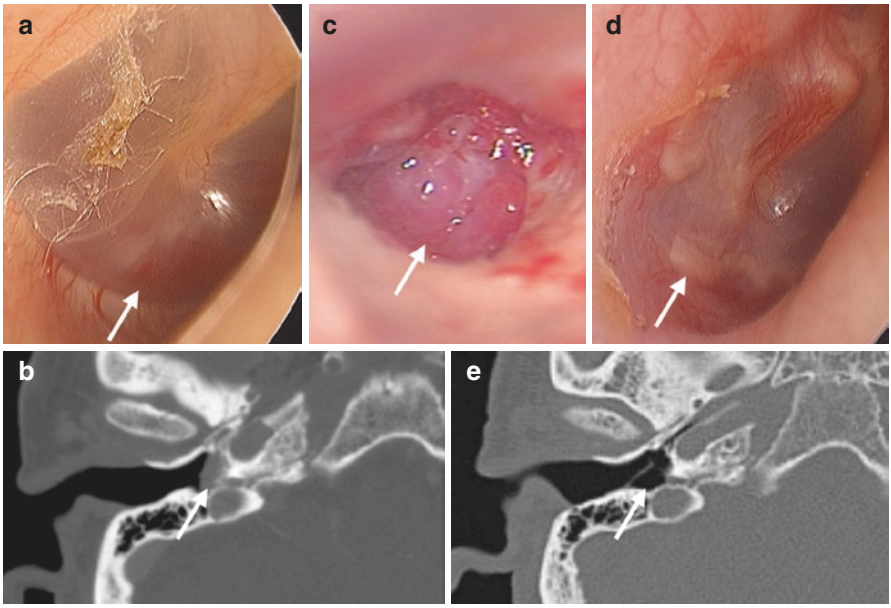

Fig. 10.2 51-year-old man with right-sided conductive hearing loss and pulsatile tinnitus with a right-sided jugular paraganglioma (**a**, **b**). A postauricular transcanal approach was utilized for removal of the *middle* ear tumor component (**c**). The patient experienced resolution of his pulsatile tinnitus following surgery. Postoperative otoscopy and CT imaging are shown (**d**, **e**)

resection has been described in symptomatic patients with a primary goal of symptom relief while avoiding cranial nerve injury. In asymptomatic patients with advanced age, conservative therapy can be considered.

Subtotal Resection for Brain Stem Decompression

Rarely, patients may present with symptomatic brain stem compression or hydrocephalus from advanced tumors. In these cases, primary radiation treatment is not advisable due to concerns for posttreatment swelling leading to progressive brain stem compression. While gross total resection is still preferred in young, relatively healthy patients, it can be extremely challenging and cause unnecessary morbidity in patients of advanced age or limited life expectancy. In this scenario, performing a subtotal resection with the primary goal of brain stem decompression is a viable strategy. Carlson et al. [14] described four cases of advanced (Fisch grade D_2) jugular paragangliomas who presented with significant brain stem compression. Subtotal resections were performed in three of these via a combined transtemporal and transcervical approach. All three patients eventually received postoperative radiation

treatment to their residual tumor. Successful decompression, as well as, long-term tumor control was achieved in all three patients with 6–9 years of follow-up.

Aggressive Subtotal Resection

Wanna et al. [15] described subtotal resection in 12 patients with Glasscock-Jackson grade 3 or 4 tumors and intact lower cranial nerves (Fig. 10.3). In eight (66.7%) cases, no subsequent growth was observed after surgery with a mean follow-up of

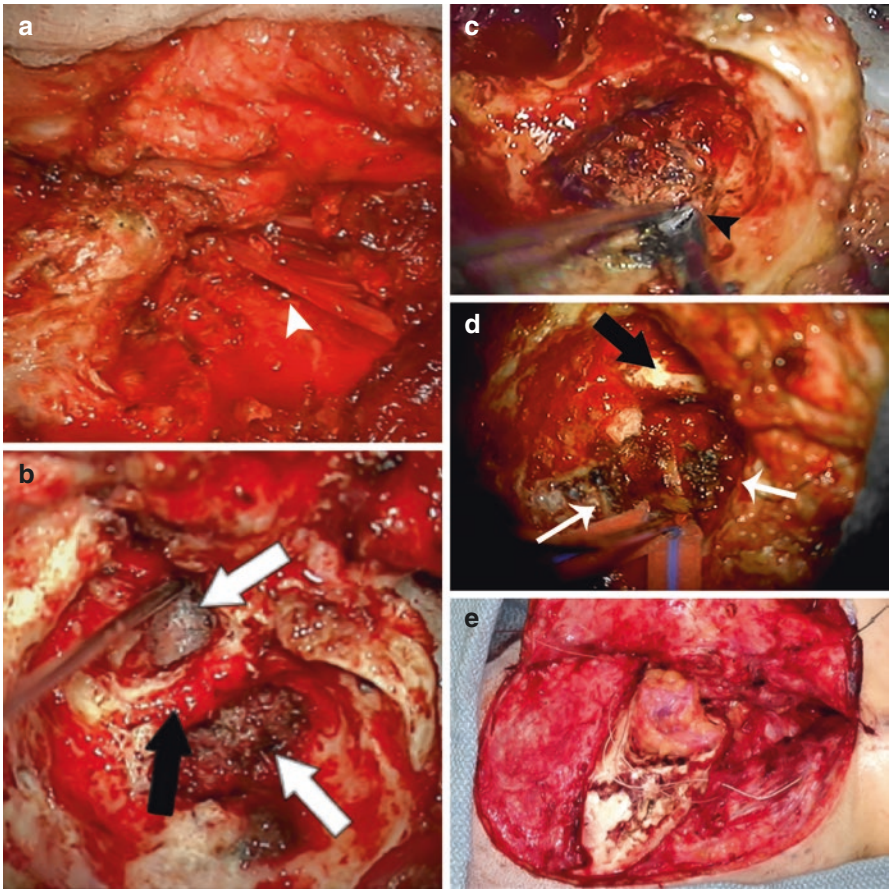

Fig. 10.3 Intraoperative photos of an aggressive subtotal resection of a large right-sided jugular paraganglioma. (**a**) Neck dissection with the *white arrowhead* pointed to the lower cranial nerves IX, X, and XI entering the skull base. (**b**) *Black arrow* pointing out the facial nerve bridge and *white arrows* denoting tumor. (**c**) The sigmoid sinus is extraluminally compressed with Surgicel packing. The *black arrowhead* points to the sigmoid opened with scissors. (**d**) The sigmoid sinus is completely transected to facilitate a transjugular approach. *White arrows* showed stumps of the transected sigmoid and the *black arrow* points to the facial nerve. Tumor lies just between the two sigmoid sinus stumps. Cottonoids are in place over the cerebellum. (**e**) Closure with an abdominal fat graft

3.7 years. The remaining four tumors grew at an average of 2 years after surgery. It was noted that the latter cases had significantly higher residual tumor following subtotal resection compared to those that showed no growth (59.2% vs. 11.9%). Moreover, no cases achieving greater than 80% of tumor resection when comparing pre- and postoperative imaging showed postoperative growth. There were no new permanent cranial nerve deficits following surgery in any of the cases, and no patient experienced carotid injury.

Extent of Resection

It is important to define the extent of surgical resection as the term "subtotal resection" is broad and could refer to anything less than gross total tumor removal. All authors [12, 13, 15] advocate for removal of the middle ear and mastoid portions of the tumor at the very least. Cosetti et al. [12] and Willen et al. [13] described resections of these portions of the tumor via a transcanal or transmastoid approach with no attempt being made to remove the jugular bulb portion of the tumor. Staged radiosurgery was used to treat the residual tumor in one series [13].

Wanna et al. [15] advocate for a more aggressive resection in most cases, usually via an infratemporal fossa approach with external ear blind sac closure and limited mobilization of the mastoid segment facial nerve. Generally, this approach would proceed toward the epicenter of the tumor and would stop before violating the medial surface of the jugular bulb to ensure that the pars nervosa of the jugular foramen was not violated. Other approaches utilized in their series include tympanomastoidectomy with or without an extended facial recess and a retrosigmoid craniotomy in one case. To date, this is the only series in the literature that quantifies the amount of residual tumor following subtotal resection and risk of recurrence. As mentioned above, the authors found that patients with greater residual tumor burden had a significantly higher risk of postoperative tumor growth. Therefore, they recommended resecting as much tumor as feasible without compromising cranial nerve function when subtotal resection is performed.

Conclusion

In the current era of evolving treatment paradigms for jugular paragangliomas, subtotal resection is a viable treatment option for patients with large tumors that are intimately involved with functional cranial nerves, the carotid artery, or in cases with significant intracranial extension resulting in brain stem compression. Additionally, limited resections of middle ear disease can be considered with or without radiosurgery to address auditory symptoms such as pulsatile tinnitus and conductive hearing loss. Given the possibility of additional tumor growth following subtotal resection, regular and indefinite follow-up should be pursued to ensure that new growth does not occur.

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Chapter 11
Tympanic Paraganglioma

Alex D. Sweeney and Matthew L. Carlson

Abbreviations

CSF	Cerebrospinal fluid
CT	Computed tomography
EAC	External auditory canal
GT	Glomus tympanicum
JP	Jugular paraganglioma
MRI	Magnetic resonance imaging
TP	Tympanic paraganglioma

Introduction

Tympanic paragangliomas (TP) are the most common, benign primary tumors of the middle ear. They originate along the tympanic plexus associated with Jacobson's (IX) and Arnold's (X) nerves and are comprised of paraganglion cells derived from the neural crest. This class of tumors can be found throughout the body, though in the temporal bone, two forms are predominantly seen depending on the site of

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origin: tympanic (tympanic paraganglioma, TP) and jugular (jugular paraganglioma, JP), the latter of which arises from the adventitia of the jugular bulb. Like many other types of paraganglioma tumors in the head and neck, TP are highly vascular, and within the small confines of the tympanic and mastoid cavity, excision can be a complicated endeavor. Furthermore, the growing body of information regarding tumor biology is beginning to influence diagnostic and management paradigms. The following chapter reviews some of the most salient aspects of TP diagnosis and management.

Historical Focus

The origin of a temporal bone paraganglioma was initially uncertain. Historic accounts suggested that within the middle ear, these neoplasms arose from glomus bodies, which are part of the smooth muscle cell lineage and are most commonly found in the dermis [1]. As time progressed, it became clear that the progenitor cell of a TP was actually a paraganglion cell, while the neoplastic process associated with a true glomus cell was an entirely distinct entity [2]. Thus, the moniker "glomus" became technically inappropriate when referring to tympanic (glomus tympanicum, GT) or jugular paraganglioma (glomus jugulare, GJ), though these two conventions continue to be used interchangeably.

In addition to controversy regarding the cellular basis of temporal bone paragangliomas, the site of origin of these tumors was initially a point of contention. Clinically, it was evident from the earliest attempts at excision that some lesions simply involve the middle ear, while others are much more extensive, eroding into the bone surrounding the great vessels in the skull base. Historically, this degree of variety was thought to represent one disease process at different points on a spectrum of tumor growth and aggressiveness. However, the work of pioneering surgeons and the advent of more sophisticated neuroradiology techniques inspired the realization that more extensive erosion around the jugular bulb may be explained by a distinct pathogenesis for some tumors. Moreover, tumors arising in this location may be associated with a different growth pattern, associated symptom profile, and, ultimately, management algorithm and prognosis when compared to traditional TP tumors [3]. Thus, jugular and tympanic paraganglioma became recognized as related but separate entities, the former arising from paraganglion cells around the adventitia of the jugular bulb and the latter from similar cells around the tympanic plexus of the middle ear. Furthermore, additional research has also suggested that paraganglion cells are present in other locations within the temporal bone, leading to the emergence of a third, considerably more rare paraganglioma focus along the intratemporal facial nerve, termed glomus faciale or facial paraganglioma [4]. Given the growing understanding of the pathogenesis of temporal bone paraganglioma, the contemporary surgeon should be armed with the knowledge necessary to properly distinguish between the different forms of this tumor.

Tumor Characteristics

TP are soft and encapsulated tumors that generally have a tan, reddish hue, reflective of their vascular nature. When seen in vivo, tumors are generally pulsatile. It is also noteworthy that growth around the bony surfaces of the tympanic cavity can give tumors an irregular, lobular appearance despite their encapsulation, leading to suspicion of a more invasive process [5].

Microscopically, most paraganglioma are readily identifiable on the basis of cellular identity and architecture. The vascular nature of these tumors is evident histologically though the appearance of an extensive capillary network, leading to a reticular pattern under magnification. Furthermore, clusters of chief cells, the primary cell of a paraganglioma tumor, are surrounded by sustentacular cells, which create the characteristic appearance of a cellular "ball," or "zellballen." Under higher magnification, chief cells generally contain granular structures, reflective of a cellular lineage capable of neurosecretory function [6]. Immunohistochemical analysis classically reveals chromogranin, serotonin, neuron-specific enolase and somatostatin expression in chief cells, and S-100 expression in sustentacular cells [5].

Though locally aggressive, TP are rarely considered to be malignant. Destruction of the temporal bone and surrounding tympanic membrane is not uncommonly seen with paraganglioma growth. However, malignant tumors are only believed to represent 5% of cases, a statistic that is complicated by the lack of a clear consensus on the criterion necessary to distinguish benign versus malignant disease [7–9]. An increased mitotic index, radiographic evidence of tumor necrosis, and evidence of invasion into vascular and neural structures of the tympanic cavity are considered to be hallmarks of more aggressive disease. Yet, classic aggressive histopathological features do not generally define malignant disease, and it has even been observed in pheochromocytomas, which arise from a similar progenitor cell, that an inverse relationship exists between clinical behavior and cellular atypia, such that some of the more histologically abnormal appearing tumors are more indolent clinically [5]. At present, malignancy in paraganglioma tumors is generally associated with the presence of metastasis, regardless of histopathology findings [5, 10].

Though paragangliomas throughout the body appear to have the capacity for neurosecretory function, actively secreting TP are exceptionally uncommon, and the presence of elevated catecholamine markers should raise suspicion for a coexistent, separate abdominal, or thoracic pheochromocytoma. Pheochromocytomas of the adrenal medulla frequently contain chromaffin paraganglion cells that secrete dopamine, norepinephrine, and/or epinephrine. Nonchromaffin paragangliomas of the head and neck, in contrast, are functional in less than 5% of cases [5, 11, 12]. Furthermore, it is also noteworthy that norepinephrine secretion generally predominates in this rare subset of cases due to a lack of the enzyme phenylethanolamine N-methyltransferase in extramedullary paragangliomas [13]. Despite it being uncommon to identify a secreting paraganglioma in the temporal bone, the consequences of encountering one unexpectedly during surgical management can be fatal. Historically, preoperative venous sampling was encouraged prior to surgical

management [7, 10, 11]. Over time, however, the diagnostic options to identify a secreting tumor have evolved such that laboratory testing of blood and urine samples can reliably identify inappropriate concentrations of catecholamines or catecholamine by-products. The diagnostic workup for functional tumors is discussed in more detail later in the chapter.

As with many tumors of the head and neck, paragangliomas have been increasingly subjected to genetic analysis. Some of the initial work in this regard identified so-called paraganglioma loci (PGL) on chromosomes 1 and 11, which were associated with co-occurrence of paraganglioma tumors and pheochromocytomas [14–17]. Presently, it is thought that a familial predisposition to tumor development is responsible for at least 10% of paraganglioma cases, and there are at least 12 distinct syndromes that carry a propensity for paraganglioma development including multiple endocrine neoplasia types 2A and 2B, neurofibromatosis type 1, and von Hippel-Lindau [18, 19]. Recent work has focused on the relevance of succinate dehydrogenase (SDH) in tumor pathogenesis, and a variety of different aberrations have been recognized [20, 21]. In some cases, Mendelian inheritance thorough an autosomal dominant pattern has been reported [22, 23]. While the relevance of tumor genetics on clinical behavior is not always clear, it has been established that certain mutations, such as those arising at SDHB, may have implications on the potential for accelerated growth and metastasis [22, 24]. Though a widely available, cost-effective means for genetic testing of paraganglioma remains elusive, current research on this subject would suggest that new diagnostic and therapeutic options targeting the genetic basis of tumorigenesis may soon be realized [18].

Diagnosis and Workup

When a TP is suspected, a thorough medial history and physical exam can provide essential information regarding the diagnosis. A large series of TP patients was recently compiled by Carlson et al., which reinforced some of the previously identified trends regarding symptom profile, exam findings, and demographics [25]. Patients were most commonly female, and a bimodal age distribution was seen with peaks in around 20 and 60 years. A majority of patients ultimately diagnosed with a TP were found to be symptomatic at the time of presentation, with pulsatile tinnitus (81.4%), subjective hearing loss (77.1%), and aural fullness (70.2%) being the most common complaints. With larger tumors, growth through the tympanic membrane or into the eustachian tube can be responsible for otorrhagia and epistaxis, respectively [25, 26]. Though the probability of encountering a secretory TP is generally low, a symptom profile that includes episodic hypertension, palpitations, headaches, flushing, or diarrhea should be noteworthy. On exam, TP generally appear as a red or flesh-colored mass within the tympanic space (Fig. 11.1). In some occasions, the mass is entirely visualized through the tympanic membrane, while in others, the full extent of the tumor cannot be seen. Brown's sign, which consists of visible tumor blanching with pneumatic otoscopy, can be seen in approximately

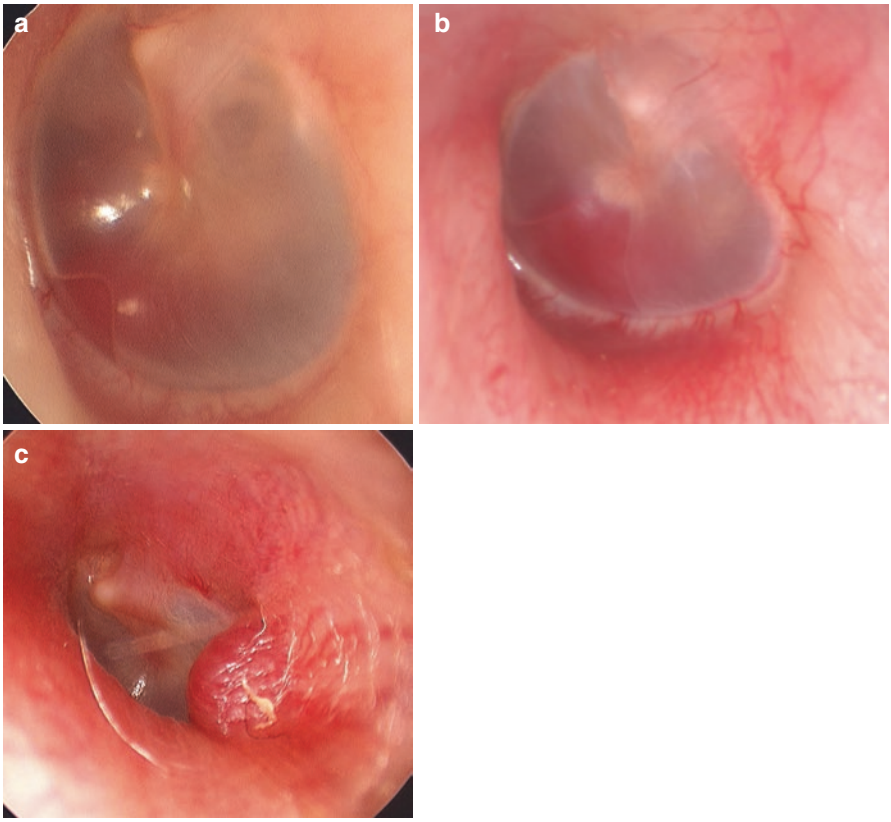

Fig. 11.1 Otoendoscopic appearance of temporal bone paragangliomas. (**a**) Tympanic paraganglioma, (**b**) jugular paraganglioma, (**c**) facial paraganglioma

half of cases [25]. As larger TP and jugular paraganglioma can have similar clinical features at the time of presentation, evaluation for lower cranial neuropathies (IX–XII) through medical history and physical exam is important to help distinguish between these two related entities. Cranial neuropathies, in general, are rare with TP tumors [25].

A comprehensive diagnostic workup is necessary in the evaluation of a temporal bone paraganglioma. Primarily, audiologic testing should be performed to objectively assess hearing. Conductive hearing losses are commonly seen, with an average preoperative air-bone gap of approximately 18 dB [25]. Sensorineural hearing loss is generally rare, though more extensive tumors can occasionally erode into the otic capsule. To fully assess the extent of disease and the structures affected by tumor growth, diagnostic imaging is of paramount importance. Historically, angiography and venography with polytomography were routinely used for diagnostic purposes [27]. In most cases involving temporal bone tumors, these modalities have largely been replaced in favor of computed tomography (CT) and magnetic

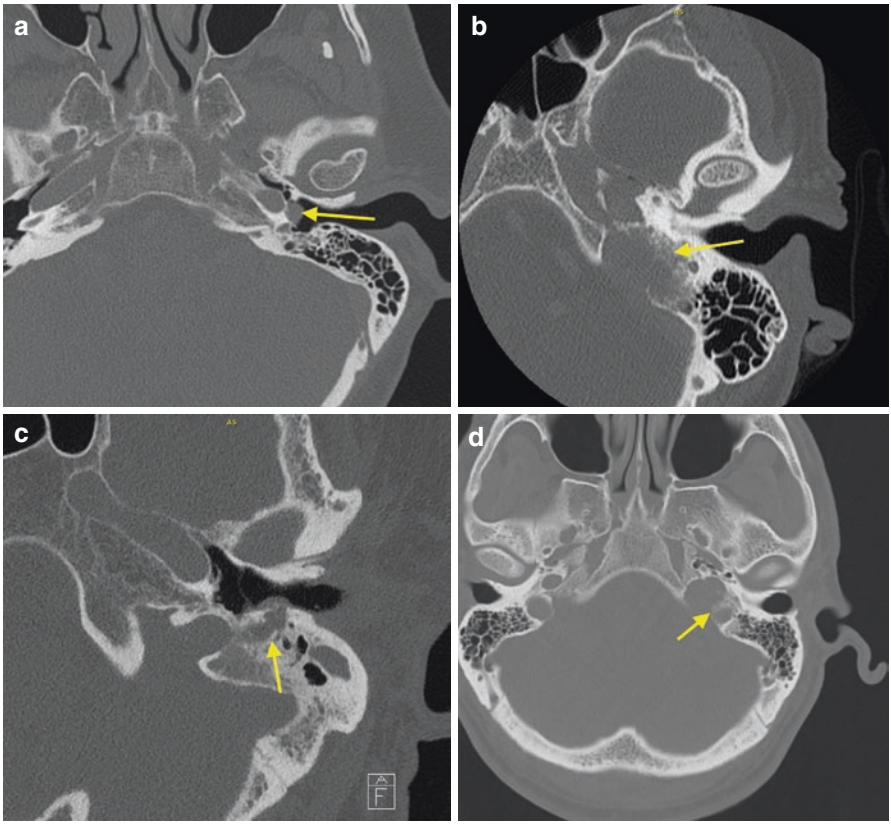

Fig. 11.2 Radiographic comparison of skull base paragangliomas using computed tomography. (**a**) Tympanic paraganglioma tumor, (**b**) jugular paraganglioma tumor, (**c**) facial paraganglioma tumor, and (**d**) vagal paraganglioma tumor

resonance imaging (MRI) (Fig. 11.2). The performance of a contrast-enhanced, high-resolution CT scan of the temporal bone affords visualization of the bony erosion associated with tumor development, which can be helpful to distinguish lesions arising from the jugular bulb from those primarily within the middle ear. Specifically, preservation of the bony floor of the hypotympanum and jugulotympanic spine suggests the diagnosis of TP over JP. Furthermore, with regard to tumor expansion, an assessment of the osseous boundaries surrounding the inner ear, facial nerve, temporomandibular joint, intracranial space, and great vessels can help with surgical planning and patient counseling. It is also valuable to note that different lesions can mimic temporal bone paraganglioma on clinical assessment, and imaging can be helpful to distinguish between potential pathologies [25]. To this end, MRI can be a valuable adjunct to CT when considering the characteristic radiologic appearance of a paraganglioma. While CT cannot readily distinguish the density of a tumor mass

within the temporal bone, a high-resolution MRI with and without contrast demonstrates the enhancement expected of this vascular tumor along with the flow voids that produce a "salt and pepper" appearance. While small TP tumors confined to the middle ear space may not always require an MRI for further characterization, this test can be particularly helpful to distinguish a larger tumor from trapped effusions within the temporal bone and to assess the presence of synchronous disease in the neck. Generally, a CT of the temporal bone and neck with and without contrast can be the primary evaluation of a patient presenting with clinical signs of a TP. If ambiguity remains, an MRI with and without contrast can provide further clarity as to the extent of disease locally and regionally.

The contemporary surgeon should consider secreting tumors and genetic predispositions to tumor development in the initial evaluation of a patient with a tympanic or jugular paraganglioma. As discussed above, certain symptoms at presentation should raise suspicion for a tumor with neurosecretory function. When these symptoms are present, analysis of serum and urine for catecholamines and catecholamine by-products is warranted. The use of ipsilateral jugular venous sampling is no longer encouraged for routine evaluation. With regard to genetic evaluation, patients with multiple paraganglioma neoplasms, with a paraganglioma tumor before 40 years of age, and with a clear family history of paraganglioma development may benefit from genetic screening [28]. In addition to the value of genetic counseling when a familial predisposition exists, genotyping may also be relevant to the potential for malignant transformation in existing tumors [22]. Knowing the wide variety of genetic aberrations that can be relevant to paraganglioma, one potential algorithm for a genetic workup suggested by Neumann et al. in 2009 includes an initial evaluation of loci relevant to SDHD and SDHB [29].

One of the final steps in TP evaluation is tumor staging. Many different classification systems have been proposed for TP, though two have historically predominated: Fisch-Mattox [30] and Glasscock-Jackson (Table 11.1) [31]. The most notable difference between the two systems is found in their handling of tympanic and jugular paraganglioma tumors. When using the Fisch-Mattox scale, tympanic and jugular paraganglioma are on one disease spectrum, while Glasscock-Jackson has separate staging tools for either tumor. At present, the most relevant use of the staging systems may lie in the determination of an appropriate surgical approach to use when planning treatment, as discussed below.

Table 11.1 The Glasscock-Jackson staging system for tympanic paraganglioma

Stage	Definition
I	All tumor margins visible on otoscopy
II	Tumor fills the middle ear, and margins are not visible
III	Tumor extends into the mastoid air cells
IV	Tumor erodes through the tympanic membrane and/or the bone of the external auditory canal

Treatment and Prognosis

Surgery remains the gold standard for the management of TP. In most cases, complete tumor excision and symptom relief are achievable. However, before proceeding to the operating room, preoperative surgical planning is absolutely necessary. Given the vascular nature of these tumors, surgery can be particularly bloody. Preoperative angiography with embolization is most commonly discussed in the context of jugular paraganglioma; however, embolization of advanced stage TP may also be considered. While intraoperative bleeding during TP excision is not expected to cause hemodynamic instability, the anesthesia team should be aware of the potential for blood loss beyond what is generally seen with chronic ear surgery. Furthermore, as with any otologic case, aggressive management of intraoperative hypertension and tachycardia may help to lessen the degree of bleeding seen while handling inflamed tissue. Facial nerve monitoring should be considered in every TP surgery, due to the probability that tumor bleeding could obscure visualization within the middle ear. In cases that involve a tumor with neurosecretory function, the surgical and anesthesia teams must be prepared for the consequences of tumor manipulation. With the assistance of an endocrinologist, perioperative pharmacologic therapy can be sought to prevent an adrenergic crisis, particularly in patients who habitually use alpha- or beta-blocker drugs [32].

The most appropriate surgical approach to a TP is dictated by the size and extent of the tumor. When considering the Glasscock-Jackson staging system, transcanal excision can be considered to address stage I disease. Atticotomy and hypotympanotomy, respectively, can also be used to address disease that extends superiorly into the attic or inferiorly into the hypotympanum [33]. With stage II–IV disease, a postauricular incision is generally performed. With exposure to the mastoid cortex, a mastoidectomy and a posterior tympanotomy can be used for additional visualization of tumor margins. In some cases, the performance of an extended facial recess can be necessary to resect inferior extension of a tumor [34]. For class IV disease with extensive ear canal erosion, a modified radical mastoidectomy can be used to ensure complete tumor extirpation. In cases where advanced sensorineural hearing loss exists preoperatively, a subtotal petrosectomy with blind-sac canal closure is considered [25].

With contemporary microsurgical techniques, total resection can generally be expected, with contemporary series reporting tumor control rates approaching 100%. In anticipation of tumor bleeding, surgeons should be prepared with substrates such as cotton and Gelfoam® (Pfizer, New York) soaked in thrombin. Bone wax can also be useful when seeking to control bleeding arising from vessels within the bone of the middle ear. Additionally, the use of a laser or micro bipolar cautery often helps to achieve timely hemostasis during tumor dissection [35–37]. Dissection initially focuses on determining the tumor extent as well as the relationship of the tumor to the ossicles, the facial nerve, the tympanic membrane, the great vessels, and the inner ear. If a tumor is found to be densely adherent to one of these structures, attention should initially focus on freeing the other parts of the tumor before ultimately

returning to the problematic area. Once the tumor has successfully been freed from its attachments, the location of the major vascular supply can be determined, and this vessel, frequently a derivative of the ascending pharyngeal artery, can be managed with cautery, laser, or bone wax [38]. The tumor is then avulsed from the middle ear cavity. Tympanoplasty, canal reconstruction, and/or ossicular reconstruction may be necessary prior to termination of the case. Rarely, tumors cannot be readily separated from important structures in the middle ear or mastoid, such as the facial nerve, or petrous carotid. In this situation, it is generally advocated that a subtotal resection be performed, leaving the tumor adherent to the vital structure in order to avoid unnecessary morbidity. Following a subtotal resection, clinical and radiographic disease observation can be utilized to monitor tumor growth, which is not assured [25].

In some cases, alternatives to surgical management must be pursued due to patient comorbidities. Not every patient with a TP tumor can withstand general anesthesia. In such a situation, clinical and radiographic tumor observation is an option, and patients should be counseled as to the potential for disease progression and the consequences associated with tumor bleeding in the ear canal as well as acquired dysfunction of the facial nerve and inner ear. However, even with large tumors, the incidence of the latter is relatively rare [25]. Since the great majority of TP can be removed safely with minimal morbidity and result in symptomatic improvement, radiosurgery is generally reserved for those that cannot tolerate surgical excision and have growing tumors [39, 40].

Looking Forward

The emergence of primarily endoscopic ear surgery may bear relevance to the surgical management of TP tumors. The degree of visualization achievable with a straight or angled endoscope is technically superior to that of an operating microscope [41]. Thus, it stands to reason that tumor extirpation may be facilitated by the use of endoscopes to a degree that would alter the standard correlations between tumor stage and recommended surgical approach listed above. However, the challenge of achieving efficient surgical dissection while simultaneously holding an endoscope and managing tumor bleeding remains problematic. For this endeavor, innovative uses of existing surgical tools, such as an ultrasonic aspirator, may ultimately prove useful [42].

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Chapter 12
Radiotherapy and Radiosurgery for Jugular Paraganglioma

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Abbreviations

JP	Jugular paraganglioma
SRS	Stereotactic radiosurgery
CN	Cranial nerve

Introduction

Surgical resection of jugular paragangliomas (JPs) is challenging. There is a very high risk of irreversible dysphagia, dysphonia, and other potentially life-threatening morbidity with gross total resection of medium and large tumors due to the tumor's inherent

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hypervascularity, insinuating growth pattern, and adherence to cranial nerves. Since the majority of JPs are benign and follow an insidious growth pattern, the focus of contemporary management has shifted from disease eradication to maintenance of quality of life by balancing morbidity incurred by tumor and treatment. This has led to the increased popularity of nonoperative treatment of these and other benign tumors of the lateral skull base, such as vestibular schwannoma. The subsequent refinement of highly conformal radiation delivery techniques and accumulation of positive experience over the last 70 years has allowed for excellent tumor control rates with minimal treatment morbidity. This chapter reviews the relevant tumor biology and history of radiotherapy for JP in the modern era and focuses on the expanding role of stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) in the primary, adjuvant, and salvage treatment of JPs. Functional outcomes are reviewed with particular focus on cranial nerve (CN) function, symptoms, and hearing.

Radiosensitivity of Jugular Paraganglioma

The rationale for irradiation of JPs is twofold: direct cytotoxicity and fibrosis of feeding vessels resulting in tumor ischemia. As a benign, slow-growing tumor, the radiosensitivity of constituent cells (chief and sustentacular cells) was questioned in initial reports. Brackmann in 1972 presented histopathologic findings in seven patients who underwent initial radiotherapy followed by surgery. Cumulative dose ranged from 20 to 40 Gy administered using orthovoltage X-rays or cobalt-60 sources. In some cases, hyalinization of vessel walls or endarteritis proliferans were discovered, but in all seven specimens, remaining cells appeared viable. Interestingly, the size and vascularity of one tumor decreased considerably; later, the residual tumor was resected, and histopathology demonstrated the same number of vascular channels present within the specimen albeit with vessel wall changes. These findings led to the conclusion that tumor cells are radioresistant and that radiation should be reserved for patients who cannot undergo surgery [1]. Indeed, it is logical that cell viability was demonstrated given that these tumors exhibited growth necessitating surgical salvage. Furthermore, in the context of modern radiation treatment protocols, the dose utilized was quite low. Two years later, Spector et al. reported histopathologic and arteriographic findings in a subset of patients with JP treated with primary, neoadjuvant, or adjuvant radiation. Chief cells exhibited greater nuclear atypia and no mitoses with surrounding inflammation. Arteriograms demonstrated persistent tumor vascularity in spite of histopathologic evidence of vascular fibrosis or degeneration [2]. In light of later series reporting either stability or tumor shrinkage after radiotherapy, one can conclude that endovascular changes combined with DNA damage that creates nonlethal cell cycle arrest render these tumors, on the whole, “radiosensitive,” even though the strictest definition of “cure” would not apply.

External Beam Radiotherapy

The earliest reports of radiotherapy for JP described the administration of orthovoltage X-rays in a fractionated manner, with a wide range of cumulative doses reported. Though the overall number of patients treated with this technique was small, the combination of variable tumor control and frequent osteoradionecrosis of the temporal bone led to its abandonment [3]. Megavoltage devices utilizing linear accelerators or cobalt-60 sources with more advanced dosimetry calculation methods were adopted and utilized widely for JPs and cervical paragangliomas throughout the 1980s and 1990s [3].

There is often an overlap in the terminology used for modern RT. For the remainder of this discussion, the term "stereotactic radiosurgery" will denote stereotactically guided, single-session radiation delivery. Stereotactic RT includes fractionated regimens (20–28 sessions) or hypofractionated regimens (3–7 sessions) [4]. The cumulative dose to the target is not necessarily equivalent, however. In fractionated RT, devices that administer megavoltage X-rays or radiation from cobalt-60 sources in a conformal arrangement are used to deliver a high cumulative dose (ranging from 30 to 60 Gy; most commonly 45 Gy) in a fractionated manner (e.g., 1.8 Gy per treatment in 25 fractions). Local control, typically defined as no radiographic evidence of tumor progression, is in the 61–99% range over 10–15-year follow-up periods [5–10]. Complications include radiation mucositis, dental caries, trismus related to temporomandibular joint dysfunction, otitis externa and media, mastoiditis, cholesteatoma, and sensorineural hearing loss. One case of a lethal radiation-induced fibrosarcoma was reported 15 years after completing RT [11]. Cranial nerve palsies, encephalopathy, and temporal bone necrosis were reported in cases where higher doses (greater than 50 Gy) were utilized [12]. Today, fractionated RT is reserved primarily for large tumors that extend beyond the treatable areas of SRS and/or entail a high risk of catastrophic cranial nerve palsy or vascular injury if surgically resected.

Stereotactic Radiosurgery and Hypofractionated Stereotactic Radiotherapy

Background

Unlike conventional EBRT, SRS and hypofractionated SRT utilize highly conformal techniques to deliver radiation with submillimeter accuracy to limit collateral effects on nearby tissues. A neurosurgeon or neurotologist, working with a radiation oncologist and physicist, develops a dose plan based on thin slice MR and CT studies and at times with the aid of angiography which may help delineate tumor boundaries. The two delivery methods studied most extensively are the Leksell Gamma Knife (Elekta AB, Norcross, GA) and linear accelerator-based systems such as CyberKnife (Accuray, Sunnyvale, CA, USA) and Novalis (Brainlab, Westchester, IL, USA). The Gamma Knife Perfexion system is shown in Fig. 12.1.

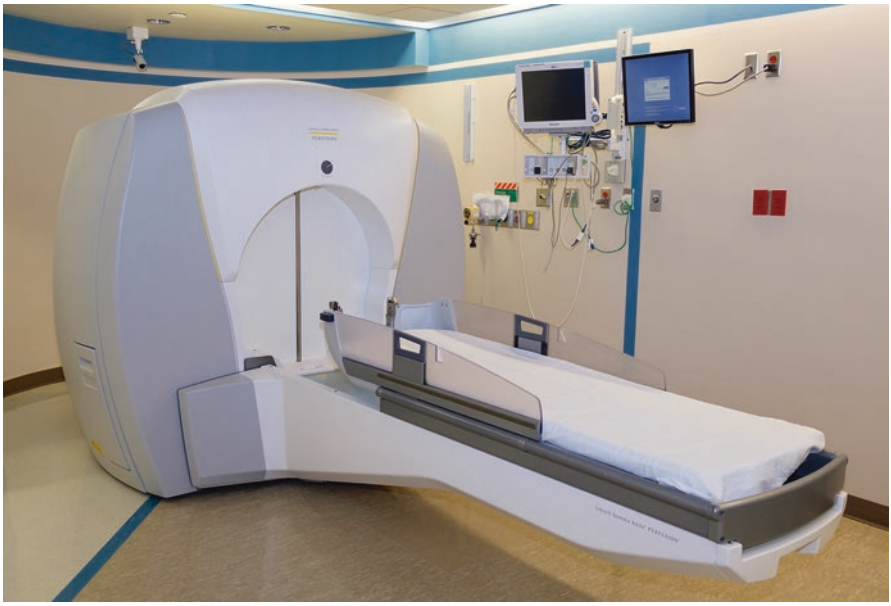

Fig. 12.1 Leksell Gamma Knife Perfexion (Elekta AB, Norcross, GA)

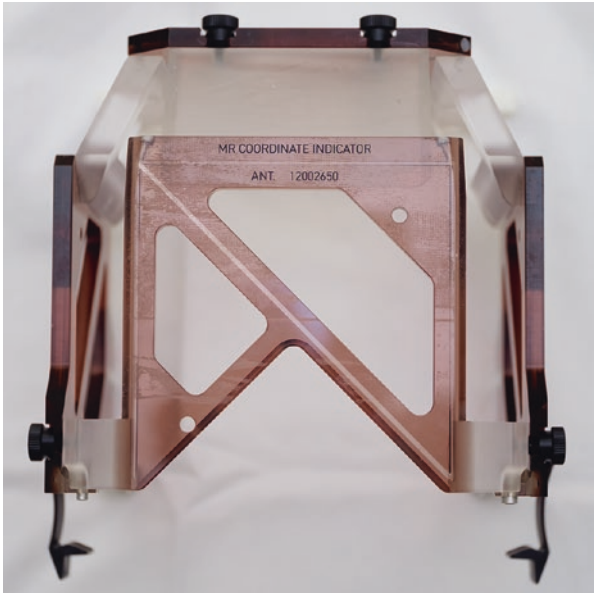

Fig. 12.2 Fiducial box utilized for pretreatment imaging (CT and MRI) prior to stereotactic radiosurgery

Developed by Lars Leksell in the mid-twentieth century, the Gamma Knife radiosurgical system utilizes a headframe apparatus (Fig. 12.2) which helps immobilize the head during treatment and also allows for fiducial markers during imaging to provide submillimeter stereotactic accuracy. Collimated beams of radiation from either 201 (models U, B, and C) or 192 (model Perfexion) cobalt-60 sources are used to produce highly conformal single fraction radiation dose plans.

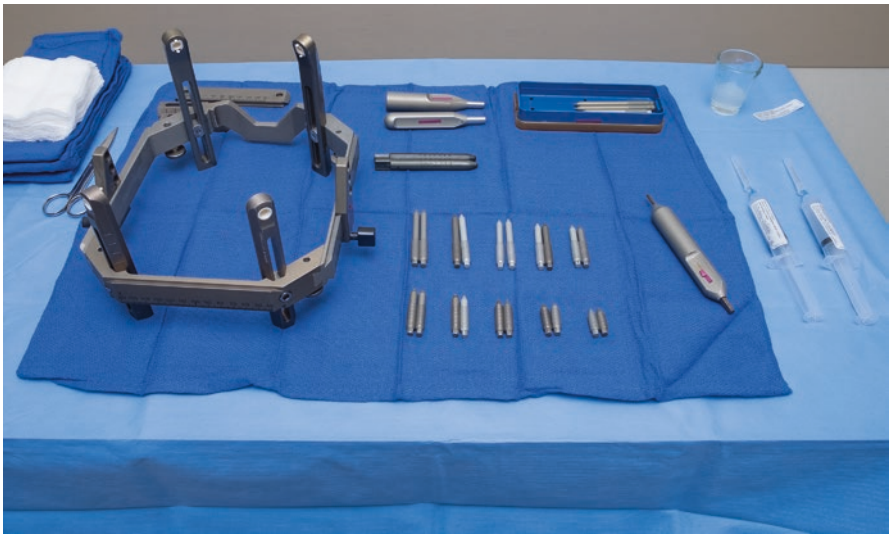

Fig. 12.3 Headframe assembly used for cranial stabilization during Gamma Knife treatment

Automated coordinate adjustments allow for rapid stereotactic dose delivery. Advantages of the Gamma Knife system include the ability to utilize multiple isocenters of radiation (ranging from a single focus to more than 20) to conform the delivery field (Fig. 12.3). This is especially useful in JPs, which grow in a more infiltrative, irregular pattern through the jugular foramen or within the temporal bone. With the latest iteration of the Gamma Knife system, tumors with extension to the C2 vertebra can be treated. Modifications including the use of a relocatable frame or frameless techniques have been used for lower cervical lesions.

Linear accelerator-based SRT systems utilize mini-multileaf collimators to focus the delivery of megavoltage X-rays. While systems in use during the 1990s required a headframe for stereotaxis, the CyberKnife system utilizes a linear accelerator attached to a robotic arm to deliver beams without the need for rigid skull fixation. Movements of the patient are detected by the system, and adjustments are made in subsequent incremental dose administrations, resulting in a negligible overall error. Continuous registration of the linear accelerator position and the patient allow for treatment of lesions below the cranial base without compromising stereotactic accuracy [13]. The CyberKnife utilizes fewer beams (roughly 100 versus 192 beams with the Gamma Knife Perfexion system), resulting in a less steep dose drop-off from the target volume [14]. The total cumulative dose is most commonly delivered in a hypofractionated manner (three to seven sessions) but can be performed in a single session. Results with each system are discussed later in this chapter.

Prior to the publication of series demonstrating successful tumor control, the typical candidates for radiotherapy were elderly, medically infirm, or those with very large tumors. With the discovery that long-term tumor control is possible with SRS or hypofractionated SRT, all patients are increasingly being offered these options as primary treatment. Certain methodological limitations of present series should be noted to interpret these data accurately. Accurate tumor size estimation and determining strict tumor control on serial posttreatment imaging is challenging in JP. Volumetric tumor

measurements performed with formulae utilizing linear or radial measurements are of questionable value given the non-ellipsoid shape of most JPs. Though rarely used, tracing the area of tumor on each MRI slice and integrating the result likely achieve the greatest accuracy in estimating tumor volume and detecting changes within the resolution of the imaging device [15]. Even with this approach, variation in scanner type and slice thickness can introduce measurement error. Relative to the slow-growing nature of most JPs, the duration of follow-up in most large series may be too short to truly detect progression. Subsequent analyses of the same patients will be valuable to validate these estimates. Finally, akin to the vestibular schwannoma literature, understanding the natural history of untreated JP will more clearly delineate tumor control rates with stereotactic radiation. Since most centers employ upfront treatment of JP, it largely remains unknown what percentage of tumors do not grow or result in progressive cranial neuropathy if left untreated. Currently, very few studies from highly selected patient cohorts have reported the clinical course of observed JP [16, 17].

In this section, the treatment of JP with SRS and hypofractionated SRT is discussed, with an emphasis on the key clinical situations where this approach may be useful: primary treatment, treatment of residual tumor after subtotal resection, treatment of tumor recurrence, and treatment of catecholamine secreting tumors. In the interest of clarity and consistency with currently accepted radiosurgical practices, the studies presented met the following criteria: (1) radiation was delivered using contemporary dose and delivery parameters, (2) appropriate reporting of serial tumor volume assessment was available, and (3) results for patients treated with primary SRS or SRT were separable from those who underwent prior treatment.

Primary Treatment

The majority of patients with JP are candidates for radiosurgery or hypofractionated SRT. Patients with tumors causing brainstem compression or obstructive hydrocephalus should be treated with surgery, reserving SRS for treatment of residual or recurrent tumor. Very large tumors may not be appropriate candidates for radiosurgery as the dose required may place nearby normal structures at greater risk. Inherent limitations of the delivery device (i.e., caudal extension below the C2 vertebra in the case of Gamma Knife) must also be taken into consideration.

Consensus regarding treatment parameters has been reached over the past two decades. The recommended marginal tumor dose (prescribed most commonly to the 50% isodose line when the gamma unit is utilized) is 15–18 Gy, resulting in a maximum dose of 30–36 Gy. In one series of 44 patients followed for a median of 118 months, the likelihood of tumor regression was higher with a minimum marginal dose of 15 Gy [18]. In the Gamma Knife system, the number of isocenters does not correlate to tumor volume and instead depends on the shape and extent of the tumor. For example, tumors may insinuate into the mastoid or petrous apex while also extending intraluminally within the sigmoid sinus or into musculature near the jugular foramen. Single fraction therapy has not been found to be significantly different than multiple fraction therapy (assuming similar total dose) in terms of tumor control or acute toxicity [19]. Table 12.1 summarizes available data for SRS and SRT in the primary treatment of JP. Two meta-analyses published in 2011

Table 12.1 Results of primary radiosurgery abstracted from available case series

Authors (date)	Radiation source	Number of tumors	Average marginal dose (Gy)	Tumor control rate (%)	Follow-up duration	Definition of failure
Chen et al. (2010) [36]	GK	11	14.4, single fraction	73	Median 32 mos.	>15% growth
Dobberpuhl et al. (2016) [31]	GK	12	15.5, single fraction	100	Mean 28 mos.	Growth
Foote et al. (2002) [46]	GK	13	15, single fraction[a]	100	Median 37 mos.[a]	Growth
Genc et al. (2010) [39]	GK	7	15.4, single fraction	10	Median 37 mos.	Growth
Gerosa et al. (2006) [47]	GK	3	16.3, single fraction	100	Median 32 mos.	Growth
Pollock (2004) [4]	GK	19	14.9, single fraction[a]	95	Mean 44 mos.[a]	Growth
Sharma et al. (2008) [48]	GK	6	17.3, single fraction	100	Median 20 mos.	Not defined, but none progressed
Sheehan et al. (2012) [30]	GK	83	14.8[a], single fraction	86[a]	Median 50.5 mos.	Growth
Hurmuz et al. (2013) [49]	CyberKnife	13[a] (one had previous surgery, unclear extent)	25, median 5 fractions	100 (13/13)	Median 39 mos.	Absence of progressive disease; regression as 20% decrease in volume
Poznanovic et al. (2006) [41]	Novalis	8	15, single fraction	100 (8/8)	Median 18 mos.	Not defined, but none progressed

[a]Actuarial tumor control rate at 5 years
[b]Reported for entire group (primary and salvage cases)

provide pooled estimates of tumor control rates with SRS or hypofractionated SRT. While primary and salvage treatment was combined in some cases, the overall tumor control rates reported by each study group were 95 [20] and 97% [21] for 335 and 339 patients, respectively, with a mean follow-up of 71 months in the latter group.

Stereotactic Radiosurgery or Radiotherapy After Subtotal Resection

Subtotal resection of large JPs is often necessary to preserve cranial nerve function and avoid vascular injury. Since up to 70% of patients with JPs exhibit normal lower cranial nerve function at presentation [22], a shift toward less aggressive surgical resection has occurred, with the goal of preserving neurologic function for as long as possible. A recent series evaluating 12 patients, with a mean follow-up of 45 months, demonstrated that the growth of residual tumor is less likely if greater than 80% of the tumor is resected [23]. Further studies with longer follow-up and larger patient numbers will be required to confirm these promising, but preliminary results. Given that the majority of tumors are embolized preoperatively potentially limiting their growth potential, it is reasonable to observe the remaining tumor until symptoms or significant enlargement is observed. In many cases, particularly in older patients, treatment may be deferred indefinitely.

While large series supporting these assertions are unavailable, SRS has been shown to be a useful salvage option with good tumor control. In spite of tumor residua often being located medial to the jugular bulb (as this is considered the limit of safe tumor dissection with preservation of lower cranial nerve function), the incidence of new cranial neuropathy after salvage radiosurgery is low [24, 25]. For this reason, planned SRS after subtotal resection (rather than observation alone) is advisable in younger patients or those with tumors that may present a future risk to cranial nerves. Prior to treatment, allowing postsurgical inflammation to resolve is helpful to better distinguish residual tumor from normal tissue, although postoperative targeting is often challenging regardless of timing.

Radiation Treatment of Recurrent Jugular Paraganglioma

Recurrent JP presents a formidable challenge. Defined as residual disease exhibiting growth, these may represent more aggressive JP variants and may exhibit greater variability in presentation and response to treatment [26]. Merely determining the extent of tumor on MR imaging is challenging; even high-resolution modern techniques are often unable to resolve differences between fibrosis, inflammation, and tumor. Large, rapidly growing, or unusually infiltrative JPs do not necessarily exhibit cytologic evidence of aggressiveness in the way that other neoplasms often

Table 12.2 Results of salvage radiosurgery abstracted from available case series

Authors (date)	Radiation source	Number of tumors	Average marginal dose (Gy)	Tumor control rate (%)	Follow up duration	Definition of failure
Chen et al. (2010) [36]	GK	4	15, single fraction	100	Median 70 mos.	>15% growth
Foote et al. (2002) [46]	GK	12	15, single fraction[a]	100	Median 37 mos.[a]	Growth
Genc et al. (2010) [39]	GK	12	15.6, single fraction	92	Median 47 mos.	Growth
Gerosa et al. (2006)	GK	17	17.5, single fraction	100	Median 41 mos.	Growth
Pollock (2004) [4]	GK	23	14.9, single fraction[a]	100	Median 44 mos.[a]	Growth
Sharma et al. (2008)	GK	4	17, single fraction	100	Median 32 mos.	Not defined, but none progressed
Sheehan et al. (2012) [30]	GK	51	14.8,[a] single fraction	90	Median 60 mos.	Growth

[a]Calculated based on data from entire cohort, which included patients treated for primary JP

do [27]. Therefore, it is difficult to predict both the growth potential of residual disease and the response of a recurrence to radiotherapy. Nevertheless, radiosurgery has been shown to play a key role in these scenarios particularly when the morbidity of repeat surgical resection with the goal of complete tumor extirpation is unacceptable. The first is the treatment of a tumor recurrence typically discovered months to years after the initial surgical resection. The second is in an adjuvant form, where a subtotal resection of recurrent tumor is performed with planned postoperative radiosurgery. The majority of available series do not differentiate between these clinical situations due to the relative rarity of each, but on the whole, salvage radiosurgery offers excellent long-term tumor control. The results of SRS in this group are summarized in Table 12.2.

Surgery Following Primary Stereotactic Radiosurgery or Radiotherapy

The findings of postradiation stromal fibrosis by Spector et al. in 1974 prompted the authors of that study to explore the role of preoperative radiotherapy. In a subset of five patients who underwent surgery for radiation failure, the authors noted increased ease of dissection [28]. This is in contradiction to the surgical consequences of neoadjuvant radiotherapy in other tumors of the head and neck. Perhaps as an effect of high radiosurgical success rates and a shift toward observation of stable tumors, this treatment strategy is seldom employed today. Occasionally, patients with stable tumors have persistent audiologic symptoms such as pulsatile tinnitus or conductive

hearing loss when a substantial middle ear tumor component is present. In these situations, the middle ear component may be safely resected with symptom improvement while leaving the remainder of the tumor undisturbed.

Functional Outcomes

Risk to Cranial Nerves

As reviewed in detail in other areas of this book, ipsilateral deficits of one or more lower cranial nerves can result in a marked detriment to quality of life. Overall, the probability of developing a new cranial neuropathy following SRS, irrespective of tumor control status, is likely between 3 and 16% [21, 29, 30]. The rate of posttreatment CN X, XI, and XII deficits was reported by Ivan et al. in 2011 in a meta-analysis of 339 patients who underwent primary SRS. Over a mean follow-up of 71 months, the rates of CN, X, XI, and XII deficits were 9.7%, 12%, and 8.7%, respectively [21]. In a large single-center experience of 75 cases, Ibrahim et al. reported that only two patients developed a permanent CN deficit following treatment (a vocal cord paresis and a partial facial nerve palsy). The median dose to the tumor margin was 18 Gy. Univariate and multivariate analysis demonstrated an increased likelihood of cranial nerve damage after SRS in patients who had a preoperative deficit or in those with larger tumors (greater than 7 cm^3) [21].

Hearing

Roughly two-thirds of patients with JP report hearing loss. The majority of available literature characterizes pretreatment hearing status as normal or abnormal and places the latter subset of patients into a "CN VIII deficit" group. However, the majority of hearing loss related to JP is conductive or mixed, and thus any increase in hearing acuity after treatment is likely related to improved ossicular chain and tympanic membrane dynamics from a reduction in middle ear tumor volume. This is countered with the potential for radiation injury to the cochlear hair cells and cochlear nerve. While hearing loss as a clinical outcome is reported among the sequelae of SRS, long-term audiologic follow-up data is not presently available in the literature. One series included pre- and posttreatment audiometric data for seven patients and demonstrated no appreciable change over a minimum follow-up of 13 months [31]. While serial audiometry was not available, Pollock reported subjective hearing decline in 19% of patients with intact hearing before SRS [32]. The potential for delayed hearing decline (as has been well documented in radiosurgery for vestibular schwannoma [33]) cannot be estimated from these data. Furthermore, the precise nature of the insult to the hearing pathway following radiotherapy for JP is likely dissimilar to that which affects vestibular schwannoma patients. In the latter group, at least five potential causes of sensorineural hearing impairment are present: the

effect of tumor apposed to the cochlear nerve, altered cerebrospinal fluid flow dynamics at the fundus, the location of maximal radiation dose being the eighth nerve itself, dose to the cochlear nucleus, and cochlear irradiation (direct hair cell damage and injury to cochlear microvasculature). In most cases, only the last element (cochlear dose) is relevant in JP. As an interesting point, in 2012 Lega et al. concluded that critical thresholds for cochlear dose derived from the vestibular schwannoma literature cannot be extrapolated to JP planning. In this study, including nine patients with a median follow-up of 26 months, three of four patients receiving a cochlear dose of > 8Gy suffered no hearing loss [34]. Long-term audiologic follow-up will be important to characterize the trajectory of hearing impairment in these patients.

Symptom or Cranial Nerve Function Improvement

Common presenting symptoms among patients with JP are discussed elsewhere in this book, but include pulsatile tinnitus, hearing loss (typically conductive), dysarthria, dysphagia, hoarseness, and shoulder weakness. Partial or complete resolution of symptoms likely related to nerve ischemia from tumor impingement has been reported in several series. The resolution or improvement of pulsatile tinnitus from radiation-induced vascular fibrosis has been reported to occur in as many as 50% of patients [30, 31, 35, 36]. The mechanism whereby improvement in vertigo or headache is less clearly understood but has been reported as well [37, 38]. Incremental facial nerve function improvement has been demonstrated in patients with pretreatment paresis [39]. This is less predictable, however, as treatment-related transient or permanent facial weakness is possible as well.

Just as subtle yet important differences in function may exist between two patients with the same House-Brackmann grade of facial paralysis, the same holds true with lower cranial nerve function. For example, a patient with a complete vagal paralysis prior to radiation treatment may report an improvement in swallowing function in spite of no appreciable change on physical examination. In one series, a patient with pretreatment hearing loss, dysphagia, and unilateral vocal fold paralysis reported improvement in swallowing after treatment in spite of no change in tumor size [40]. Though others have reported resolution in hoarseness and tongue atrophy, data regarding objective measures of laryngeal or tongue muscle function are unavailable [41]. While it is difficult to separate treatment effect from compensation, the thought that subclinical improvements in nerve function may occur remains a possibility warranting further study. This said, the opposite situation (i.e., a patient with a preexisting CN palsy exhibiting *poorer* function after direct CN injury) is possible, and more common, after surgery or irradiation. For example, a patient with unilateral vocal fold immobility suggestive of vagal nerve palsy with satisfactory swallowing function who undergoes treatment may experience worsening after treatment. This phenomenon may be attributable to a more complete nerve injury manifesting in loss of vocal fold bulk or tone, combined with loss of pharyngeal muscle coordination and sensation.

Secreting Tumors

Achieving both functional and biologic normalization of catecholamine secretion is important to limit morbidity in patients with secreting tumors, particularly in situations where gross total resection bears unacceptable risk. Radiosurgery has been utilized in the primary treatment of three functional JPs [32, 42, 43] and as salvage treatment after tumor recurrence in one [44]. In each case, near complete normalization was achieved biochemically with concomitant clinical responses over a roughly 3-year follow-up period. In one case, the plasma fractionated normetanephrine concentration increased by roughly 1.5 times within the first 10 months and subsequently fell. Since the patient was on alpha- and beta-blockade, this posttreatment catecholamine "surge" had no appreciable clinical consequence. Normalization or near-normalization of urinary catecholamine levels was achieved in all cases over a roughly 3-year period. Tumor control was achieved in all cases as well. While published experience is limited, these findings render radiosurgery a promising option for secreting tumors. Pharmacologic adrenergic blockade should be considered on a case-by-case basis.

Radiosurgery for Jugular Paraganglioma: The 26-Year Mayo Clinic Experience

Since 1990, over 80 JPs have been treated with radiosurgery at the Mayo Clinic in Rochester, Minnesota. Our protocol consists of outpatient, single-session SRS using Gamma Knife. Prior to treatment, local anesthetic (lidocaine with epinephrine 1:200,000) is infiltrated subcutaneously prior to headframe fixation (Fig. 12.1). The fiducial box (Figs. 12.2 and 12.3) is attached to the frame for same-day imaging, consisting of a 1.0-mm slice thickness non-contrast CT study and a 1.0-mm slice thickness, three-dimensional, gadolinium-enhanced spoiled gradient echo (SPGR) MR study. Data from each study can be fused within the Leksell Gamma Plan (Elekta AB, Norcross, GA) software for treatment planning. For JP, treatment is carried out to the 50% isodose line with a dose to the tumor margin of 16 Gy, such that the maximum tumor dose is 32 Gy; there is little variation in these parameters (Fig. 12.4). If it is anticipated that collateral cochlear irradiation may occur, the cochlea is segmented as a volume within the Gamma Plan software to allow for the minimum, maximum, and mean dose to the entire cochlea volume to be calculated. After the treatment is delivered, patients are dismissed from the facility after a 2-hour observation period. The first posttreatment MRI is obtained at 6 months. Subsequent imaging is obtained at years 1, 2, and 3 and every two years thereafter for tumor surveillance. Additionally, audiometry is performed at each follow-up interval and referral for indirect laryngoscopy, or formal swallow evaluation is undertaken if new symptoms warrant.

Publications by Foote et al. and Pollock summarize available data on tumor control and functional outcomes after SRS for JP at our institution [32, 45, 46]. The

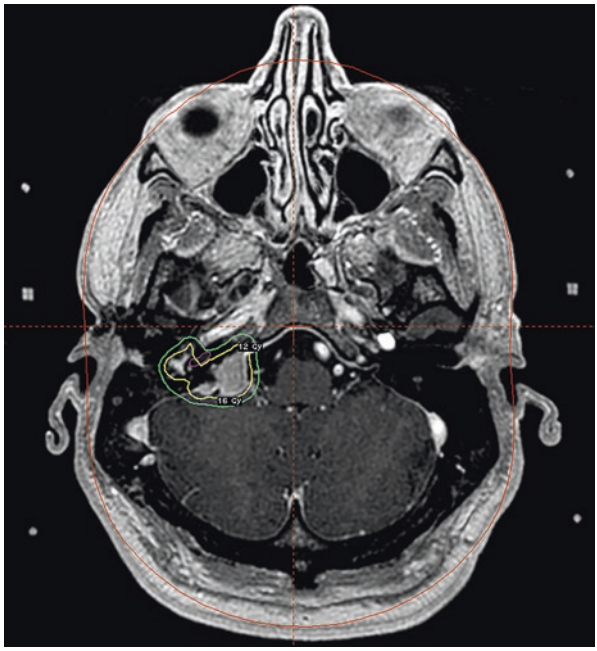

Fig. 12.4 Example of treatment plan using Leksell Gamma Plan software (Elekta AB, Norcross, GA). Isodose lines are marked in yellow and green, with the yellow line representing the 50% isodose line (marginal dose 16 Gy, maximum dose 32 Gy). Note segmentation of the cochlea, allowing for calculation of point dose to the modiolus

overall tumor control rate was 98%, with actuarial progression-free survival of 100% at 7 years. One tumor exhibited growth during follow-up and was treated with a marginal tumor dose of 12 Gy; due to advanced age, he was retreated 8 years later with a marginal tumor dose of 14 Gy. The tumor decreased in size over a 5-year radiographic follow-up interval. The patient above developed an ipsilateral true vocal fold paralysis after salvage radiosurgery. No other patient suffered a new lower cranial nerve deficit following SRS. As cited previously, Pollock reported an actuarial rate of hearing preservation of 81% at 4 years of post-SRS. Given the natural history of late radiation effects, these patients are followed closely to determine if delayed cranial nerve deficits present.

Conclusions

Radiation treatment of JPs has evolved considerably over the last several decades. Modern SRS achieves tumor control in greater than 90% of cases as primary or salvage treatment and has therefore become first-line treatment for primary JP at many centers. Given the slow growth rate of most JPs, it is possible that studies with extended follow-up may reveal a lower tumor control rate due to delayed tumor progression. Therefore, close clinical and radiographic follow-up is warranted for years after initial treatment. Staged SRS following subtotal resection for large tumors or in tumors likely to recur is an effective strategy to achieve symptom

control, limit morbidity, and arrest further tumor growth. Based on published experience from our institution, primary or salvage SRS (for tumor recurrence after surgery) can achieve tumor control rates of over 90% with very low risk of new lower cranial neuropathy. The rate of subjective hearing decline is 19% at 4 years and is likely related to cochlear irradiation. Future study with extended follow-up will aid in determining long-term tumor control, hearing decline, and other risks following radiosurgery.

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Chapter 13
Cranial Nerve VII Rehabilitation

Austin Adams, Alexander Langerman, and Scott Stephan

Introduction

Jugular paragangliomas (JPs) arise from the paraganglion cells located within the adventitia of the jugular bulb [1]. Although typically slow growing and histologically benign, JPs commonly invade the middle ear, mastoid, and neural compartment of the jugular foramen, thereby causing facial nerve and lower cranial nerve (IX, X, XI, XII) deficits. Furthermore, operative intervention and radiotherapy may also result in cranial nerve deficits, and it is important to be aware of and manage cranial nerve injury to minimize their clinical impact on the patient.

In this chapter, we will discuss management of CN VII paralysis and facial nerve rehabilitation. Lower cranial nerve deficits will be addressed in the following chapter when discussing the management of speech and swallowing dysfunction (CN IX–XII) in the setting of JPs.

Risk of Injury

Tumor Invasion

Preoperative cranial neuropathies are common findings, occurring in 10–50% of patients diagnosed with JPs [1, 2]. The lower cranial nerves are most commonly involved; however, facial nerve involvement occurs in as high as 10% of patients [3, 4]. This functional deficit is most commonly caused by direct invasion of the vertical

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(mastoid) segment of the facial nerve, and symptoms can include a wide range of findings including frank paralysis or paresis to more subtle facial twitching or hemifacial spasm [5].

Posttreatment Deficit

Treatment practices for JPs vary among physicians and institutions; however, when intervention is required, management consists of total or subtotal surgical excision and/or radiotherapy. When surgery is performed, preoperative embolization of the lesion is also often utilized. All treatment options have risks and benefits that must be considered as they relate to each individual patient; here we will focus on the implications for facial nerve function.

Selective transfemoral arterial embolization of the tumor's feeding vessels is utilized to decrease operative blood loss which allows for better visualization during resection and reduction in operative time. This is thought to decrease postoperative morbidities and improve the chances of achieving a total resection [1]. At the author's institution, we most commonly embolize with a nonadhesive mixture of ethylene vinyl alcohol, dimethyl sulfoxide (DMSO), and micronized tantalum powder (Onyx; Covidien, Ireland). Cranial neuropathies, including CN VII weakness, have occurred as a direct result of embolization. Gartrell et al. reported a ~ 6% theoretical risk that a patient may harbor a vascular pattern that increased the risks of ischemic injury to the facial nerve if embolization takes place. The facial nerve becomes more vulnerable to ischemic injury when its extratemporal segment derives its vascular supply solely from the stylomastoid artery, a branch from the occipital artery. Similarly, in patients without this vascular pattern, ischemic injury becomes more likely with increasing number of vessels embolized [6].

Surgical removal of tumor poses a more direct risk to the facial nerve. Decisions balancing surgical exposure, extent of tumor removal, and protection of the facial nerve are common surgical dilemmas. Postoperative facial nerve paralysis has been reported as high as 25.5% in patients who underwent total and subtotal resections of JPs [7, 8].

Facial nerve function is also placed at increased risk when facial nerve rerouting is performed to enhance surgical exposure for tumor resection. When compared to leaving the facial nerve in a fallopian bridge (i.e., non-rerouting), short rerouting techniques (mobilizing the mastoid segment from stylomastoid foramen to the second genu) result in similar facial nerve function outcomes. However, when long anterior rerouting (mobilizing the facial nerve from the stylomastoid foramen to the geniculate ganglion), a substantial decline in postoperative facial nerve function is noted. A recent literature review by Odat et al. that included 15 studies and 688 patients examined this issue. Patients in the non-rerouting and short rerouting groups had postoperative House-Brackmann scores of I–II in 95% and 90%, respectively, whereas only 67% of patients in the long rerouting group retained a House-Brackmann score of I–II [9]. This greater risk of facial nerve dysfunction with

greater mobilization may reflect the extent of tumor burden and/or vascular and traumatic changes as a result of mobilization, and decisions must be made on a case-by-case basis. The values provide a guide for operative planning and patient discussions regarding treatment options and anticipated outcomes.

Radiotherapy is a well-validated alternative to surgery that has evolved greatly over the past two decades due to its effectiveness and reported lower morbidity when compared to radical surgical resection [7, 10]. Overall tumor control rates have been reported between 89–100% in the literature, and because of this, radiosurgery is sometimes preferred as the primary treatment modality in select patients [8, 11, 12] Although radiosurgical techniques have limited morbidity, complications may still occur in a small percentage of patients. The most commonly reported cranial nerve complication occurs in CN VIII and lower cranial nerves. One study by Scheick et al. looked at long-term complications of stereotactic radiosurgery with a mean follow-up of 5.3 years. This study showed 7 of 11 (64%) patients reporting worsening CN VIII function, 3 patients (27%) having deficits in CN IX and X, and a 10% rate of injury to CN VII, XI, and XI [12]. Additionally, a meta-analysis by Ivan et al. supported these rates of lower cranial nerve injury by reporting CN IX–XII injury ranging from 9–12% of cases treated with stereotactic radiosurgery [8, 11]. There are studies, however, that have also shown stability and even improvement of cranial nerve function, including improvement in CN VII[10]. Due to the heterogeneity of reporting results of facial nerve function. House-Brackmann grading is difficult to quantify and compare across these studies, and long-term data are required to further characterize tumor control and functional outcomes.

Facial Nerve Repair and Reanimation

As treatment techniques have evolved, the methodology of facial nerve management has advanced as well. As a result of refined radiotherapy, subtotal resection has become a reliable and attractive option for surgeons, especially for tumors intimately involved with the facial nerve or lower cranial nerves [7]. However, facial nerve paresis, from rerouting or from unintentional injury, may occur, and a thorough understanding of repair techniques and management practices will enable appropriate rehabilitation when required.

Facial Nerve Repair and Reinnervation Procedures

Primary Anastomosis

The importance of maintaining facial function combined with improved adjuvant therapies has enabled a more conservative approach toward disease intimately involved with the facial nerve. Although surgical injury or resection is becoming

less common, intraoperative sacrifice of the facial nerve still may be required in some select cases. In these circumstances, the best course of action is primary coaptation when tension-free anastomosis is possible. Primary anastomosis, rather than interposition nerve graft, limits the number of splice interfaces to one rather than two. Both suture techniques as well as fibrin glue have been described when anastomosing the intratemporal segment of the facial nerve [13–15]. Typically two or three interrupted 8–0 or 9–0 monofilament sutures are placed through the epineurium to provide approximation and alignment of the fascicular units. However, the intratemporal and intracranial segments of the facial nerve do not have an epineurium layer to assist with anastomosis. In these circumstances both suture repair and sutureless anastomosis techniques have been described. When sutures are used, they are placed superficially through the perineurium with attempts to avoid disruption of the fascicular units as much as possible. In areas where bony anatomy can assists with keeping the nerve fascicles of the proximal and distal ends of the nerve in alignment, absorbable materials such as Gelfoam (Pfizer Inc., New York, NY), collagen matrix, and fibrin adhesive have been used to assist with neural coaptation [15, 16].

Intratemporal facial nerve mobilization can provide added length when required. However, the blood supply received from the periostium of the fallopian canal is compromised with rerouting, placing theoretic limits on the length of consequence-free mobilization. Despite this limitation, primary anastomosis is thought to be optimal for resected segments 18 mm or less [15]. When tension-free closure is not possible, other repair techniques must be employed.

Interposition Graft

Interposition grafting is the next best option to primary repair. Multiple donor nerves have been described with the most common being the great auricular nerve, medial antebrachial cutaneous nerve, and sural nerve. The great auricular nerve has the advantage of anatomic proximity to JPs and is often times within the surgical field. The path of the great auricular nerve is classically described as originating midway along the SCM coursing superiorly along the lateral aspect of the muscle for approximately 6 cm until it branches into anterior and posterior branches [17]. The medial antebrachial cutaneous nerve and sural nerve provide the advantage of length and are able to provide up to 25 cm of nerve for grafting. The harvesting of these latter nerves requires separate surgical sites with additional morbidities; however, using stair-step incisions provide acceptable cosmetic results. When interposition grafts are anticipated, it is important to counsel patients preoperatively on hypesthesia and loss of sensation in sensory distributions of graft options. The periauricular area is likely to be numb as a result of extensive surgery around the auricle, again favoring the greater auricular nerve. Dorsolateral foot and medial/ulnar surface of the forearm, though well tolerated and "worth" the trade-off for a good donor nerve, are an additional morbidity to be evaluated in the context of patient preference.

With primary repair and interposition grafting, initial return of facial function can be seen at 6 months postoperatively with maximal facial function taking as long as 12–18 months [15]. For these reasons, additional facial reanimation procedures are not typically considered until 1 year postoperatively when satisfactory results have not been obtained. A satisfactory and optimal result in the setting of interposition grafting is considered a House-Brackmann score of III or IV. Therefore, adjuvant procedures may be indicated depending on individual patient's results and personal expectations.

Transposition Grafts

Transposition grafts are an excellent option for facial nerve reinnervation and are often used when a suitable proximal nerve stump is not available, when interposition grafting has failed, or when facial function has not returned in cases where the nerve was not transected. The timing of this technique is an important factor to consider. Although the utility of earlier intervention is under investigation, most clinicians will allow 12–18 months to pass prior to implementing transposition grafting for dynamic facial reanimation. Proponents for earlier repair site the risk of distal motor end plate degeneration as a reason to intervene sooner; however, this must be balanced with the risk of interrupting a regenerating facial nerve. Electromyography (EMG) can be used to help investigate the progress of neural regeneration. EMG begins to demonstrate fibrillation potentials approximately 2–3 weeks after nerve transection, signifying viable but denervated muscle end plates. As neural regenerating is taking place, EMG demonstrates polyphasic action potentials and observation for facial nerve recovery should be considered. For successful reinnervation, a functional motor end plate-muscle unit must be present; therefore, patients are offered transposition grafting when preoperative work-up reveals fibrillation potentials without signs of polyphasic action potentials on EMG. Conversely, if both fibrillation and polyphasic action potentials are absent, there is irreversible fibrosis and facial muscle atrophy resulting in poor candidacy for reinnervation procedures [15, 17].

Several cranial nerves have been evaluated for use in transposition grafting due to the anatomic location and robust amount of myelinated motor axons. Ipsilateral cranial nerves V, IX, XI, and XII have been used in addition to the contralateral cranial nerve VII [17]. A special consideration that must be made with JPs is that ipsilateral lower cranial nerves may not always be suitable given the potential for disease- and treatment-related injury. Furthermore, paresis of the hypoglossal nerve from transposition in a patient that already has a high vagal nerve injury may have devastating consequences to upper aerodigestive function. As with harvesting sensory nerves for interposition grafts, motor deficits with transposition grafting are important to discuss preoperatively with patients and may need to be addressed postoperatively to limit the morbidity associated with resection of these motor nerves.

Masseteric Branch of V3

The trigeminal nerve is comprised of both sensory and motor axons, and it is the motor component of the masseteric nerve that makes it most useful for facial reanimation. The masseteric-facial transposition was first described in 1977 and has become a reliable option for establishing resting tone as well as restoring facial movement [18, 19]. By activating the mastication muscles, the patient is able to elicit facial movements, including smile. This degree of facial animation can vary depending on the intensity of masticatory activation. It has been reported that patients can achieve a full smile with lighter activation of these muscles and experience synkinesis with heavier activation [17]. This ability can enable patients to control upper and lower facial movements somewhat independently for more natural expression. Donor site morbidity is extremely low and almost nonexistent with only a few reports of impairment including masseter muscle atrophy and decreased oral aperture that resolved with physical therapy [20–23]. Due to its acceptable outcomes, low donor-site morbidity, and favorable anatomic location, the masseteric-facial graft is considered a great option for reanimation.

Cranial Nerve XII

The use of the hypoglossal-facial transposition graft is another reliable option for the reconstructive surgeon. Similar nerve caliber and proximity to the extratemporal segments of the facial nerve allow for good anastomosis with limited surgical morbidity. Proponents of this graft have also noted a “functional synergism” between these two nerves citing the mutual participation of cranial nerves VII and XII in speech articulation, swallowing, and mastication [24]. Many anastomosis techniques have been described; however, the end-to-end technique is considered the gold standard due to superior axonal regeneration documented by electrophysiology studies [25]. Other techniques include side-to-end anastomosis, jump grafts, and split hypoglossal graft techniques. A meta-analysis reviewing outcomes from varying techniques found that the great majority of cases achieved House-Brackmann grade IV function or better [26]. As with all techniques, this study also showed patients who underwent surgical intervention within a year of facial nerve loss had better outcomes.

The major drawback of the XII–VII transposition is the varying degrees of hypoglossal nerve deficit that may occur. The various techniques have been developed in attempts to limit the degree of hypoglossal dysfunction; however, all methods require total or partial transection of cranial nerve XII. Speech and articulation difficulties and dysphagia can result after surgery with reports showing that 45–74% of patients experience functional difficulties with speech and swallowing after end-to-end anastomosis [27–29]. These deficits in lingual function can be decreased by

utilizing the end-to-side anastomosis technique. Samii et al. reviewed 17 patients repaired with end-to-side anastomosis and reported one patient (5.8%) with hemiatrophy of the tongue, two patients (11.7%) with swallowing difficulty, and no patients with postoperative speech disorder. Facial nerve function was not found significantly different when compared to the nine patients who underwent end-to-end anastomosis in this same study [30]. The effect of hypoglossal dysfunction on swallowing is obviously attenuated or exacerbated by the functional status of cranial nerves IX and X, which are also at risk when treating JPs.

Cross-face Facial Nerve

Cross-face facial nerve grafting utilizes the contralateral functioning facial nerve to restore facial function on the effected side. This technique has been described in several different ways including direct interposition grafting as well as neurotization of free muscle transfers. One advantage to the cross-face technique is the ability to achieve spontaneous and natural facial movement and smile [17]. A large study that included 548 patients showed that 100% of study participants achieved restoration of a spontaneous smile after undergoing cross-face facial nerve grafting using various techniques [31]. Unfortunately, results are variable and can be inconsistent even when performed by a single surgeon using the same technique [17]. Donor nerve function typically remains fully intact; however, there is an ever-present concern for facial nerve injury or dysfunction on the functional side when using this technique. To limit this risk, more distal branches are utilized. Trying to balance the risks and benefits of this technique, however, leads to less power provided to the paralyzed side. Additionally, surgical morbidity is increased due to the harvest of grafting material, which could include the sural nerve or free tissue transfer of neuromuscular tissue. Given the inconsistent results and risk of bilateral facial nerve dysfunction, many are reluctant to utilize cross-face facial nerve grafting as sole treatment for facial reanimation.

Cranial Nerve XI

The use of the spinal accessory nerve as a transposition graft has been shown to provide tone, facial symmetry, and even voluntary expression [32]. Although the results are encouraging, there are significant downsides to this technique. Mass facial movement with arm movement as well as significant synkinesis has been reported [17]. Significant donor-site morbidities have been reported including deficits in upper extremity abduction and shoulder stiffness and pain [32, 33]. For these reasons, this technique is not widely used.

Adjunctive Procedures

Although facial reanimation and nerve repair can offer reliable and acceptable results, the full range of facial nerve function is not always restored by these aforementioned procedures. In many cases alternative procedures may be required in addition to nerve grafting or as a sole intervention to achieve the desired functional and cosmetic results.

Eye Closure

One of the most important functions of the facial nerve is contraction of the orbicularis oculi muscle to achieve eye closure. This provides mechanical protection of the globe and facilitates lubrication of the surface of the eye. Poor eye closure requires medical management with lubricating eye drops and ointments as well as protective measures while sleeping. If surgical intervention is required, upper lid lagophthalmos can be addressed with gold or platinum weight implants [34]. This may require a brow lift and tarsorrhaphy and lower lid tarsal strip with or without medial canthal plication to achieve optimal functional and cosmetic results.

Synkinesis

The Sunderland classification system describes 5° of injury ranging from compression injury (grade I) to complete transection (grade V). Grades III and higher involve disruption of the endoneurium surrounding the individual nerve fibers. When this is violated, proximal axons can enter any distal endoneurial tubule leading to the loss of individualized muscle contraction and resultant synkinesis [35]. An important management technique of synkinesis is prevention. Early post-injury and postoperative physical therapy are important in reeducating and rehabilitating facial function [17]. Even in the setting of existing synkinesis, passive muscle activation with massage, active stimulation of facial muscles, and voluntary exercises can optimize facial nerve reinnervation and improve the neural plasticity required for relearning facial muscle control after reanimation procedures. Biofeedback rehabilitation can improve facial nerve outcomes, and many therapist will have these exercises performed in front of a mirror to improve their efficacy [17] [35].

Botulinum toxin A is also used in the treatment of facial synkinesis to selectively weaken facial muscle groups to obtained more natural facial contractions and movement. Botulinum toxin A blocks presynaptic release of acetylcholine to inhibit muscle contraction at the level of the motor end plate. The success of this treatment is widely accepted; however, the results are not permanent. Patients require treatment every 3–6 months as the synkinesis returns [35]. Less commonly, highly selective neurectomy or myectomy can be performed for severe synkinesis.

Nonoperative Facial Nerve Rehabilitation

Facial nerve injury and paralysis is a complex problem that requires treatment from a multidisciplinary approach. Physical therapy and rehabilitation play a significant role in achieving optimal outcomes in both the postoperative setting and in situations in which facial reanimation procedures were not required. Nonoperative facial rehabilitation may employ several strategies including rehabilitation with reeducation, mobilization of the facial muscles, and meditation-relaxation techniques. Together, these interventions have been shown to result in long-term improvements in the facial grading scores of patients with chronic facial paralysis [36]. Many systematic reviews have analyzed several modalities including electrical stimulation, shortwave ultrasound, laser, mime therapy, and EMG mirror biofeedback [37–40]. Despite showing efficacy of treatment, no one modality stands superior. As a result, therapists will often utilize a combination of techniques to achieve the optimal outcomes.

Role of Therapists

In general, physical therapy is beneficial and indicated for patients with facial paresis, paralysis, and synkinesis as a result of viral etiologies, tumor resection, traumatic injury, and congenital paresis. For these patient populations, therapists not only provide a comprehensive plan for facial nerve rehabilitation, but they also provide psychological support with the goal of achieving improved health, self-esteem, and quality of life [41].

It is important for the surgeon to be aware of the benefits of physical therapy and the role of the therapist to ensure proper timing of referrals. In the setting of paresis or paralysis after tumor resection with or without the need for reanimation procedures, appropriate time must be given for healing. Once sufficient recovery has taken place, patients must begin to show some signs of neural regeneration for therapy to be effective. However, postsurgical patients should be referred within 1 year as subclinical regeneration can be present [41].

Conclusion

The treatment of facial nerve paralysis is complex and multifaceted. Posttreatment management of facial nerve weakness or paralysis requires a comprehensive understanding of the tools available for intraoperative repair, postoperative reanimation, adjuvant therapies, and neuromuscular rehabilitation. Best outcomes of facial nerve function depend on a multitude of factors including repair technique, timing of interventions, and a multidisciplinary approach that include specialized physical therapy.

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Chapter 14
Rehabilitation of Speech and Swallow

Alexander Gelbard and James L. Netterville

Introduction

Sustained improvements in surgical technique now allow safe resection of JP with minimal mortality. Yet a major cause of morbidity remains the cranial nerve deficits resulting from both tumor growth and surgical extirpation [1]. These impairments may dramatically influence multiple defining elements of the human condition: vision, hearing, speech, and deglutition. Recovery may be incomplete and often requires a prolonged period of rehabilitation. When multiple cranial nerves are affected, the effects on overall quality of life can be devastating. While those deficits produced by tumor growth generally occur progressively over many months, the acute postsurgical deficit is not nearly as well tolerated.

In the past, studies of JP treatment have focused on traditional end points, such as completeness of tumor removal, response to radiation, survival, and local control. More recently, investigators have begun to appreciate the importance of quality of life (QOL) outcomes in the setting of skull base surgery (composed of composite speech, swallowing, and symptom-specific domains) [2]. The impact of surgery on QOL outcomes in skull base paragangliomas directly relates to the speech and swallowing deficits that can occur with treatment [3]. Although in the largest series to date 98% of patients returned to their previous occupations within 2 years after surgery, only 75% returned to their preoperative baseline overall QOL levels owing to sustained swallowing deficits. These results stand in contrast to the results of patients undergoing surgical resection for acoustic neuroma (AN) where infrequent low QOL scores were specifically

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associated with postoperative headache symptoms after surgical excision [4], while study of 105 surgically resected skull base meningiomas [5] that showed persistent impairments at 1 year were attributed to physical handicaps and low energy levels.

A detailed understanding of the unique speech and swallowing deficits following surgical excision of paraganglioma is critical to help surgeons improve the initial multidisciplinary assessment and postoperative management of these patients. It allows identification of specific impediments as early as possible during follow-up and allows application of appropriate medical interventions to patients with increased risk of poor outcome. Equally as critical, providing patients detailed information about their disease and the expected outcomes of therapy prior to any intervention can markedly improve patients' satisfaction with their treatment decisions.

The lower cranial nerves function as a complex team orchestrating the function of the upper aerodigestive tract. Thus, the primary dysfunction, with the loss of these nerves, is alterations in swallowing, speech, and airway protection. Many surgical procedures are available as adjuncts to rehabilitation of lower cranial nerve defects. With therapy most patients compensate for damage to any one of these cranial nerves in isolation. However, damage to more than one nerve significantly prolongs the period of recovery and impairs the overall outcome of rehabilitation.

Glossopharyngeal (CN IX) Injury

Physiologic impairments: Chronic parotitis, Reduced pharyngeal elevation and sensation

The function of the glossopharyngeal nerve (IX) is broad in scope. It possesses fibers responsible for brachial motor function (stylopharyngeus), a general sensory component (afferent feedback from the ipsilateral oropharynx), and a visceral sensory component (feedback from the carotid body and carotid sinus).

Its *brachial motor function* is restricted to the stylopharyngeus, generating pharyngeal elevation during swallowing and speech. Isolated loss of function of this muscle would have little effect on swallowing. However, when its loss is combined with damage to the vagus nerve, it further compounds swallowing rehabilitation.

The glossopharyngeal nerve also carries a *visceral motor component* responsible for the parasympathetic control of the parotid gland. As cranial nerve IX exits the skull base through the jugular foramen, the parasympathetic motor fibers depart from the ninth cranial nerve and pass through the tympanic plexus in the middle ear, progressing back up through the middle fossa floor, then descend through the foramen ovale to the otic ganglion. From the otic ganglion, they travel with the auriculotemporal nerve to reach the parotid gland. Injury to these fibers can occur at many levels and result in a decrease in parotid salivary flow. Infrequently, this may lead to chronic parotitis.

The *general sensory component* provides afferent feedback from the base of the tongue and lateral pharyngeal wall. A small branch also provides sensory fibers to the external ear and the inner aspect of the tympanic membrane. These fibers make up the extracranial portion of cranial nerve IX as it runs on the deep surface of the

stylopharyngeus muscle, passing through the middle constrictor to reach the mucosa of the base of the tongue. Loss of this sensory feedback results in significant alterations in the oropharyngeal phase of swallowing, with the food bolus being delayed on the involved side. When this defect is combined with the loss of cranial nerves X or XII, dysfunction becomes severe. Therapy for oropharyngeal sensory loss from glossopharyngeal nerve injury involves extended swallowing therapy to try to maintain passage of the food bolus adjacent to the contralateral sensate side of the pharynx.

The final function of the glossopharyngeal nerve is *visceral sensory*, providing feedback from the carotid body and carotid sinus. It appears that unilateral loss of this feedback loop does not alter the integrity of the system, but bilateral loss results in marked abnormalities in postoperative blood pressure and pulse. This can occur when the patient has undergone a previous contralateral cervical dissection where the nerve fibers could have been resected or injured. In this situation the postoperative course is remarkably similar to a patient with an existing pheochromocytoma. If bilateral loss can be predicted ahead of time, preoperative planning in conjunction with an intensivist can greatly facilitate the patient's postoperative course.

Vagal Nerve (CN X) Injury

Physiologic impairments: Sensory loss to laryngopharynx, Delayed gastric emptying, Velopalatal insufficiency, Pharyngeal plexus weakness, Paralysis of intrinsic laryngeal musculature

The vagus nerve is the most complex of the lower cranial nerves. Comprised of general sensory, visceral sensory, visceral motor, and branchial motor components, loss of its function is far reaching and creates a greater functional defect in speech and swallowing than isolated loss of the other cranial nerves.

Its *general sensory* component provides afferent signals from the external auditory canal, tympanic membrane, supraglottic larynx, and the lateral pharyngeal wall. Two ganglia are formed within the vagus as it exits the skull base through the jugular foramen. The superior (jugular) ganglion is seen within the jugular foramen, while the inferior (nodose) ganglion is located 1–2 cm outside the foramen. The sensory fibers from the supraglottic larynx form the superior laryngeal nerve, which passes deep to the external and internal carotid arteries to join the vagus at the nodose ganglion. Compensation for sensory loss to the laryngopharynx generally gradually improves with time and swallowing therapy.

The *visceral sensory and motor* components of CN X provide sensory feedback and parasympathetic function to the larynx, trachea, and esophagus, along with thoracic and abdominal viscera. The most common symptom secondary to the loss of these fibers is a decrease in gastroesophageal motility. This is much more severe with bilateral vagal injury but can occur with unilateral injury. Gastric emptying can be delayed, not only limiting adequate nutrition but also resulting in regurgitation in the early postoperative period, which can compromise the airway

as well as cause marked intracranial pressure changes. Pain medication and drying agents, for pharyngeal secretions, can add further to gastric stasis. Therapy for parasympathetic loss to abdominal viscera consists of metoclopramide hydrochloride (Reglan) with a temporary decrease in feeding. These symptoms typically gradually improve with time.

The *branchial motor* component of cranial nerve X provides motor function to the palate, pharynx, and larynx, (except for the stylopharyngeus and the tensor veli palatini muscle). These fibers depart from the vagal nerve in three major branches:

I. First motor branch: The pharyngeal branch departs from the vagus at the nodose ganglion, passing over the internal carotid and deep to the external carotid artery to enter the pharynx at the upper border of the middle constrictor. Damage to this branch results in unilateral palatal and pharyngeal paralysis (pharyngeal atonia). In the early postoperative period, unilateral palatal paralysis does not cause significant morbidity, but with time as the other major problems resolve, the resultant velopharyngeal incompetence (VPI) is quite bothersome. Both nasal regurgitation of food and extreme nasality of speech can occur.

Multiple procedures have been designed to correct VPI by addressing a specific anatomic or functional deficit. These have included augmentation of the posterior nasopharyngeal wall by the use of an implant or local tissue flap, creating a better seal of the nasopharyngeal port by palatal lengthening or pharyngeal flap, or recreation of the nasopharyngeal sphincter by the use of innervated muscular flaps. Velopharyngeal incompetence secondary to a high vagal deficit is not well rehabilitated by the above-mentioned methods because of persistent severe atonia of the lateral pharyngeal wall. Given the limitation of these approaches, our center employs unilateral adhesion of the palate to the posterior wall of the nasopharynx [6]. We have described the outcomes of this procedure in 31 patients with VPI secondary to proximal vagal injury [7] showing decreased postoperative nasality in 96% of patients, improved nasopharyngeal reflux in 83%, with only three patients (11%) showing minor wound breakdown postoperatively (all of which healed completely with conservative management). We initially performed several of these procedures primarily at the time skull base resection resulting in vagal sacrifice, but now feel the added time to these lengthy procedures is not warranted given the initial postoperative VPI does not severely hamper swallowing rehabilitation. Additionally, initially, there was concern that moderate sleep apnea might be produced by this procedure, but thus far no symptoms have occurred in our series.

Treatment for pharyngeal atonia is primarily swallowing therapy. The effect of paralysis of the superior middle and inferior constrictor muscles causes more morbidity than the palatal dysfunction. As the food bolus passes into the oropharynx, the paralyzed side dilates laterally and forms a pseudopocket that detains the bolus. The contralateral normal contraction pushes the bolus into this region rather than down into the hypopharynx. This delay interrupts the normal timing of the swallowing event. Thus, when the larynx reopens, the food bolus, which should be in the esophagus, is still partially in the hypopharynx, resulting in aspiration. A head positioning technique is learned that will physically obliterate the paralyzed side and force the food bolus over into the normal side. We are beginning to look at the pos-

sibility of lateral pharyngeal imbrication or partial resection of the deinnervated muscle with hopes of preventing the outward ballooning of the lateral pharyngeal wall that occurs with swallowing.

II. Second motor branch: The external branch of the superior laryngeal nerve provides motor control to the ipsilateral cricothyroid muscle. Loss of this nerve results in a decreased vocal range. This results in restricted dynamic vocal range, but it is usually only a significant problem in professional voice users.

III. Third motor branch: The third branch is the recurrent laryngeal nerve that provides motor innervation to the intrinsic laryngeal musculature. True vocal cord paralysis results from resection or neural injury at the time of surgery. The resultant glottal incompetence produces poor voice quality, aspiration, and inefficient cough, which results in poor pulmonary hygiene. These effects are magnified by the concomitant sensory loss to the laryngopharynx. Overall these dual deficits manifest as poor coordination of the oro- and hypopharyngeal phases of swallowing and severe dysphagia. Thus, the management of UVCP relating to proximal vagal injury differs considerably from managing UVCP caused by recurrent laryngeal nerve damage.

In an effort to gain immediate glottal competence, prevent pneumonia, and obviate the need for tracheotomy in the postoperative period, primary injection medialization is performed at the end of the skull base procedure (or 2–5 days post-procedure during the initial hospitalization). This greatly facilitates early deglutitive rehabilitation, decreases the incidence of tracheotomy, reduces the length of postoperative hospital stay, and reduces the time to adequate oral intake. Patients are treated with glycopyrrolate (Robinul~) (0.2 mg) every 6 h for 3 days postoperatively to decrease salivary secretions. Patients are monitored over the next 4–6 months for sustained glottic competence, and recurrent symptoms are treated with a permanent silastic medialization thyroplasty as previously described [8].

Accessory Nerve (CN XI) Injury

Physiologic impairments: Weakness of sternocleidomastoid and trapezius and subsequent shoulder instability and pain

The spinal accessory nerve (XI) has only one component, branchial motor, which supplies the sternocleidomastoid and the trapezius. It passes through the jugular foramen, then usually laterally over the internal jugular vein to pierce the sternocleidomastoid. Loss of the sternocleidomastoid function is not usually noticed, but loss of trapezius innervation often results in severe shoulder disability.

For patients with accessory nerve injury, if grafting cannot be undertaken, then a shoulder-strengthening exercise program is outlined through the physical therapy department to strengthen the levator, scalene, and rhomboid muscles to aid in shoulder support. This program should go on indefinitely or shoulder droop with severe pain will occur with time.

Cervical Sympathetic Chain Injury

*Physiologic impairment: Loss of sympathetic innervation to the parotid gland and subsequent pain experienced in the parotid region associated with eating (*i.e., *first bite syndrome)*

The sympathetic innervation to the head and neck structures originates in the upper thoracic segment of the spinal column. The preganglionic fibers ascend in the sympathetic chain to exit it through one of its four ganglia. With resection of high vagal paragangliomas, the cervical sympathetic chain often is damaged or resected. In this group, frequently a prolonged course of pain is experienced in the parotid region associated with eating. This pain is characterized by a severe cramping quality in the parotid region with the first bite of each meal. The patients describe this as a spasm overlying the region of the parotid gland. It then subsides over the next several bites. The intensity of this pain increases with strong sialogogues such as pickles, Italian dressing, and lemon juice. At first, in the early postoperative period, the pain can be so severe that it deters oral intake. Slowly, over time, the symptoms improve. Early treatment of first bite syndrome consists of dietary modifications with bland food and oral carbamazepine (Tegretol), initially starting at a dose of 100–200 mg twice daily (b.i.d.). Although this pain is similar to glossopharyngeal neuralgia, it appears to have characteristics that distinguish it as a separate entity.

Special Considerations: Elderly Patients

Damage to the lower cranial nerves results in sufficient morbidity to warrant therapy. After vocal cord medialization and palatal adhesion, younger healthier patients will eventually resume adequate oral intake. However, the time it requires to return to a reasonably enjoyable diet often extends up to 1 year postoperatively. A few never attain the goal of enjoyable intake and continue to struggle to maintain adequate nutrition. The latter situation is the rule, not the exception, in the elderly population. Our experience over the years has led us to a more conservative treatment of paraganglioma tumors in the elderly debilitated patient. In this age group, rehabilitation of swallowing may be impossible with the combined loss of these nerves. In dealing with the elderly, the surgeon may plan preoperatively for subtotal resection, or favor radiation therapy, rather than subject the patient to such severe disability.

Conclusion

The most difficult aspects of surgical therapy for jugular paraganglioma are not the technical elements of the dissection. Rather, the critical decisions are when and to whom surgery should be offered. Obviously, the loss of cranial nerves plays a major role in this decision-making process. Although increasing efforts have been made to

develop new surgical approaches and novel adjuvant modalities for the treatment of JPs during the last century, little progress has been made in developing new techniques for improving patient quality of life after therapy. Effective prevention and management of poor speech and swallowing outcomes following therapy is a critical element of future progress in our management of this disease.

While lower cranial nerve monitoring of the larynx and pharynx is not carried out with the frequency of facial nerve monitoring, lower cranial nerve injury has a dominant role in poor quality of life outcomes suffered by JP patients. Demonstrating improvements in speech and swallowing outcomes with intraoperative lower cranial nerve monitoring is a concept ready for rigorous scientific study.

Summary

Glossopharyngeal (CN IX) injury

- *Chronic parotitis*: Supportive therapy with hydration and sialogogues
- *Oropharyngeal sensory loss*: Swallow therapy with maneuvers aimed at maintaining passage of the food bolus adjacent to the contralateral sensate side of the pharynx

Vagal (CN X) Injury

- *Delayed gastric emptying*: Immediate reglan
- *Palatal dysfunction (VPI)*: Palatal adhesion (typically 6–8 months after initial surgery)
- *Pharyngeal dysfunction*: Swallow therapy with maneuvers aimed at closing the flaccid ipsilateral pharyngeal wall
- *UVFP*: TVF injection medialization (immediate), with permanent silastic medialization thyroplasty performed at 6–12 months (with or without arytenoid adduction)

Accessory (CN XI) injury

- *Shoulder weakness*: Shoulder-strengthening exercise program

Sympathetic chain injury

- *First bite syndrome*: Bland food and oral carbamazepine (Tegretol) 100–200 mg BID

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Chapter 15
Familial Head and Neck Paraganglioma and Genetic Testing

Brendan P. O'Connell and George B. Wanna

Introduction

Paragangliomas are rare vascular tumors of neuroectodermal tissue arising from neural crest cells. They can be found at various locations of the paraganglion system throughout the body. Tumors originating from chromaffin cells of the adrenal medulla are referred to as pheochromocytomas. Most paragangliomas are benign, but morbidity can result from either growth and compression of nearby structures or physiologic derangements secondary to abnormal secretion of catecholamines. The vast majority of head and neck paragangliomas are non-secretory [1, 2].

It has long been recognized that paragangliomas manifest as both sporadic and hereditary tumors. However, the molecular genetic basis for hereditary tumors has only begun to be elucidated in the past 15 years [3]. Given that phenotypic expression of disease (location of tumors, likelihood of malignancy, penetrance) differs according to the underlying germline mutation identified, an understanding of heritable paraganglioma syndromes is important. This chapter will focus on the molecular genetics of head and neck familial paragangliomas, clinical manifestations of specific gene mutations, and the implications for genetic testing in this population.

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Genetic Basis for Paragangliomas

Familial predisposition to paragangliomas was initially recognized by Chase et al. in 1933, in which the authors described two sisters with bilateral carotid body tumors. Despite an increasing number of reports of hereditary tumors since that time, it was not until the year 2000 when Baysal et al. first identified the genetic basis for familial paragangliomas [3]. Their group identified a mutation encoding the D subunit of succinate dehydrogenase (SDH), an enzyme involved in both the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Subsequent research has gone on to identify germline mutations in other predisposition genes, most of which encode for additional subunits of the SDH protein complex. Until these studies began to elucidate the genetic mechanism of familial paraganglioma syndromes, it was felt that the vast majority of paragangliomas were sporadic [4]. Germline mutations are now reported to account for roughly 30–50% of all paragangliomas [5–7].

Germline Mutations Responsible for Head and Neck Paraganglioma

Since the 1970s, studies have suggested a link between oxidative stress and the development of paraganglioma [8, 9]. Arias-Stella et al. cited an association between high altitudes and the presence of carotid body tumors in 1973 [10]. Around that time, Cornog et al. described giant mitochondria in extra-adrenal paraganglioma [9]. As researchers endeavored to find specific germline mutations responsible for familial predisposition to paragangliomas, investigation of hypoxia-responsive genes became increasingly relevant. In 1976, Watanabe identified decreased SDH activity and giant mitochondria in patients with adrenal pheochromocytoma [11]. Mounting evidence was therefore implicating impaired function of mitochondria in tumorigenesis. SDH was thought to play a role as deactivation of this enzyme increases oxidative stress. Specifically, succinate accumulates and stabilizes hypoxia-inducible factor (HIF). In turn, this precipitates a "pseudohypoxic" state which can promote angiogenesis and cell survival [6].

In 2000, Baysal et al. were the first group to discover the germline mutation in SDH genes responsible for familial paraganglioma. Specifically, a mutation within a region at chromosome 11q23 that encoded the D subunit of SDH was identified [3]. Accordingly, the gene was termed *SDHD*. Interestingly, this was the first time a gene mutation encoding a component of the energy metabolism pathway in a human tumor model had been described [6]. Germline mutations in other *SDHx* genes (*SDHA*, *SDHAF2*, *SDHB*, and *SDHC*) were subsequently described [12–16]. *SDHx* gene mutations have been shown to be the most common genetic cause of hereditary paragangliomas [15, 17]. Specifically, about 70% of familial case of head and neck

paraganglioma has been associated with mutations in *SDHB*, *SDHC*, or *SDHD* [12]. The exact molecular pathogenesis leading to tumor development in patients with *SDHx* mutations remains unclear [6, 18].

Other well-known germline mutations associated with multisystemic disorders have also been associated with predisposition to head and neck paraganglioma; these include von Hippel-Lindau (*VHL*), *RET*, and *NF1* [18]. In a large series, the prevalence of germline mutations in patients with non-*SDHx* head and neck paraganglioma was 0.9% [18]. Given the extremely low incidence of head and neck paragangliomas associated with non-*SDHx* mutations, attention will be focused on the *SDHx* mutations henceforth.

Cellular Physiology of Succinate Dehydrogenase

Given the importance of *SDHx* gene mutations in familial paraganglioma, a basic understanding of SDH is required. In general, SDH participates in both the respiratory chain and the TCA cycle within mitochondria of human cells.

Oxidative phosphorylation is a metabolic pathway in which nutrients are oxidized and energy is used to make ATP (Fig. 15.1). This process occurs within mitochondria and is largely driven by the electron transport chain, or respiratory chain, that is located in the inner mitochondrial membrane. The electron transport chain consists of five main protein complexes; complex II is SDH. Succinate dehydrogenase is a heteroligomer comprised of the SDHA, SDHB, SDHC, and SDHD subunits. In addition, other proteins (SDHAF2) participate in enabling the assembly of the aforementioned subunits [6].

These five enzyme complexes transfer electrons from donors to recipients, and oxygen is ultimately reduced to form water. As this is occurring, protons are pumped across the inner mitochondrial membrane into the intermembrane space creating an

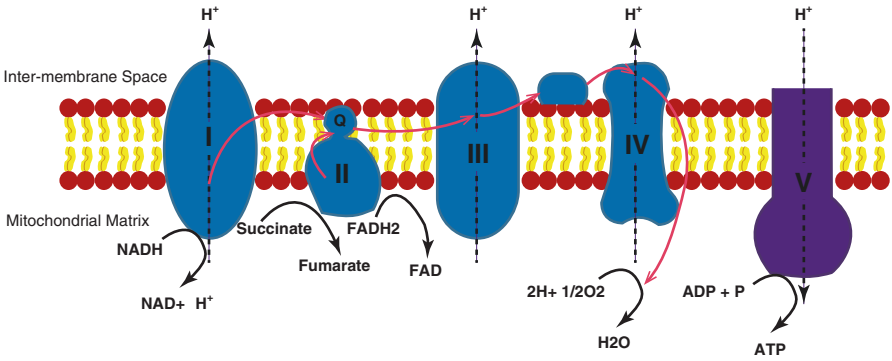

Fig. 15.1 Oxidative phosphorylation and the electron transport chain. Succinate dehydrogenase (SDH) comprises complex II. Various mutations in SDH subunits have been implicated in hereditary paraganglioma syndromes

electrical potential across the inner membrane. The protons flow back across the membrane and down the electrical gradient which supplies the energy that is used to form ATP.

In addition to its contribution to the electron transport chain, SDH participates in the Krebs cycle. In this process, it catalyzes the conversion of succinate to fumarate. The consequence of SDH deactivation is therefore an accumulation of succinate and reactive oxygen species, which has been postulated to contribute to build up of HIF and potentially tumor development as discussed previously.

Mutations in the genes that encode succinate dehydrogenase proteins are generally inactivating and can occur either somatically or in the germ line (hereditary form ensues). While mutations in all four subunits can lead to development of paraganglioma, the clinical presentation and inheritance pattern vary depending on which gene is mutated.

Paraganglioma Syndromes

Paraganglioma syndrome is a clinical term that describes a group of inherited diseases characterized by the presence of paragangliomas and/or pheochromocytomas. Patients demonstrate variable risk of developing gastrointestinal stromal tumors (GISTs), renal cancers, or pituitary tumors [17]. Paraganglioma syndromes have been classified into five entities as follows: PGL1, PGL2, PGL3, PGL4, and PGL5. Each of these has been associated with a germline mutation in a gene encoding a component of SDH. Generally speaking, the PGL syndromes are inherited in autosomal dominant fashion, with maternal imprinting implicated in PGL1 and PGL2 subtypes. Patients with hereditary PGL syndromes are more likely to present at an earlier age and have multiple tumors when compared to non-PGL individuals with sporadic tumors [19]. The penetrance of tumor development is highly variable among the different syndromes. Data for each syndrome are detailed below and summarized in Table 15.1.

Table 15.1 Hereditary head and neck paraganglioma syndromes

	PGL1	PGL2	PGL3	PGL4	PGL5
Gene	*SDHD*	*SDHAF2/SDH5*	*SDHC*	*SDHB*	*SDHA*
Inheritance	Maternal imprinting	Maternal imprinting	Autosomal dominant	Autosomal dominant	Autosomal dominant
Chromosomal locus	11q23	11q13.1	1q21	1p35–36	Unknown
Pheochromocytoma risk	Intermediate	Low	Low	Intermediate	Low
Multifocality risk	High	High	Low	Intermediate	Low
Malignancy risk	Low	Low	Low	Intermediate	Low

PGL1 Syndrome

PGL1 syndrome is associated with mutations in *SDHD*, which is located on chromosome 11q23 [3]. The D subunit of SDH encodes an anchor protein in complex II. Mutations in *SDHD* predispose to the development of multifocal head and neck paragangliomas. Mutations in *SDHD* have been reported in 52% of hereditary head and neck paragangliomas [7]. Abdominal paragangliomas and pheochromocytomas have been reported but are less common than head and neck tumors [20]. Renal cancers and pituitary tumors have occasionally been reported in association with PGL1 [21, 22].

Paragangliomas in patients with PGL1 exhibit a low rate of malignancy and are nonsecretory. They typically present around the third decade of life [23]. Benn et al. reported a high lifetime penetrance, with 75% of patients manifesting disease by the fourth decade of life [24]. *SDHD* mutations exhibit maternal imprinting [25–27]. In this pattern of inheritance, the maternally derived allele for *SDHD* is imprinted (silenced), and the expressed allele is entirely dependent on its paternal origin. For this reason, phenotypic expression of PGL1 can skip generations.

PGL2 Syndrome

PGL2 is rare and is associated with *SDHAF2* germline mutations [28]. The *SDAF2* gene, also referred to as *SDH5* in some studies, encodes a protein that is necessary for the assembly of the A subunit of SDH. These mutations have only been reported in a few families [14, 29, 30]. Patients with PGL2 tend to develop multifocal head and neck paragangliomas [30]. Like PGL1, the inheritance pattern is maternal imprinting, and the penetrance is high. Although data are limited, neither paragangliomas outside the head and neck nor pheochromocytomas have previously been reported [17].

PGL3 Syndrome

The *SDHC* gene, encoding the SDHC anchor protein in complex II, is mutated in PGL3 [15]. This mutation occurs less frequently than *SDHB* and *SDHD* mutations. Germline mutations in *SDHC* have been reported to account for 14% of hereditary head and neck paragangliomas [7]. This condition is inherited in autosomal dominant (AD) fashion. Head and neck paragangliomas are the predominant tumor in PGL3 syndrome. These tumors are almost exclusively benign, rarely multifocal, and typically nonsecretory [31, 32]. Mutations in *SDHC* are rarely identified in patients with thoracic/abdominal paragangliomas and pheochromocytomas [17, 31]. The typical age of presentation is in the fourth decade of life [28, 31].

PGL4 Syndrome

The *SDHB* gene encodes the catalytic subunit of complex II and is located on chromosome 1p35–36. Initially described in association with paragangliomas in 2001 by Astuti et al., mutations in *SDHB* have since been implicated in PGL4 syndrome [16]. Mutations in *SDHB* are estimated to account for 22–38% of hereditary tumors [33, 34]. Patients with this condition most commonly develop paragangliomas in extra-adrenal abdominal locations, but head and neck paragangliomas are often present as well. That being said, PGL4 is marked by significant heterogeneity in presentation, even within families that carry the same mutation [35]. Multifocal tumors have been reported in 28% of patients with PGL4 [23].

Mutations of *SDHB* are associated with a higher rate of malignancy than other *SDHx* mutations, particularly as it pertains to extra-adrenal abdominal paragangliomas [23, 36]. Malignant disease occurs in around one third of patients [37]. In addition, *SDHB*-related mutations are associated with an increased risk of secondary neoplasms such as renal cell cancer and GISTs. Renal cell cancer has been reported in roughly 14% of patients with PGL4 [17]. The reason for the apparently more aggressive nature of tumors in *SDHB* mutations remains unclear.

The inheritance pattern for *SDHB* mutations is AD. Compared to *SDHD* mutation carriers, the age-related penetrance of tumor manifestation is considerably lower, with roughly 40–50% of patients manifesting disease by the age of 40 [23, 38]. This contrasts with the aforementioned 75% disease penetrance of *SDHB*-associated mutations. If head and neck paragangliomas are examined separately, earlier onset is again observed in *SDHD* mutation carriers compared to *SDHB* mutation carriers [23]. In a series of 348 patients with *SDHB* and *SDHD* mutations, *SDHD* induced head and neck paragangliomas about 20 years earlier than *SDHB* mutations [21].

PGL5 Syndrome

SDHA is part of the catalytic subunit of the SDH complex. Mutations in *SDHA* have traditionally been described to cause ataxia, optic atrophy, and Leigh syndrome [4]. There is emerging data, albeit limited to case reports and small case series, to suggest that *SDHA* mutations should be considered a paraganglioma susceptibility gene [13]. Currently, only two patients with *SDHA* mutations and head and neck paragangliomas have been reported, while a few others with non-head and neck tumors have been described [13, 39]. The exact phenotype and chromosomal location for *SDHA*-related tumors remains unclear.

Genetic Testing and Clinical Surveillance

With the discovery of paraganglioma susceptibility genes, genetic testing is now possible. Genetic testing is performed on DNA extracted from peripheral blood. Currently, no consensus exists as to the role of genetic testing in patients with head

and neck paragangliomas. In all cases, a thorough discussion should occur between clinician and patient to determine the most appropriate strategy individualized to that patient's situation. This notion is supported by recent clinical practice guidelines, which recommend that all patients with paragangliomas be engaged in shared decision making for genetic testing [40].

There are a number of potential advantages to molecular genetic testing. If germline mutations are present, testing (1) identifies individuals at risk for development of other tumors, (2) identifies carriers that can pass along disease to their offspring, and (3) prompts evaluation of family members that may have occult tumors. If germline mutations are not found, testing is also beneficial as it identifies those not at risk for development of metachronous tumors, thus avoiding unnecessary lifelong surveillance. The disadvantages of testing include the associated cost, the need for lifelong screening in cases in which germline mutations are identified, and the psychological burden that patients may bear from not knowing if and when a tumor will develop. Financial cost of genetic testing is an important consideration and will hopefully decrease with the adoption of next-generation sequencing methods in the future.

As mentioned above, genetic counseling should be performed in all patients. A referral to medical genetics should also be offered to patients. Genetic testing for germline mutations should be considered based on clinical presentation, medical history, and family history. Predictors of hereditary tumors include a family history, syndromic features, concomitant pheochromocytoma and extra-adrenal paraganglioma, multiple head and neck paragangliomas, malignant paragangliomas, and young age at presentation [2, 40, 41]. If any of these features are present, strong consideration should be given to genetic testing. It should be emphasized that a negative family history does not preclude an inherited tumor, given the variable penetrance and inheritance patterns (maternal imprinting) associated with different germline mutations. That being said, the role of genetic testing in patients with solitary, benign disease, and a negative family history is less clear [42].

Currently, the selection of genes to be tested should be prioritized to an individual's clinical presentation [40]. For patients with nonmetastatic head and neck paragangliomas, most authors recommend testing initially for *SDHD*, *SDHB*, and *SDHC* mutations [40, 42]. If metastatic disease is present, priority should be given to *SDHB* sequencing. The other *SDHx* mutations can be tested if these are negative. If testing reveals a germline mutation in an *SDHx* index case, posttest counseling should be performed to ensure the patient understands the implications of the diagnosis (prognosis, treatment options, recurrence risk, testing of relatives) [43]. Testing should also be offered to all first-degree relatives. Immunohistochemical information, as discussed below, may also be helpful in determining sequential genetic testing in index cases.

Immunohistochemical Staining

For patients who undergo surgical removal of their tumor, immunohistochemical staining is possible. Tumors that demonstrate loss of staining with anti-*SDHB* antibodies have been associated with germline mutations in not only *SDHB* genes but also *SDHC* and *SDHD* genes [44, 45]. The reason for this is that a mutation in any

of the *SDHx* genes disrupts the overall SDH protein complex and alters immunohistochemical staining with anti-SDHB antibodies. There is emerging data that suggests SDHA staining is also possible and loss of staining is noted in patients with germline mutations in the *SDHA* gene [39].

Immunostaining can therefore be used as a screening method to select patients for molecular genetic testing. If loss of staining for SDH complex proteins is noted on immunohistochemistry, genetic counseling and testing to determine the affected gene locus are advised [1]. The obvious limitation with this methodology is that the tissue is required, which is relevant as the role of observation/nonsurgical therapy for these lesions has expanded in recent years [46–48].

Clinical Screening and Surveillance in Hereditary Paraganglioma Syndromes

In patients diagnosed with germline mutations in paraganglioma susceptibility genes, lifelong biochemical and clinical surveillance is recommended. The purpose of surveillance is early detection and treatment, which is important as the risk of complications increases with increasing tumor size [49]. In children, initiating screening between ages 5 and 10 is advisable [49, 50]. While there is no algorithm for surveillance, the underlying mutation should be taken into consideration when determining a screening protocol.

Given the significant risk of malignant disease associated with *SDHB* mutations, most authors recommend annual testing of plasma/urinary metanephrines and imaging from the skull base to the pelvis [35]. Given that *SDHD* tumors grow slowly and are unlikely to be malignant, annual screening may not be necessary [23]. The approach to surveillance in patients with *SDHA*, *SDHAF2*, and *SDHC* mutations is not well described.

Recent clinical practice guidelines suggested computed tomography (CT) rather than magnetic resonance imaging (MRI) be used as the first-choice imaging modality in the work-up of paragangliomas [40]. The same group recommended MRI in patients with metastatic disease or head and neck paragangliomas; therefore, MRI may be most appropriate when screening patients with germline mutations [40]. Radionuclide imaging is also sensitive in detecting metastatic lesions [51, 52].

Conclusions

In recent years, remarkable progress has been made with identification of paraganglioma susceptibility genes. While the genetic basis for paragangliomas is complex and evolving, mutations in *SDHx* genes are now recognized as the main cause of hereditary paragangliomas in the head and neck region. Genetic counseling should be performed in all cases, and testing offered to those at risk for hereditary

pathology. Clinical features differ according to the mutated gene, and research is ongoing to better characterize the exact relation between certain genotypes and phenotypic expression. Together, this knowledge has the potential to increase early detection of tumors, prompt timely intervention, and improve outcomes.

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Chapter 16
Special Considerations in Management of Jugular Paraganglioma

Jacob B. Hunter

Introduction

Paragangliomas are neuroendocrine neoplasms that arise from chief cells in extra-adrenal paraganglia of the peripheral nervous system. While previous chapters have expanded upon historical, diagnostic, and management issues pertaining to paragangliomas, this chapter will discuss the management and prognosis regarding multicentric paragangliomas, malignant tumors, catecholamine-secreting paragangliomas, high-risk anesthetic patients, and future directions. Due to the paucity of literature on these particular topics, studies analyzing other head and neck paragangliomas, as well as non-head and neck paragangliomas and pheochromocytomas, are reviewed when relevant to highlight special considerations in management.

Multicentric Paragangliomas

The incidence of multicentric paragangliomas, including jugular, vagal, and carotid body, ranges from 1 to 80%, with more recent studies quoting between 10 and 20% [1, 2]. Al-Mefty and Teixeira reviewed 43 cases of what they defined as complex jugular paragangliomas (JP), observing multicentricity in 34.5% of patients [2]. Multicentricity is more common in familial cases, with one report observing that bilateral tumors occurred in 31.8% of familial cases and only 4.4% of sporadic cases [3]. However, recognizing that familial tumors tend to demonstrate more rapid growth, many hypothesize that multicentric tumors may be more likely diagnosed

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in familial cases due to differences in growth rates compared to nonfamilial cases [1]. Assessing a single institutional head and neck paraganglioma cohort, Szymanska et al. found that 16.6% (14/84) patients had two or more head and neck paragangliomas [1]. In 8 of those patients, 13 synchronous tumors were asymptomatic and thus discovered with imaging studies [1]. Assessing all 14 patients, 37 head and neck tumors were identified, 30 of which were synchronous, with the remaining seven metachronous, diagnosed between 2 and 18 years after removal of the first tumor [1]. In addition, eight cases of bilateral carotid body tumors were identified, which is the most commonly occurring bilateral paraganglioma, while no bilateral JPs were observed, reinforcing previously published data [1]. Genetic studies have noted that *SDHD* mutations, whether spontaneous or inherited, are more frequently associated with multiple paragangliomas [4].

Management of multicentric paragangliomas is complicated, especially when bilateral cervical or skull base tumors are present. Multicentricity raises questions of which tumors to treat, when, if, and with which modality given the significant risk of lower cranial nerve deficits [2]. Szymanska et al. emphasized that in the case of bilateral paragangliomas, surgical planning must depend upon the management plan of the contralateral tumor or tumors, such as deciding whether to sacrifice the ipsilateral internal carotid artery or pursue subtotal resection [1]. In the case of ipsilateral paragangliomas, both Szymanska et al. and Al-Mefty and Teixeira recommend concurrent excision of all ipsilateral paragangliomas [1, 2]. When confronted with bilateral JPs, Al-Mefty and Teixeira recommend that the contralateral side should only be treated surgically if there were no essential cranial nerve injuries after the first resection [2]. Szymanska and colleagues added that in patients with multicentric paragangliomas, specifically bilateral vagal and JPs, vagal function and hearing must be preserved on at least one side [1]. Given these considerations, in order to preserve vagal function on at least one side, some advocate for a wait-and-scan policy, recommending surgery in those patients with either life-threatening intracranial growth or progressive cranial nerve deficits [1, 5]. The factors and complexity associated with multicentric paragangliomas clearly highlight that these tumors should be managed with a multidisciplinary approach by an experienced center.

Complex Tumor Management

There is a no standard definition of a complex JP. Al-Mefty and Teixeira identified 43 patients with complex JPs, self-defined either by giant size, multiplicity, catecholamine hypersecretion, malignancy, associated lesions, or the patient that had undergone previous treatments with adverse outcomes that increased the surgical risk [2]. In these cases, Al-Mefty and Teixeira recommended that the surgeon should modify the surgical technique to minimize the risk of bilateral deficits, which may include avoiding facial nerve mobilization, maintaining the integrity of the medial jugular bulb to prevent lower cranial nerve injuries, accepting subtotal

removal in an attempt to preserve lower cranial nerve function, abandoning blind-sac closure of the external ear canal, and considering radiosurgery for contralateral tumors [2].

Multiple issues must be considered when managing patients with JPs, regardless of the complexity. Given their generally benign nature, combined with historically morbid surgical outcomes, extra caution must be undertaken before treating elderly or medically infirm patients. Similarly, those patients with neurovascular compromise or who have undergone prior intervention require a complete investigation of their anatomy and discussion of their options. For instance, in those patients who have contralateral lower cranial nerve deficits, one may be more inclined to radiate an ipsilateral JP to avoid injuring the ipsilateral lower cranial nerves. Emphasizing the role for preoperative imaging, in patients that have undergone previous embolization or carotid artery occlusion, Al-Mefty and Teixeira state that the most important aspect of angiographic evaluation is identifying new feeding vessels [2]. Specifically, previous embolization or occlusion of the carotid artery leads to development of a new blood supply, which could increase the risk of arterial dissection, an important consideration during treatment planning [2].

Piazza et al. described the case of a patient with a right-sided jugular and vagal paraganglioma with the absence of the contralateral internal carotid artery [6]. Though Al-Mefty and Teixeira do not believe that carotid artery sacrifice is ever warranted, stating that they can consistently develop a plane between the tumor and adventitia, in the case described by Piazza et al., the patient had a contralateral carotid body paraganglioma excised 15 years previously, wherein their left internal and common carotid artery had been ligated [2, 6]. In the follow-up report, Piazza and colleagues emphasize the role of preoperative imaging to determine the vascular involvement of the paraganglioma, specifically to determine if the carotid wall is involved [6]. Though they suggested that permanent balloon occlusion is the most effective method to manage an extensively infiltrated internal carotid artery, having only one carotid artery is an absolute contraindication to the technique [6]. Given that the right-sided internal carotid artery was irregular and stenotic, and unable to perform a balloon occlusion, Piazza and colleagues stented the artery in the cervical and intratemporal segments, followed by embolization 7 weeks later with surgical excision 2 days following embolization [6]. They reported that stenting the carotid reinforced the arterial wall, assisting surgical dissection in a subadventitial plane, thus reducing the risk of vessel injury during surgery [6]. Nonetheless, any patient who undergoes stenting requires lifelong antiplatelet therapy, with thrombosis and distal embolization as the main risks [6]. In Piazza and colleagues' case, Doppler ultrasound was performed at the time of discharge, in addition to 6 and 18 months following surgical excision, with the carotid artery remaining patent throughout [6].

Piazza et al. did acknowledge that continued observation and a by-pass procedure were two other options available for the patient, though neither are without risks [6]. Another alternative is radiotherapy, with some authors supporting its use in situations when surgery would require reconstruction or ligation of the carotid artery [7]. However, Piazza and colleagues disagree with radiotherapy, believing it should be reserved for small residual tumors following subtotal resection, elderly

patients, and those patients with contralateral cranial nerve deficits [6]. And while subtotal resection is another option, many surgeons struggle with how much resection is too much or too little. Wanna and colleagues reported the subtotal surgical resection outcomes of 12 patients with advanced JPs and intact lower cranial nerves, concluding that residual tumor was less likely to grow if more than 80% of the tumor was resected [8]. Sanna and colleagues, reviewing their experience of 53 Fisch class C and D JPs, noted that dominant sigmoid sinuses, absence of collateral flow on temporary occlusion of the internal carotid artery, and advanced age with a poor general condition were factors that led to subtotal resections [9].

In addition to neurovascular issues, giant tumors with significant intracranial involvement also add a layer of complexity to patient management. Sanna and colleagues tend to stage the resection in patients with large intracranial involvement, but in those rare cases when an anesthetically high-risk patient has significant brainstem compression, they prefer to sufficiently decompress the brainstem during the initial stage [9]. In contrast, Al-Mefty and Teixeira do not stage tumors with intradural extension [2].

Malignant Paragangliomas

The first reported case of a metastatic temporal bone paraganglioma was in 1949, with metastasis to the liver [10]. Since then, few additional cases have been identified. Nonetheless, several studies have attempted to investigate their incidence, as well as factors that predict their development. It is estimated that less than 5% of all types of paragangliomas are malignant, occurring most commonly in vagal tumors [1]. Brewis et al. estimated an incidence between 1 and 4%, while Lee and colleagues reviewed the National Cancer Database records from 1985 to 1996 and found 59 malignant paragangliomas, estimating an incidence rate between 6 and 24% for non-adrenal paraganglia [11, 12]. Manolidis and colleagues reviewed the incidence of temporal bone paraganglioma malignancy in a large skull base center, defining malignancy as the presence of tumor located in a regional lymph node or within distant organs [13]. They identified nine malignant cases, or 6.3% of all JPs [13]. But while the range of incidence rates may be the result of sampling biases, to date, no chemical, biological, or histopathological feature has been able to distinguish nonmalignant paragangliomas from malignant paragangliomas. Though Lack writes that two of the following three criteria are required to define malignancy, mitotic abnormalities, lymphatic and vascular invasion, and central necrosis, it is generally recognized that metastases are identified when paraganglionic cells are found in another tissue where neuroendocrine cells are not normally present, outside the original tumor bed, with identical cytological features between the aberrant tissue and primary tumor [14, 15]. However, a recent study that assessed 365 patients with pheochromocytoma and paraganglioma metastases showed that plasma levels of a dopamine metabolite, methoxytyramine, are a possible useful biomarker in detecting metastases [16].

In an earlier study reviewing 53 previously published JPs with metastases, Brewis and colleagues sought to determine various characteristic features of meta-

static JPs, comparing sites and presenting features, age, and gender, among other characteristics, to nonmetastatic JPs [11]. They identified 100 metastasis sites, including bone (33), most frequently to the vertebrae, followed by lungs (23), lymph nodes (19), liver (9), and other sites (16) [11]. Comparing the various features of these tumors with nonmetastatic JPs, only pain and a lower incidence of hearing loss were significantly more likely to occur in metastatic tumors as compared to nonmetastatic tumors [11]. Manolidis and colleagues noted that malignant paragangliomas tend to have more severe symptomatology, with more rapid progression and more advanced staged disease at the time of presentation as compared to benign paragangliomas [13].

Similarly, Chapman and colleagues reviewed all types of paragangliomas at one institution, seeking to identify features that suggested malignant behavior [17]. In identifying 84 paragangliomas, seven were malignant, six of which were carotid body tumors, with one vagal paraganglioma [17]. They found that malignancy was associated with younger patients, as well as pain at presentation [17]. Appreciating that all patients with metastases demonstrated perineural invasion, Chapman and colleagues hypothesized that the perineural invasion is the likely cause of the pain [17]. And like previous reports, they identified no common imaging findings that differentiated between benign and malignant paragangliomas [17]. However, the authors noted that the collective presence of multiple histologic features in a single tumor, such as poor circumscription and invasion through the fibrous capsule, perineural invasion, lymphovascular invasion, high cellularity with a diffuse growth pattern, widespread profound nuclear pleomorphism, increased or atypical mitotic figures, and necrosis, may predict metastatic disease and a poorer prognosis [17].

Other studies have suggested that tumors larger than 5 cm in diameter, greater than 80 g in weight, or recurrent tumors are all clinical signs that may suggest malignancy [18]. Remine and colleagues suggested that catecholamine-secreting paragangliomas may be more likely to be malignant (38%) compared to nonsecreting paraganglioma tumors (less than 10%) [19]. And while other studies have noted similar comparisons, in contrast, Linnoila and colleagues noted that malignant paragangliomas express considerably lower levels of neuropeptides [20, 21].

Several attempts have been made to utilize newer imaging technologies to identify occult tumors, such as somatostatin receptor imaging with ^{111}In-octreotide scintigraphy, ^{18}F-fluorodopamine positron emission tomography-computed tomography (^{18}F-DOPA), and ^{131}I and ^{123}I-metaiodobenzylguanidine (MIBG), with varying reliability [14, 21]. Hoegerle and colleagues showed that ^{18}F-DOPA demonstrated a low sensitivity for detecting metastases, especially in subjects with *SDHB* mutations, which occur most frequently in head and neck paragangliomas [21, 22].

Prognostically, Brewis et al. found that the rates of persistence or recurrence were 97 and 51% in metastatic and nonmetastatic paragangliomas, respectively, with the mortality rate of 68 and 10% in metastatic and nonmetastatic cases, respectively, both of which were statistically different [11]. In Lee and colleagues' review of 59 malignant paragangliomas, they found that patients with regional metastasis demonstrated a 76.8% 5-year survival rate, as compared to 11.8% in those with distant metastases [12]. Spetz et al. reviewed 154 patients with pheochromocytomas and paragangliomas and observed that those patients who developed metastases

following primary surgery had better prognoses than those patients who presented with locally advanced disease and or distant metastases [23]. Mediouni and colleagues reviewed 11 malignant paragangliomas at a single institution and found that the mean metastasis-free interval was 8 years, ranging from 1 to 25 years [21]. Thus, while malignant paragangliomas carry a poorer prognosis than benign disease, development of malignancy following primary surgery, which can occur between 1 and 25 years later, leads to a better prognosis than those patients who initially present with malignant paragangliomas.

In terms of management of metastases, little data is available. Massey and Wallner performed a single institutional retrospective review of six patients who received chemotherapy or radiation therapy for malignant paragangliomas [24]. Though only four of the patients had disease originating in the head and neck, of four patients who received chemotherapy, none had significant subjective or objective responses to treatment, while three patients who had nine painful metastatic sites radiated reported complete subjective responses to treatment at eight of nine locations [24]. Noting the extremely slow growth rates of paragangliomas, Massey and Wallner were not surprised by the lack of response to single-agent or multiple-agent chemotherapy, suggesting that continuous infusion medications, or chronic low doses, may be more effective [24]. Mediouni and colleagues postulate that surgery is the only curative treatment for metastatic paragangliomas, acknowledging that most metastases involve the bone, most frequently the vertebrae, and thus is not amenable to resection [21]. They recommend surgery for isolated or multiple lymph node metastases, as well as neck, chest, or abdominal metastases, including liver metastases, which can also be treated with radiofrequency ablation [21]. For vertebral metastases, they encourage a combined medical and surgical approach, including analgesics, anti-inflammatory drugs, bisphosphonates, and localized radiotherapy [21].

While there is a paucity of data regarding systemic chemotherapy for metastatic head and neck paragangliomas, when reviewing the metastatic pheochromocytoma and non-head and neck paraganglioma, most studies are retrospective with small cohorts [25]. The best studied regimens are either cyclophosphamide or dacarbazine based on vincristine or doxorubicin, appearing to be clinically beneficial in 50% of patients, with no changes in overall survival [25]. Other treatment options include metabolic radiotherapy and targeted molecular therapy, both of which will be discussed later.

Catecholamine-Secreting Paragangliomas

Although discussed separately in an earlier chapter, catecholamine-secreting paragangliomas are complex and require special consideration. Depending on the study, catecholamine-secreting JP incidence rates range from 1 to 8% [26, 27]. Symptomatically, these patients frequently demonstrate hypertension, palpitations, headache, sweating, flushing, tachycardia, and/or diarrhea as a result of excess

catecholamines. Though JPs have occasionally been identified as catecholamine-secreting tumors when the patient fails to respond to antihypertensive medication, most studies recommend screening urine metabolites or assessing plasma levels to identify catecholamine-secreting tumors [26]. This is further reinforced with Colen and colleagues observing that symptoms, including elevated blood pressure, are not often apparent until catecholamine levels are 4–5 times their normal levels [28]. Thus, symptoms are not reliable indicators to decide who gets screened. Furthermore, it is important to identify catecholamine-secreting paragangliomas pre-operatively since alpha- and ß-blockade should be considered for those patients with secreting tumors in order to prevent intraoperative blood pressure fluctuations and end-organ damage.

While not universally practiced, Teranishi and colleagues provide continuous intravenous infusions of magnesium sulfate during pre-treatment imaging to inhibit catecholamine secretion secondary to contrast medium injection [27]. With catecholamine release causing vascular constriction, magnesium sulfate inhibits catecholamine secretion from both the adrenal medulla and peripheral adrenergic nerve terminals, as well as its receptors, thereby preventing vascular constriction [27, 29]. Goutcher and colleagues also described using magnesium sulfate to control blood pressure intraoperatively in two catecholamine-secreting JPs with intracranial extension [29]. They concluded that magnesium sulfate intraoperatively minimizes blood pressure changes, thus improving hemodynamic stability [29].

In catecholamine-secreting JP, other considerations must be addressed. Colen and colleagues observed that patients with catecholamine-secreting paraganglioma, have an elevated hematocrit as a result of catecholamine stimulation, the byproduct of vascular constriction, and a reduction in the relative circulating plasma volume [27, 28]. Thus, in those patients undergoing surgery, they recommend that patients preoperatively donate autologous packed cells [28]. In addition, most patients with catecholamine-secreting paragangliomas have left ventricular hypertrophy, the result of prolonged exposure to excess catecholamines that leads to a form of dilated cardiomyopathy associated with ventricular failure in one third of patients [28]. Given these cardiac issues, Colen et al. recommend obtaining an electrocardiography (EKG), echocardiography, chest X-ray, and cardiac enzyme measurements in those patients with catecholamine-secreting paragangliomas [28].

Further considerations include those patients who undergo embolization. While embolization is often performed for paragangliomas prior to undergoing surgical excision, additional risks have been noted in those patients with catecholamine-secreting paragangliomas. Several reports have documented hypertensive crises, hypotension, wide fluctuations in blood pressure, asystole, and even death with embolization, all thought to be secondary to tumor necrosis and subsequent release of catecholamines into the systemic circulation [28, 30, 31]. Additionally, certain drugs should also be avoided in catecholamine-secreting paraganglioma patients to avoid further secretion, such as the antiemetic droperidol and metoclopramide, narcotics that release histamine (morphine, Demerol), and anticholinergic medications (atropine, glycopyrrolate, and scopolamine) [28].

In those patients who undergo surgery, intraoperatively, hypotension can develop with small-volume losses if the circulating blood volume is not corrected during tumor excision and the subsequent decrease in catecholamine levels [27]. However, too much volume loading can lead to intracranial pressure elevation [27]. Teranishi and colleagues warn that surgery can lead to catecholamine over secretion, leading to blood pressure instability and fatal arrhythmias [27]. They also observed that vasopressors are usually needed following excision due to a reduction in catecholamines [27]. And lastly, hypoglycemia is commonly encountered postoperatively as a result of the rebound effect from chronic catecholamine excess and its effects on glucose metabolism [28].

While early evidence suggested that catecholamine-secreting chief cells are radioresistant, which led to the recommendation that catecholamine-secreting paragangliomas undergo surgical resection, there are several reports describing treating catecholamine-secreting paragangliomas with radiotherapy [32]. Fussey and colleagues described a woman with a 42 × 36 mm sized catecholamine-secreting JP who received 14 Gy to 50% isodose [32]. After 37 months of follow-up, the tumor had reduced to approximately 60% of its original size, and the patient's serum normetanephrine and urinary noradrenaline had fallen to normal limits [32]. In addition, Castrucci and colleagues described a case of a catecholamine-secreting JP who was treated with pharmacologic catecholamine blockade and single-fraction gamma-knife radiosurgery, with near normalization of catecholamine levels and control of tumor growth at 32 months of follow-up [33]. Thus, not only is stereotactic radiosurgery a viable treatment option for JPs, but it should also be considered in those patients with catecholamine-secreting paragangliomas.

Concomitant Intracranial Masses

There appear to be only two case reports when another intracranial mass was identified along with a JP. Mittal et al. described the case of a 65-year-old woman with a left JP and a large olfactory groove meningioma, initially removing the meningioma, followed by resecting the paraganglioma 1 year later [34]. Similarly, Fukusumi and colleagues described a case of a patient with a JP and convexity meningioma [35]. It is generally accepted that the spontaneous occurrence of multiple different brain tumors is about 0.3%, usually occurring in those patients with phacomatoses or prior cranial radiation [34, 36]. In the absence of phacomatoses or previous cranial radiation, several hypotheses could explain the occurrence of two distinct primary brain tumors: [1] coincidence; [2] carcinogenic stimulus can develop tumors in multiple locations; [3] the initial tumor can stimulate the neighboring cerebral parenchyma or meningeal tissue, inducing another tumor; and [4] a residual embryonic structure acts as the basis for the development of different brain tumors [34, 36, 37]. Management plans must not only consider the tendency for the JP to be slow-growing and benign but also the pathology and prognosis of the other lesion.

Concomitant intracranial masses could also raise similar issues as was discussed with multicentric paragangliomas, namely, consideration of cranial nerve function and possibly injury with treatment.

Future Directions

Several therapies for paragangliomas are currently being investigated to assess their efficacy. Some groups have attempted radiopharmaceutical treatment, observing that neuroendocrine tumors, including paragangliomas, possess a high concentration of somatostatin hormone-binding sites [38–40]. It has been shown that octreotide analogues have a high affinity for the somatostatin type 2 receptor present in neuroendocrine tumors, with studies showing that somatostatin and its analogues have properties that directly or indirectly inhibit cellular growth factors and directly inhibit angiogenesis [39]. Rafferty and colleagues reported the outcomes of two patients with JPs treated with octreotide, one who had a poor response to radiation therapy and the other with extensive residual tumor following subtotal resection [39]. While the most common side effects were diarrhea and fatty stools, both tumors remained stable at the last follow-up [39].

Given these results, Duet and colleagues prospectively investigated a long-acting somatostatin analogue (OCT-LAR) on the tumor volume of 18 head and neck paragangliomas [41]. Excluding malignant paragangliomas, prior to treatment, all patients underwent ^{111}In-penetrreotide scintigraphy to determine a tracer uptake index for each tumor to determine the density of somatostatin receptors [41]. Undergoing three monthly intramuscular injections, 8 of 9 patients completed the entire treatment, while one patient stopped the study after experiencing significant nausea and diarrhea [41]. Comparing tumor volumes before and following treatment, the average absolute change in tumor size was 1.02 ± 3.82 cubic centimeters, which was not significant, and the average percent of shrinkage was 4.0 ± 10.0% [41]. Using the tracer uptake index, they found no correlation between tumor reduction and somatostatin receptors, concluding that OCT-LAR has a weak, if any, effect on the size of paragangliomas [41].

However, other groups have shown shrinkage in pituitary adenomas with somatostatin analogues, in addition to stabilization of gastroenteropancreatic tumors [40, 41]. Thus, Duet and colleagues hypothesized that the variability in tumor response to somatostatin analogues could be explained by the absence of specific subtypes that bind octreotide with high affinity or by a nonhomogenous distribution of somatostatin receptors [41]. They further add that a longer treatment period may lead to more dramatic shrinkage [41].

Similarly, MIBG, also known as iobenguane, similar to noradrenaline, is an agent that is concentrated into vesicles or neurosecretory granules of neuroendocrine tumors [18]. While ^{123}I-MIBG has been used for imaging paragangliomas, high-dose ^{131}I-MIBG was first used in 1984 to treat metastatic paragangliomas [25]. Gonias and colleagues conducted a phase II prospective study assessing its

role in metastatic pheochromocytomas and non-head and neck paragangliomas, with a 22% response rate in those receiving high doses, minor responses in 35%, and stable disease in 8% [42]. While it has been observed that high cumulative activities are associated with increased risk of myelodysplastic syndrome and acute myelogenous leukemia, there appear to be no studies assessing its role in JPs [42].

Several groups have also investigated targeted molecular therapies in treating metastatic pheochromocytomas and paragangliomas, not including head and neck paragangliomas [43]. It has been identified that tumors with germline mutations of succinate dehydrogenase subunits exhibit hypoxia-inducible factor dysregulation, which leads to the production of growth factors, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) [43]. One such molecular therapy is sunitinib, a receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity, which targets both PDGF and VEGF receptors [43]. In three patients with abdominal paragangliomas, one patient achieved a near-complete response, while the remaining two patients had partial responses [43]. Investigators are also looking into targeting VEGF, mammalian target of rapamycin (mTOR), propyl hydroxylase, and hypoxia-induced factor-1-alpha [23]. While many of these preliminary studies focus on pheochromocytomas and non-head and neck paragangliomas, future studies will hopefully include head and neck paragangliomas.

Conclusion

JPs remain a challenging entity to manage even without multiple foci, altered surgical anatomy, catecholamine secretion, metastases, or poor surgical candidates. While a multidisciplinary approach is needed to manage these complex tumors, careful consideration of the patient's prognosis, as well as their quality of life, is mandatory to appropriately manage each patient. Future therapies, including radiopharmaceuticals and targeted molecular therapies, may lead to improved outcomes in not only complex JPs but in all patients with paragangliomas.

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