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# Carotid Body and Vagal Paragangliomas: Epidemiology, Genetics, Clinicopathological Features, Imaging, and Surgical Management

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**Abstract:** Carotid body and vagal paragangliomas, although considered indolent tumors, represent a challenge for the treating physician. This is mainly because of their peculiar localization, in close proximity with important anatomical structures. In addition, there is no chemotherapy available for these

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tumors, the role of radiation therapy is debated, and the only successful therapy is surgery. However, to achieve the best treatment goals, it is fundamental for the professional caregiver to master not only the clinical and surgical procedures but also the genetic backgrounds and the histopathological features of these tumors. We provide in this chapter a comprehensive review of the above mentioned aspects, with the aim to address the complexity of these tumors with a multidisciplinary approach.

**Keywords**: Carotid body paraganglioma; Digital subtraction angiography; Neuroendocrine tumors; Shamblin classification; Vagal paraganglioma.

## INTRODUCTION

Carotid body paragangliomas (CBPs) and vagal paragangliomas (VPs) comprise a set of rare, slow-growing neuroendocrine tumors arising in the anterolateral aspect of the upper neck. CBPs arise from the carotid body, located at the carotid bifurcation, and VPs arise from the paraganglia along the vagus nerve, particularly the inferior nodal ganglion. VPs are less common than carotid body and tympanojugular paragangliomas. Overall, CBPs and VPs represent a surgical challenge because of their close proximity to the internal and external carotid arteries, the lower cranial nerves, and the internal jugular vein and because of their possible extension to the skull base. The clinical and surgical management may be further complicated by the fact that CBPs and VPs can show a bilateral and/or multiple presentation, especially in familial forms; metastases, on the other hand, are very uncommon (1).

In the recent decades, CBPs and VPs have received a great deal of attention from pathologists, radiologists, and surgeons, which has led to better understanding of the pathology and, hence, to better management. Various terminologies were used in the past to designate CBPs and VPs, including chemodectoma, glomus tumor, etc. Histopathologically, these tumors have been proven to originate from chromaffin-negative paragangliar tissue. Hence, the most appropriate terminology is paraganglioma (PGL).

## EPIDEMIOLOGY AND GENETICS

It is estimated that head and neck PGLs (HN-PGLs) constitute 3% of all PGLs, 0.6% of all HN cancers, and 0.03% of all tumors (2).CBPs, the most common form of HN-PGL, represent about 65% of all HN-PGLs and have been extensively characterised. VPs account for less than 5% of all HN-PGLs, and, because of their rarity, their epidemiological and genetic features have not been analyzed independently from those of other HN-PGLs. However, in VPs the male to female ratio is estimated to be 1:1.87, and the mean age at diagnosis is about 45 years in familial forms and 60 years in sporadic forms. In VP patients with familial PGL, the incidence of multicentric PGLs was reported as 78% versus 23% in patients with nonfamilial PGL (3).

The incidence rate of CBPs is overall higher in populations living at altitudes higher than 2000 meters above the sea level (4). In this regard, it has been proposed that environmental hypoxia modulates genetic predisposition to CBP (5).

CBPs can be classified into three different forms: sporadic (60%), familial (10–50%), and hyperplastic, that is, associated with CB hyperplasia due to chronic hypoxemia, as in subjects living at high altitudes or in patients affected with cardio-respiratory diseases (6).The latter form may occur in both familial and sporadic cases. Familial PGLs most commonly develop in the head and neck, usually in the carotid body, and up to 80% of familial paragangliomas are multifocal, compared to only 10–20% of sporadic PGLs (7).

Patients without family history present succinate dehydrogenase (SDH) mutation only in 11% of cases, while those with familial history carry SDH mutation in 83% of cases. Patients without *SDH* mutation reportedly present a mean age of 50.3 years at diagnosis, while those with *SDH* mutation report a mean age of 38 years at diagnosis. Genetic testing is advised in case of CBPs, familial history, multicentric presentation, and young age at diagnosis (8).

PGLs, together with the related pheochromocytomas, are considered the tumors with the highest degree of hereditability in humans. Sporadic forms account for about 60% of the cases and familial (or hereditary) forms account for about 40% (9).The most frequently involved predisposition genes are those coding for the subunits of the SDH enzyme, a multiprotein complex composed of proteins encoded by the *SDHA*, *SDHB*, *SDHC*, and *SDHD* genes and by an assembly co-factor encoded by the *SDHAF2* gene (10).

The hereditary paraganglioma pheochromocytoma syndrome is inherited in an autosomal dominant pattern and results from mutations in one of the four *SDH* genes. The *SDH*-related familial PGLs can be distinguished into four (10) or five (11) types: type 1, associated with *SDHD*, which is of particular interest here because *SDHD* is the gene most frequently mutated in HN-PGLs; type 2, which is rare and associated with *SDHAF2* mutations; type 3, which is associated with *SDHC*; and type 4, which is associated with *SDHB* (12). Furthermore, familial PGLs can be associated with germline mutations in other genes, including *RET*, *NF1*, *VHL*, *HIF2A*, *FH*, *TMEM127*, and *MAX*, some of which are related to syndromic entities in which PGL may be linked to other neural crest tumors, such as multiple endocrine neoplasia (*RET*), von Hippel-Lindau (*VHL*) syndrome, neurofibromatosis type 1 (*NF1*), Carney–Stratakis syndrome, and the Carney triad (13).

However, the PGL-associated *SDH* gene variants have incomplete penetrance: in the case of *SDHA* only 1.7%, for *SDHB* 22.0%, and for *SDHC* 8.3% (14). Furthermore, engineered mice mutated in *sdhb*, the homolog of human *SDHB*, do not develop any cancer (15), which suggests that *SDH* gene mutations *per se* might not be sufficient to cause PGL.

Somatic mutations that often insist on pathways linked to PGL predisposition are clearly involved in CBP and VP, as in other PGLs. Interestingly, at the somatic level, an exome analysis performed in 52 CBPs revealed in both hereditary and sporadic cases potential tumor-associated driver mutations in genes affecting metabolism and DNA repair, including, in order of frequency, *SDHD* (13.5%), *IDH1* (7.7%), *ARNT* (5.8%), *SDHC* (5.8%), *KMT2D* (5.8%), *TP53BP1* (5.8), etc. (16).

The hyperplastic form of CBP has been mainly described in individuals living at high altitudes and in patients suffering from chronic obstructive pulmonary disease or cyanotic heart disease (6), which result in chronic exposure to low partial pressure of oxygen. This upregulates the physiological functions of the carotid body, which essentially monitors the fluctuating concentrations of oxygen, carbon dioxide, temperature, and pH in the arterial blood and hence regulates the cardiorespiratory centers in the medulla oblongata via the afferent branches of the glossopharyngeal nerve. Interestingly, there is an association between environmental hypoxia and gender: in fact, at sea level, the male to female CBP ratio is 1:1.4, while at high altitude it decreases to 1:8.3—a phenomenon which is still unexplained (17). Finally, hypoxia has been proposed as a modulator of *SDHB/D* mutations penetrance (5, 18, 19).

## GROSS PATHOLOGY

Occurring in the cervical region, where they can freely expand, CBPs and VPs come to the clinical attention as an enlarging cervical mass; at resection, their maximum diameter generally ranges from 2 to 6 cm (20). At gross pathological examination, these PGLs present as well-circumscribed, reddish-brown, fusiform or globular rubbery masses, often invested by a thin continuous or partial fibrous pseudo-capsule. However, their enucleation through a cleavage plane is rarely possible (21), as CBPs often encase a carotid artery and infiltrate its adventitia, while VPs infiltrate the perineuria of local nerves and may as well extend to and infiltrate the skull base. The cut surface, due to the occurrence of hemorrhages and fibrosis, is usually variegated rather than homogeneous, with yellow, tan, red, and brown areas. The specimens coming to the pathologist usually consist of quite large fragments and, notwithstanding the frequent occurrence of necrosis, hemorrhage, and iatrogenous artifacts, a definite histological diagnosis is generally easily achievable.

## HISTOPATHOLOGY

The microscopic morphology of CBPs and VPs is comparable to that of other HN-PGLs, with subtle differences concerning features related to the generally larger tumor size, allowed by the specific site of origin, which permits relatively free expansion. These features include well-circumscribed profile, often with evidence of a fibrous pseudocapsule (Figure 1A), rarity of bone infiltration, frequent occurrence of extensive areas of fibrosis, presence of myelinated fibers or ganglionic structures peripheral to the tumor, and, lastly, size of the tumor cells, which, in our experience, tends to be larger than in tympanojugular PGLs.

CBPs and VPs show the characteristic "zellballen" pattern, that is, a reticular network of interlacing neuroepithelial sheets of varying thicknesses, separated by a rich microvascular bed (Figure 1B). In the microscopic section plane, this "zellballen" pattern takes the appearance of roundish or elongated oval clusters of cells. The thickness of these clusters varies from about 20 microns

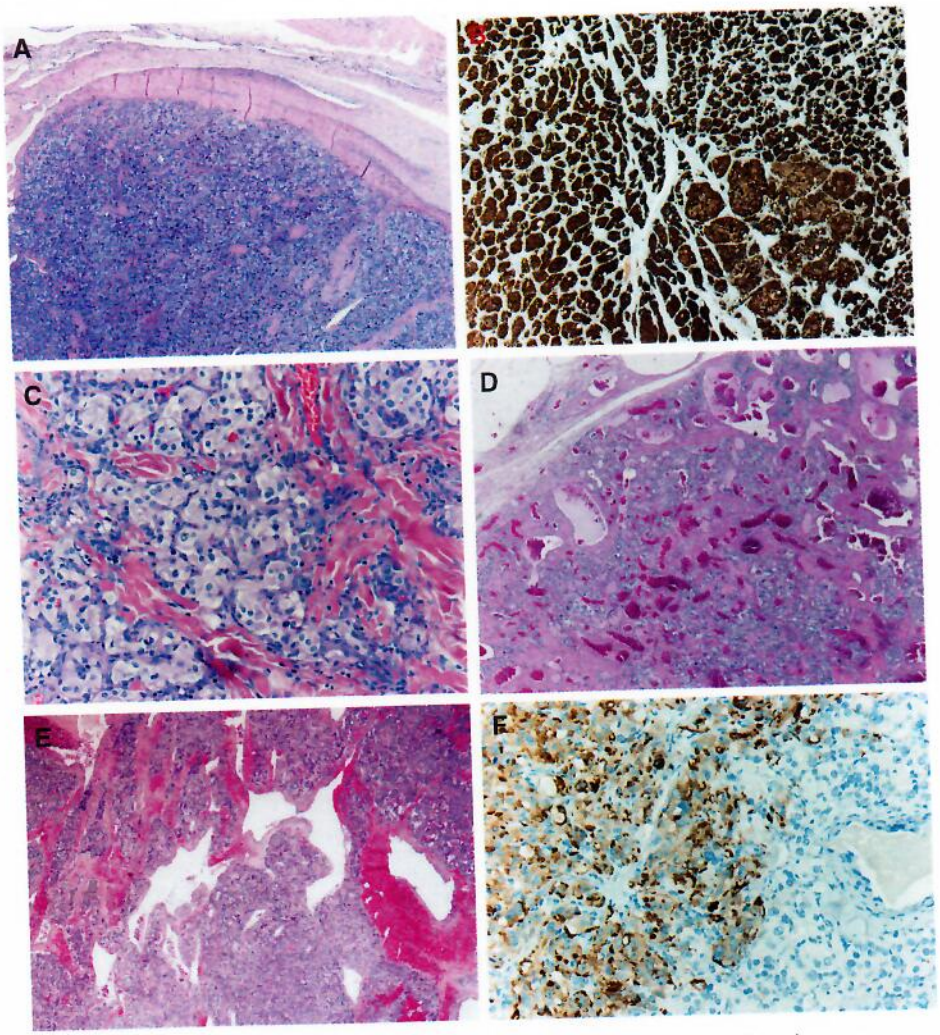


**Figure 1 Histological patterns of vagal and carotid body paragangliomas.** (A) Vagal paraganglioma with well-formed pseudocapsule (HE, 40x). (B) Carotid body paraganglioma: the meshwork of chief cells is highlighted by synaptophysin immunostaining (40x). (C) Carotid body paraganglioma: sclerotic septa and large chief cells with oncocytic appearance (HE, 200x). (D–E) Hemangiopericytomatous patterns in carotid body paragangliomas (HE, 40x). (F) Carotid body paraganglioma: wide variability of chromogranin A immunostaining of chief cell.(200x).

(approximately two neuroepithelial cells) up to several hundred microns, being highly variable, even within the same tumor. In our case series, a thin generally incomplete pseudo-capsule was nearly constantly observed (Figure 1A), as well as fibrosis, in the form of irregular septa between zellballens or of large sclerotic areas (Figure 1C). The extension of the fibrotic areas may vary from 5 to 90% of the tumor section surface. Ectatic, irregularly angulated, or arciform blood

vessels are frequently observed, in association with both sclerotic areas and with florid tumor parenchyma. In a few cases, the aberrant vascular network is so prominent that it gives a "hemangioperycitomatous" pattern to the tumor (Figure 1D, 1E). Focal hemorrhage and necrosis are common, both as a spontaneous event and as a consequence of preoperative embolization. Other iatrogenous artifacts, mainly thermal and electrosurgery-related, are present in nearly all cases.

Cytologically, the zellballens contain a main population of "chief" (type 1) or neuroepithelial cells, and a minor population of "sustentacular" (type 2) cells, the latter mainly at the zellballen's periphery. Chief cells are quite large, epithelioid, and sometimes fusiform, with extensive, finely granular, and eosinophilic cytoplasm, but can also be amphophylic or clear or even vacuolated. The chief cells, identified by their immunoreactivity for chromogranin, synaptophysin (Figure 1B, 1F), NSE, and other neuroendocrine markers, contain neurosecretory granules, visible by electron microscopy and absent in sustentacular cells. In our experience, synaptophysin, a marker of the envelop of these granules, is excellent in defining the tumor structure, while chromogranin in most cases gives non-homogeneous results, with variable immunostaining from area to area and frequent occurrence of completely negative areas. Vimentin, a mesenchymal marker, results always positive in all cell types, both vascular and neural, with variable staining intensity.

In our experience, the size of the chief (neuroepithelial) cells of CBPs and VPs ranges from 9 to 36 microns. The nuclei appear round or oval, with "salt and pepper" granular chromatin, without evident nucleoli. As in other neuroendocrine tumors, there are often isolated larger, sometimes frankly "monster" cells with giant, irregular, lobulated, and hyperchromatic nuclei, often containing vacuolar pseudoinclusions (Figure 2A). The cause of this phenomenon has not been clarified, but it does not seem to be related to malignant behavior (21). Rarely the chief cells can assume a fusiform shape, giving rise to a pseudosarcomatous pattern (21) (Figure 2B). Overall, the sustentacular cells account for only 1–5% of the tumor cells (21). Of supposedly Schwannian origin, these cells, characterized by an elongated, endothelial-like, or quasi-stellated shape with long, subtle cytoplasmic processes, surround chief cells aggregates and are brightly highlighted by S-100 immunostaining (Figure 2C, 2D). Their number varies even within each single tumor (in our experience, from 15 to 60 per high-power microscopic field) and seems to be inversely related to the thickness of the zellballen (in areas with thin zellballens, the number of sustentacular cells tends to be higher). We believe that small zellballen size may reflect regenerative phenomena after tissue injury. In fact, when the zellballens are very reduced in size, the chief/sustentacular cell ratio may decrease to 1/2 in the section surface. Variability in sustentacular cell number seems to be greater in VPs compared to CBPs. In most cases (>60%), the proliferative index, as investigated using the Mib1 antibody, is low (≤1%); in the remaining cases, it may range from 2 to 10%. Only occasionally, and particularly near sclerotic and/or necrotic areas, there is evidence of a high proliferative index (≥10%). Chronic inflammatory infiltrates are usually absent, except occasionally and focally, next to areas of embolization (21). In a few VPs we observed peripheral infiltration of troncular or ganglionar neural structures, but we never found bone infiltration or evidence of direct vascular invasion.

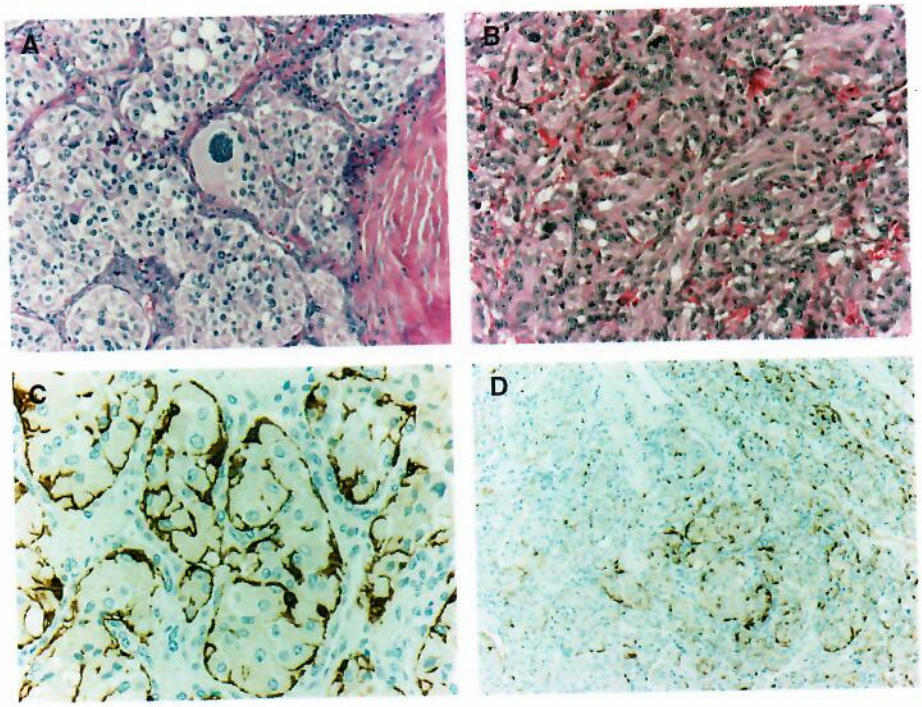


**Figure 2 Atypical patterns and sustentacular cells in carotid body and vagal paragangliomas.** (A) Atypical monster cell in carotid body paraganglioma (HE, 200x). (B) Carotid body paraganglioma with a pseudosarcomatous pattern (HE, 200x). (C) Carotid body paraganglioma with dendritic processes of sustentacular cells highlighted by immunostaining with antibody to S-100 (400x). (D) Carotid body paraganglioma showing dishomogeneous distribution of the sustentacular cells, immunostained with anti-S-100 (100x).

## DIFFERENTIAL HISTOPATHOLOGICAL DIAGNOSIS

Imaging data are often resolutive in diagnosing CBPs and VPs. However, histopathological analysis should always rule out other tumors with similar morphology that may occur in the cervical region. These include lymph node metastases of neuroendocrine carcinomas, anaplastic carcinomas, melanomas, or renal cell carcinomas, as well as medullary carcinoma of the thyroid and other thyroid and salivary tumors with oncocytic appearance, which can mimic chief cell morphology. In this regard, immunohistochemistry for keratins and S-100 is quickly resolutive.

## METASTATIC BEHAVIOR

The incidence of metastases in HN-PGLs as a whole is lower than 5% (22) and, among all HN-PGLs, CBPs have the lowest risk of metastasis (6, 23). Large series of treated patients with long follow-up indicate a 2% rate of malignancy

in CBPs (21, 24, 25). In the smaller group of VPs, the reported frequency of metastasis varies between 7 and 10.6% (20, 21, 26). Nevertheless, the current opinion is that all PGLs should be regarded as malignant, that is, potentially able to metastasize, although such potential is usually very low (22, 27). The real problem is that of stratifying the metastatic potential according to predefinable clinical or pathological indicators. In this regard, variable criteria have been proposed, but reliable histological parameters are not available at present. Features such as cell "atypia," infiltrative profile of the tumor edge, bone invasion, or infiltration of vascular and neural structures (surely detrimental to the patient) are unreliable in predicting a metastatic behavior. Even proliferative activity does not help. Nevertheless, it is suggested that proliferative activity data based on Ki-67 immunohistochemistry should be provided in the pathological report (22).

## CORRELATIONS BETWEEN GENETIC AND PATHOLOGICAL FEATURES

An integration between histopathological and genetic data is the key for the better management of a PGL patient. In particular, mutations in the *SDH* genes are among the most relevant in defining tumor behavior and are present in sporadic and familial cases (10). Mutations in these genes define four (10, 28) or five (11) PGL syndromes. PGL1 syndrome, associated with mutations in *SDHD*, is the most frequent in HNPGLs, particularly in CBPs (12), but CBP patients often present also other HN-PGLs and/or phaeochromocytoma and/or sympathetic trunk PGLs. Regardless of multiple presentation, the PGL1 syndrome confers a low risk of metastasis. In contrast, the PGL 4 syndrome, due to constitutional mutations in *SDHB*, is generally associated with single HN-PGLs, but implies a high risk of metastasis (30–50%) (12, 23, 28, 29, 30, 31). In this regard, a recent study of 54 patients carrying *SDHB* germline mutations, with a total number of 62 HN-PGLs, revealed the presence of multiple tumors in 15% of the cases, phaeochromocytoma in 2%, metastasis in 6%, and additional non-paraganglionic tumors in 6% (32). The non-paraganglionic tumors are of particular relevance, as they include aggressive cancers, such as renal clear cell carcinoma and gastrointestinal stromal tumors (GISTs), as well as pituitary tumors (32, 33). These data emphasize the importance of detecting *SDHB* mutations in all HN-PGLs, as they are potential drivers of metastasis, which entails more stringent clinical follow-up.

Importantly, mutations in any of the *SDH* complex genes (*SDHA*, *SDHAF2*, *SDHC*, and *SDHD*) lead to loss of immunohistochemical expression of the SDHB protein, generally limited to chief PGL cells (32–34). Thus immunohistochemistry provides a clear indication for SDH genes testing (32). In our CBP and VP series, *SDHB* immunostaining resulted positive in all the paraganglioma cell types—in only 6 (4 CBPs and 2 VPs) of 21 cases, with a mild/moderate intensity of staining—and negative, only in the PGL chief cells, in the remaining 15 cases (Figure 3A, 3B). SDHA was strongly positive in all but one of the tested cases; this case was also negative for SDHB (Figure 3C, 3D).

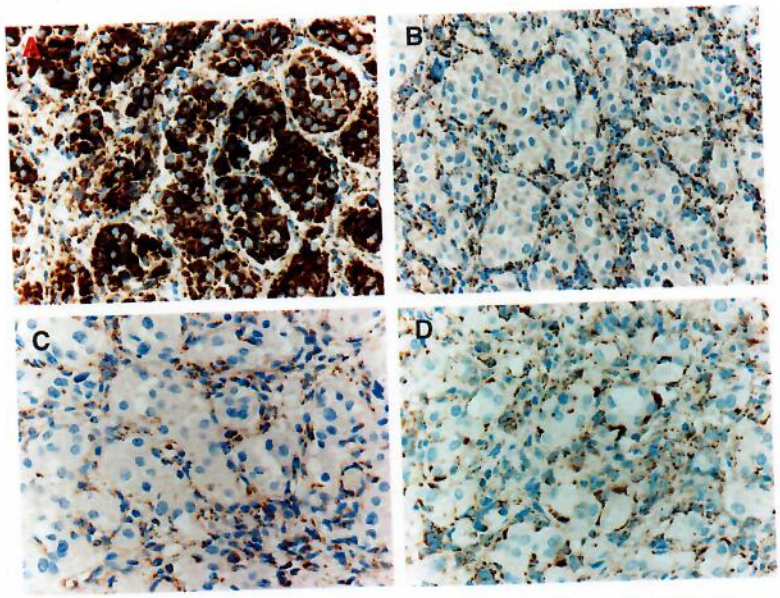


**Figure 3 SDH immunostaining in vagal and carotid body paragangliomas.** (A, B) Vagal paraganglioma: marked immunoreactivity for SDHA in all cell types (A) and no immunoreactivity of chief cells for SDHB (B) (400x). (C) Carotid body paraganglioma: faint staining for SDHB of sustentacular and endothelial cells, with negativity of chief cells (400x). (D) Carotid body paraganglioma: moderate staining for SDHA of sustentacular and endothelial cells, with negativity of chief cells (400x).

## CLINICAL FEATURES

Both CBPs and VPs are invasive but indolent tumors. Jansen et al. (35) determined that the average growth rate of CBPs was 0.83 mm per year, about the same as that of other HN-PGLs. In obese patients, these tumors may go unnoticed and thereby present in advanced stages. Both set of tumors are characteristically diagnosed by their pulsatile nature and their limited mobility in their supero-inferior axis when compared to the lateral axis (Fontaine's sign) (36). They are only rarely associated with catecholamine hypersecretion and, hence, urinary catecholamine screening is often performed only in the presence of symptoms like tachycardia and/or hypertension or in case of a family history of paraganglioma. Preoperative cranial nerve paralysis is a feature of advanced lesions. Medially growing tumors may cause swelling of the oropharynx, leading to hoarseness, dysphagia, or foreign body sensation that are symptoms of the compression of cranial nerves IX, X, and XII. Furthermore, these tumors can also reach the skull base and extend intracranially (37, 38). Involvement of the sympathetic chain can lead to symptoms characteristic of Horner's syndrome (39, 40).

As mentioned earlier, VPs usually originate from the inferior vagal ganglion, also called the nodose ganglion. When they arise from the middle and superior

ganglia, the jugular foramen, and, possibly, the atlas, may be involved. Intracranial extension associated with the cervical component gives rise to a dumbbell-shaped tumor (41).

## DIAGNOSTIC INVESTIGATIONS

Neuroradiological imaging methods play a pivotal role in the diagnosis and surgical planning of CBPs and VPs. Contrast CT and MRI are complementary and are the investigations of choice, since they are able to identify the anatomical location and vascularity of these tumors. They help to differentiate PGL from other prestyloid or poststyloid tumors and from tumors that originate from the deep lobe of the parotid. They also provide vital information on potential intracranial and/or intradural spread. Specific imaging characteristics, like salt-and-pepper appearance in contrast MRI, are crucial to differentiate CBPs from other tumors of the parapharyngeal space (PPS) and dictate the need for further workup, as well as choice of surgical approach (42). CT is indicated for tumors invading the skull base, to better delineate the details of the bony erosion and the extension. MRI is indicated in most cases and is complementary to CT. It will be evident radiologically that VPs are located behind the internal carotid artery (ICA), unlike CBPs, which are found at the carotid bifurcation. VPs will be characteristically found to displace both the internal and external carotid arteries anteriorly, while the internal jugular vein is compressed and displaced posteriorly (43). Digital subtraction angiography is the gold standard to study ICA infiltration, which will be seen as stenosis of the arterial lumen. It is also useful to detect the feeding vessels supplying the tumor, to check the collateral circulation through the circle of Willis and to determine the status of the venous drainage of the brain (44). It is usually performed 24– 48 h before surgery to enable embolization of the feeding vessels. CBPs and VPs are also studied with functional imaging techniques, such as 18F-fluorodihydroxiphenylalanine (18-F-FDOPA), positron emission computed tomography (PET/TC), 18F-fluorodopamine (18F-FDA) PET/TC, or 123I-metaiodobenzylguanidine (123I-MIBG). Positron emission tomography (PET) is now being used successfully for these tumors, which express large numbers of somatostatin receptors and can be helpful in the detection of metastatic disease (37).

## CLINICAL CLASSIFICATION OF CBPS

The classification proposed by Shamblin (45) has been widely accepted. However, this classification has its limitations. To truly asses a tumor, a clinical classification that helps in surgical planning and predicting outcomes is desirable, and this is where the Shamblin classification is found lacking. In fact, the Shamblin classification is essentially an anatomical and radiological classification that subdivides CBPs based on the encirclement of the internal and external carotid arteries. However, the involvement of the external carotid artery and its excision, if required, do not lead to any significant morbidity.

Shamblin's classification also does not predict true arterial infiltration and thereby preoperative intra-arterial management. Luna-Ortiz et al. (46) rightly pointed out that small tumors (Shamblin type I) might also infiltrate the carotid arteries, thereby making excision difficult. These authors proposed a further distinction of Shamblin type III into types IIIa and IIIb, wherein small tumors infiltrating the carotid are included under type IIIb. In an attempt to make the classification more predictive, Arya et al. (47) described Shamblin types I, II, and III tumors according to the radiological degree of involvement of the ICA as ≤180°, >180° but <270°, and ≥270°, respectively. However, this is at best an extension of the existing Shamblin classification and does not accord any additional benefit in terms of surgical management or prediction of outcome. The vertical growth of CBPs poses a specific surgical challenge when these tumors reach the infratemporal fossa (skull base) and involve the carotid canal or the jugular foramen, and also this is not addressed by the Shamblin classification. Considering this, we propose a modification to the Shamblin classification, as shown in Figure 4, which allows complete and systematic assessment of CBPs and the surgical planning thereafter. This classification takes into account the involvement of the ICA and the application of intra-arterial stenting according to the infiltration of the artery. It also takes into account the compartmentalization of the PPS into upper, middle, and lower compartments and the extent of tumor spread accordingly. The choice of surgical approach is determined by the extent of the spread according to these compartments.

## EMBOLIZATION

As in the case of other PGLs, also in the case of CBPs and VPs preoperative embolization is supported by the fact that these are highly vascularized tumors. However, while some authors advocate preoperative embolization (38, 41), others do not (48, 49). In our practical experience, tumor embolization usually facilitates gross total tumor removal, minimizes intraoperative bleeding, and decreases the incidence of cranial nerve paralysis (50). The decision for embolization depends on tumor size and angiographic findings. In small tumors with a minimal blood supply, embolization is not performed. When the size ranges between 3 and 5 cm in diameter, embolization of external carotid artery branches, such as the ascending pharyngeal and the occipital arteries, is performed.

## SURGICAL TREATMENT

The factors to be considered in the treatment of CBPs and VPs are age, lower cranial nerve paralysis, internal carotid artery involvement, and multicentricity. As a general rule, in young patients, a total tumor resection must be attempted, as they usually tolerate the loss of lower cranial nerve function; on the contrary, a wait-and-scan policy or radiotherapy may be adopted for older patients or patients who are not fit for surgery.

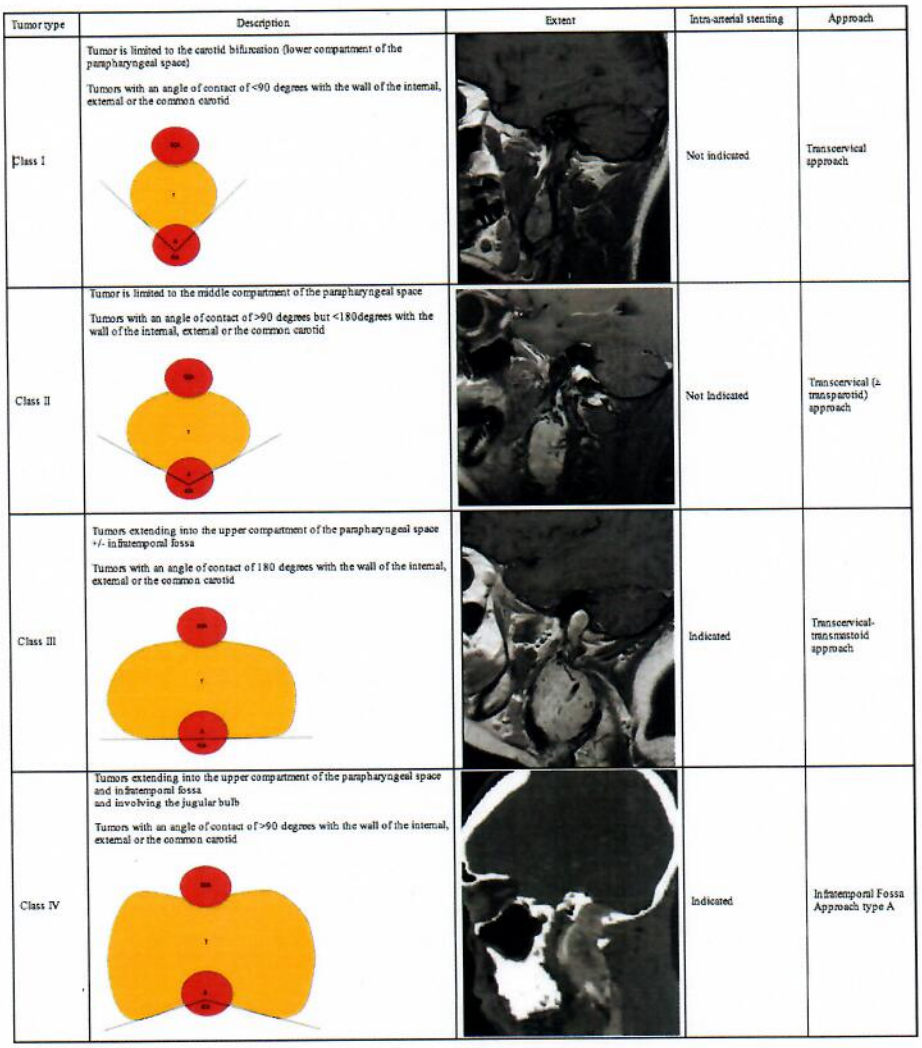


**Figure 4** Modification of the Shamblin classification.

## Surgical planning and intra-arterial stenting of the carotid

Surgery is the treatment of choice for all neck paragangliomas, and this is reinforced by the fact that 6–12.5% of them have a malignant potential (51). Surgical planning involves the evaluation of (i) tumor extent, (ii) neural involvement, and (iii) ICA involvement and possible infiltration. The extension of the tumor must be evaluated not only in the horizontal dimensions, but also along the vertical dimension. In our earlier report on PPS tumors, we proposed to divide this space into upper, middle, and lower compartments (52). Such division enables us to apply appropriate

surgical approaches to tumors in the relevant compartments. While a trans-cervical approach (with or without a transparotid extension) may be enough to manage any extension of the tumor into the lower or middle PPS, this is not always adequate to manage tumors involving the upper PPS or the infratemporal fossa.

Involvement of the ICA is one of the crucial factors that determines the surgical strategy for CBPs. It is best to identify the danger to the ICA due to its relationship with the tumor and deal with it preoperatively. A significant proportion of the mortality in HN-PGL surgery, reported in earlier series, was due to injury injury or resection of the ICA (53). ICA manipulation can be extremely dangerous, as it can result in spasm, thrombosis, rupture, massive stroke, and even death (54, 55). The intraoperative risk of vascular injury is especially high in irradiated or previously operated cases. The application of intra-arterial stenting in the management of ICA has proven to be of enormous benefit to the patient, especially in the case of Shamblin classes II and III tumors and complex tumors (*i.e.*, associated with other PGLs), and this merits to be part of the standard protocol of CBP management. The presence of the stent greatly facilitates dissection and mobilization of the ICA (Figure 5). The greatest risk is a potential injury at the transition point of the stented and non-stented artery, and

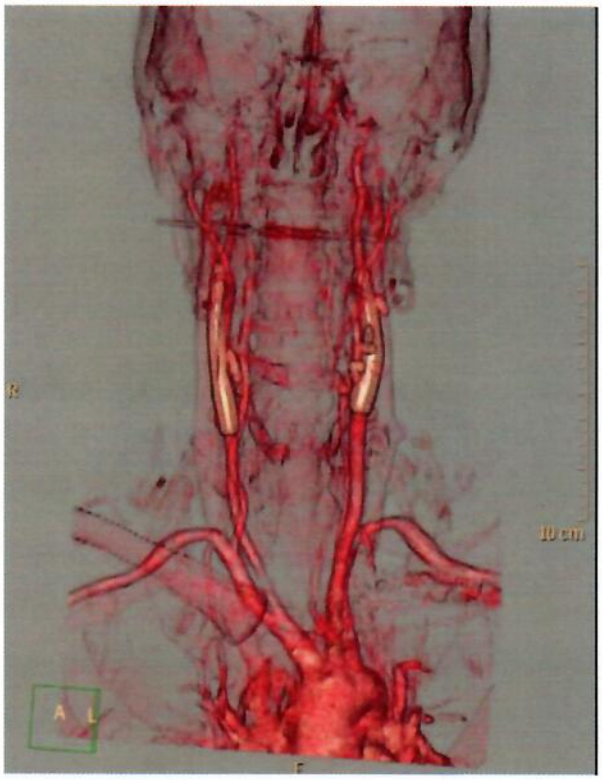

**Figure 5** Digital subtraction angiography showing intra-arterial stenting in a case of CBT.

minimization of traction is essential at this point. To reduce this particular risk, we ensure that the stent covers the ICA 1 cm proximal and distal to the tumor. Potential complications associated with lifelong antiplatelet therapy (i.e., gastrointestinal ulcers and mucosal bleeding) are the main drawbacks associated with ICA reinforcement with stent. However, the risk is diminished with the low dose of aspirin generally prescribed.

The following surgical approaches are used based on the compartmentalization of the PPS into upper, middle, and lower PPS:

- *Transcervical approach (TCA) for tumors of the lower PPS*—In this approach, the posterior belly of the digastric muscle is resected, the extra-temporal facial nerve (FN) is identified, and the styloid process is transected to allow larger and safer access to the PPS (Figure 6).
- *Transcervical-transparotid approach (TC-TPA) for tumors of the middle PPS*—In addition to the TCA, this procedure includes parotidectomy with preservation of the FN.
- *Transcervical-transmastoid approach (TC-TMA) for tumors of the upper PPS with a posterior extension*—In this approach, the TCA is extended to the postauricular region, with a view to open the lateral skull base. In this procedure, the mastoid tip is removed, leaving the VII nerve in its canal. This is followed by infralabyrinthine dissection to expose the sigmoid sinus and the jugular bulb in order to control the uppermost part of the tumor.
- *Infratemporal fossa approach-type A (ITFA-A) for tumors of the upper PPS with extension to the vertical tract of the ICA* and the jugular bulb—In this approach, a permanent anterior transposition of the facial nerve is performed to provide optimal exposure of the uppermost parapharyngeal ICA, the vertical portions of the petrous ICA and the jugular foramen.

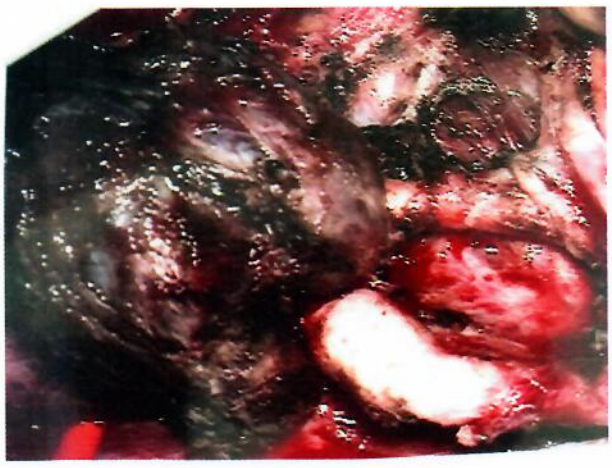

**Figure 6** Intraoperative view of a massive CBP being separated from the ICA.

## CONCLUSION

CBPs and VPs are frequently associated with genetic predisposition, particularly with mutations regarding *SDH* genes. As in the case of other PGLs, genetic counseling is recommended since they can occur in familial forms and can have bilateral or multicentric presentations. CBPs are most frequent in populations living at high altitudes. The microscopic morphology of CBPs and VPs is comparable to that of other HN-PGLs. Overall, they are challenging lesions to treat and no drug therapies are currently available; however, since they are mostly non-metastatic, surgical success rates are high if the preoperative assessment is undertaken carefully. Preoperative endovascular intervention in the form of intra-arterial stents in the cervical and petrous segments of the ICA has transformed the therapeutic management of CBPs. Stenting of the ICA gives a chance for complete tumor removal with arterial preservation. It reduces the risk of injury to the artery during surgery and also eliminates the need of potentially troublesome maneuvers like permanent balloon occlusion, bypass procedures, and arterial repair or reconstruction in case of a damage. TCA is the ideal approach for tumors of the lower compartment of PPS, TCA/TC-TPA is the ideal approach for the middle compartment, and TC-TMA or the ITFA type A are the ideal approaches for the upper compartment. The use of an operating microscope combined with bipolar cautery during surgeries leads to improved results and decreases postoperative complications.

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# Tympanojugular Paragangliomas: Surgical Management and Clinicopathological Features

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**Abstract:** In this chapter, we provide a focused review on a highly challenging subset of head and neck paragangliomas, that is, those arising from the skull base (jugulotympanic region). Presently, these tumors can be cured only with surgery, which must be performed in highly specialized skull base surgical centers. We review here the clinical presentation, diagnostic workup, classification, and surgical management of these rare but important tumors, together with currently available evidence concerning genetics, developmental origin, and pathology.

**Keywords**: Angiography; High-resolution computed tomography; Infratemporal fossa approach; Modified Fisch classification; Tympanojugular paraganglioma

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## INTRODUCTION

Paragangliomas of the head and neck can be classified as temporal bone paragangliomas (TBP) (tympanomastoid and tympanojugular paragangliomas [TJPs]) and neck paragangliomas (vagal and carotid body paragangliomas) according to their presentation (1). Indeed, paragangliomas can arise from more than 20 locations in the head and neck, but they are very rare in other sites. Tympanomastoid paragangliomas arise within the inferior tympanic or mastoid canaliculi, while TJPs arise from the paraganglia of the adventitia of the jugular bulb (JB).

TJPs present a challenge for the treating physician because of the fact that these tumors are vascular, locally aggressive, and involve important neurovascular structures, like the internal carotid artery (ICA), the JB, the facial nerve (FN) and the lower cranial nerves (LCNs, CN IX, X, XI, XII). Because of their slow and silent growth, there is often a delayed presentation, with cranio-temporo-cervical extensions that, in the past, left them inoperable. However, many developments in the past decades have changed this situation. Various rational approaches have been described to access different parts of the skull base after a thorough understanding of the anatomical and surgical characteristics, making it easy and safe to remove tumors in the area. This has also been aided by technical advances in microsurgery, neuromonitoring, neuroanesthesia, and neuroradiology. All this has resulted in surgery having emerged as the mainstay of treatment for TJPs. According to the Fisch classification of TBPs, TJPs are traditionally classified into classes A, B, C, and D based on the location and extension assessed by high-resolution computed tomography (HRCT). This was subsequently modified by Sanna (2) to include sub-classifications and an additional class V, comprising tumors that involve the vertebral artery (VA) (Table 1).

## CLINICAL PRESENTATIONS

A pulsatile middle ear mass is pathognomonic of a temporal bone paraganglioma (3, 4, 5, 6). The classically described blanching of the middle ear component, that is, Brown's sign, is present in 20% of the cases (6). Otoscopy alone is not reliable to assess the extent, most significantly related to the degree of hypotympanic extension (6). TBPs invading the tympanic bone from the jugular fossa may show what is called the "rising sun" sign. Paragangliomas can also extend through the tympanic membrane and be confused with an inflammatory polyp. Occasionally, otorrhagia can be a significant clinical symptom.

The most common presenting symptom of a TJP is that of hearing loss, present in approximately 60–80% of the cases, with pulsatile tinnitus also affecting the majority of the patients (60–80%) (3, 6–26). Hearing loss is usually conductive because the tumor compresses or erodes the ossicular chain, or due to effusion. Given the slow growth and the nonspecific nature of the symptoms, patients present with an average of 2–3 years delay after the onset of the symptoms.

When the inner ear is invaded, there can be sensorineural hearing loss or vestibular symptoms. Lower cranial nerve deficits usually develop secondary to invasion of the medial wall of the jugular fossa. Cranial nerve deficits can be

**TABLE 1 Modified Fisch classification of 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 |

masked, due to slow progression, aided by gradual compensation from the contralateral nerves. In approximately 10% of the cases, cranial nerve palsies can be silent. Palsies of cranial nerves IX and X are seen in approximately 35–40% of the cases, and those of cranial nerves XI and XII are seen in about 21–30% of cases. Involvement of the FN is reported in 10–39% of the cases (3, 8, 25–29).

A jugular fossa pathology must be kept in mind for patients presenting with isolated or multiple LCN palsies. Vocal fold paralysis, presenting with a change in voice, is the most common clinical scenario (30). Palatal asymmetry strongly

suggests a skull base pathology involving the glossopharyngeal or vagus nerves. Complete cranial nerves examination, including palpation of the neck and upper aero-digestive tract endoscopy, is an integral part of the examination for TBPs.

## DIAGNOSTIC WORKUP

The study of axial and coronal HRCTs is mandatory for the diagnosis of TJPs. When the jugular foramen is involved, T1, T2, and T1 with gadolinium-enhanced sequences, MR angiography and venography are necessary (31). A 4-vessel angiography is reserved for difficult cases with ICA and VA involvement. Since TJPs cannot be biopsied due to their vascularity, the diagnosis is based solely on radiology. Hence, it is important to identify and diagnose the pathologies by radiology, which in turn influences management options, surgical approach, and prognosis (31).

### High-resolution computed tomography

The bone erosion seen on high-resolution CT scans of TJPs is classically described as a "moth eaten" appearance. The margins of the jugular fossa may be irregular and expanded, with evidence of erosion of the caroticojugular crest or jugular spine. In advanced cases, the entire jugular foramen may be destroyed. However, it is very important to differentiate tympano-mastoid paragangliomas from TJP by identifying the margins of the jugular foramen. If the jugular foramen is found to be by and large free of tumor or anatomical distortion, it is most likely to be a tympanomastoid paraganglioma. Magnetic resonance imaging (MRI) can be done then to distinguish the two entities (6).

### Magnetic resonance imaging

MRI is very useful in mapping TJP. It provides information about the extent of the tumor, both into the neck and intracranially. The incidence of intracranial extension in TJPs is about 60–75% and the rate of intradural involvement is approximately 30% (3, 8, 32, 33). Paragangliomas show low to intermediate intensity in T1 signal and high intensity in T2 signal. A classic "salt and pepper" pattern appearance can be seen in lesions >2 cm, especially in T2 images. This is due to areas of hyperintensity on T2 images because of slow flow within the tumor and the presence of intratumoral vasculature appearing as flow voids (31, 34, 35). Dural invasion is difficult to detect due to the fact that the dura is often pushed medially rather truly infiltrated. MRI also gives information regarding invasion into the marrow spaces of the skull base, with obliteration of the normal fatty signal. Along with T1, T2, and contrast studies, other sequences used to study paragangliomas are dual T2 fast spin echo sequences, non-contrast and contrast time of flight sequences, as well as contrast magnetic resonance angiography (MRA) and venography (MRV) along with three-dimensional (3D) reconstructions (36).

### Angiography

Angiography is important both for the diagnosis and for the management of TJPs. Paragangliomas demonstrate a characteristic blush and rapid venous diffusion. Angiography also demonstrates the vascular supply of the tumor, the degree of ICA involvement, the contralateral cerebral blood flow, the venous drainage, and aids in pre-operative embolization in case of surgery.

## CHOOSING THE RIGHT APPROACH FOR THE JUGULAR FOSSA

The jugular foramen is a very complex area closely encompassing critical neurovascular structures. The most important goal with surgeries in this area is to achieve optimal exposure of the structures while minimizing the damage and to obtain proximal and distal exposures of the important arteries and veins (13, 37, 38). The two essential facts to be considered while obtaining adequate surgical exposure are (i) whether the FN needs to be mobilized and (ii) whether the middle ear can be preserved. The next most important aspect is the degree of ICA involvement, followed by the extent of intracranial extension.

The infratemporal fossa approach (ITFA) type A is the workhorse of TJP surgery ever since it was first described by Fisch and Pillsbury in 1979 (39). ITFA-A allows access to the jugular foramen, the infralabyrinthine areas, the apical compartments of the petrous bone, and the vertical segment of the internal carotid artery (Figure 1A). The key feature in this approach is the anterior transposition of the FN, which opens up the above-mentioned areas for dissection (Figure 1B). The other structures that prevent lateral access to these areas include the tympanic bone, the digastric muscle, and the styloid process (Figure 1C), which are removed to obtain unhindered access. The morbidity with ITFA-A includes conductive hearing loss, temporary or permanent dysfunction of the FN, and temporary masticatory problems.

## SURGICAL STEPS

A postauricular skin incision is performed. A small, anteriorly based musculoperiosteal flap is elevated to help in closure afterward. The external auditory canal is transected as before. The FN is identified at its exit from the temporal bone. 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 the 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 are removed. A canal wall-down mastoidectomy is

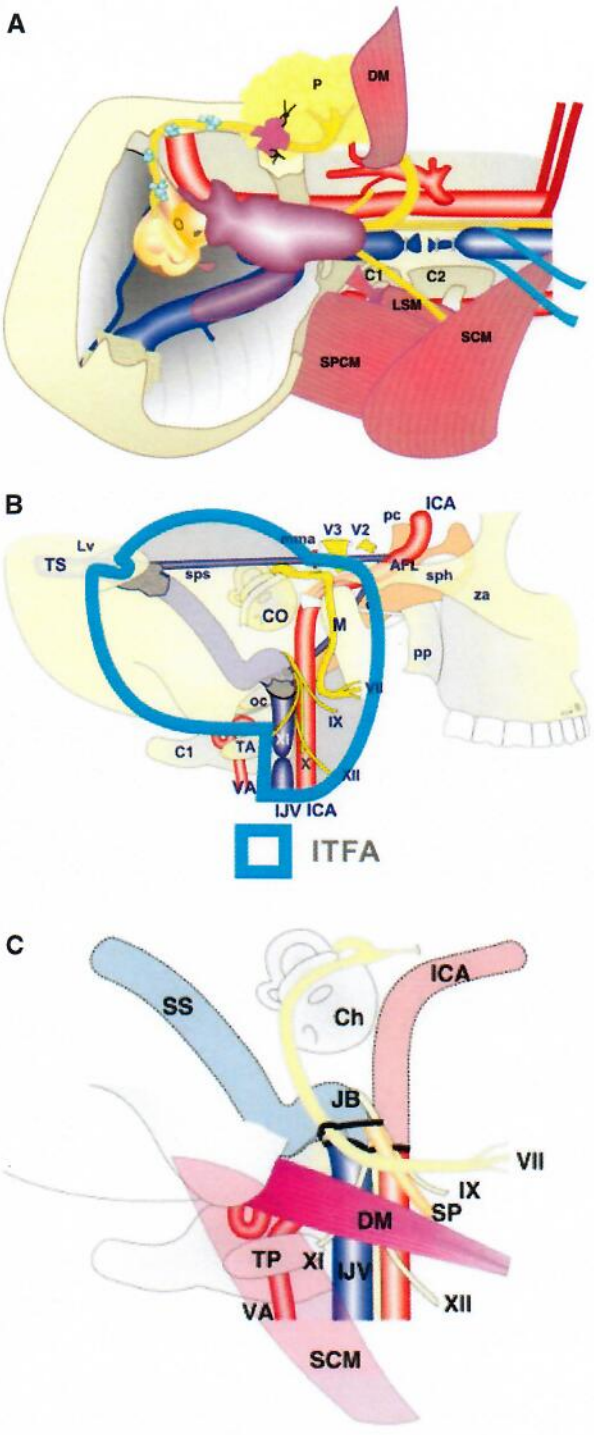


**Figure 1 Illustrations for ITFA type A.** (A) surgical view in ITFA, (B) surgical limit in ITFA, and (C) obstacles to approach the jugular bulb.

C1, atlas; C2, axis; Ch, cochlea; CO, cochlea; DM, posterior belly of the digastric muscle; ev, emissary vein; Involvement of the facial nerve (FN); ICA, internal carotid artery; IJV, internal jugular vein; IX, glossopharyngeal nerve; JB, jugular bulb; LSM, levator scapulae muscle; Lv, vein of Labbe; OC, occipital condyle; P, parotid gland; pc, clinoid process; pp, pterygoid plate; M, mandible; SCM, sternocleidomastoid muscle; SP, styloid process; SPCM, splenius capitis muscle; sph, sphenoid sinus; za, zygomatic arch; sps, superior petrosal sinus; TA, transverse process of atlas; TP, transverse process of the atlas; TS, transverse sinus; V2, maxillary branch of trigeminal nerve; V3, mandibular branch of trigeminal nerve; VA, vertebral artery; VII, facial nerve; XI, spinal accessory nerve; XII, hypoglossal nerve.

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 with microscissors. 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. 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. 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 carefully elevated, using a curved 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. A tunnel is created in the parotid gland to lodge the transposed nerve. The tunnel is closed around the nerve using two 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. Drilling of the infralabyrinthine cells is completed, and the vertical portion of the internal carotid artery is identified. 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. The sinus is closed by double ligation with a Vicryl suture. 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. The structures attached to the styloid process are severed. The styloid is fractured using a rongeur and is then cut with strong scissors. The remaining tough fibrous tissue surrounding the internal carotid artery at its ingress into the skull base is carefully removed using scissors. The internal jugular vein in the neck is double ligated and cut or closed with vascular clips (easier and faster method). The vein is elevated superiorly, with care being taken not to injure the related LCNs. In cases in which the 11th nerve passes laterally, the vein has to be pulled under the nerve 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. Removal continues down to the level of the JB. The lateral wall of the JB is opened. Bleeding usually occurs from the apertures of the inferior petrosal sinus and the condylar emissary vein. This is controlled by Surgicel packing. If there is limited intradural extension, the dura is opened without injury to the endolymphatic sac. At the end of the procedure, the Eustachian tube is 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 esthetic problems but the sternocleidomastoid muscle and the digastric muscle are sutured together and the temporalis muscle is left in its place.

## EXTENSIONS OF THE INFRATEMPORAL FOSSA TYPE A APPROACH (ITFA-A)

Based on the ITFA-A approach, various extensions can be added depending on the extent of the pathology. The standard extension we use is a transcondylar-transtubercular extension for C2–C4 tumors (Figures 2 and 3). 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. 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.

## TRANSCONDYLAR-TRANSTUBERCULAR EXTENSION OF THE ITFA-A

The classic ITFA-A of Fisch permits only superior and anterior exposure of the JB and is indicated for class C1 and certain C2 tumors. For larger tumors, such as classes C2–C4 tumors involving the LCNs, a transcondylar-transtubercular extension is required in addition to the classic ITFA-A. This extension facilitates inferomedial access to the JB above the lateral mass of the atlas and occipital condyle.

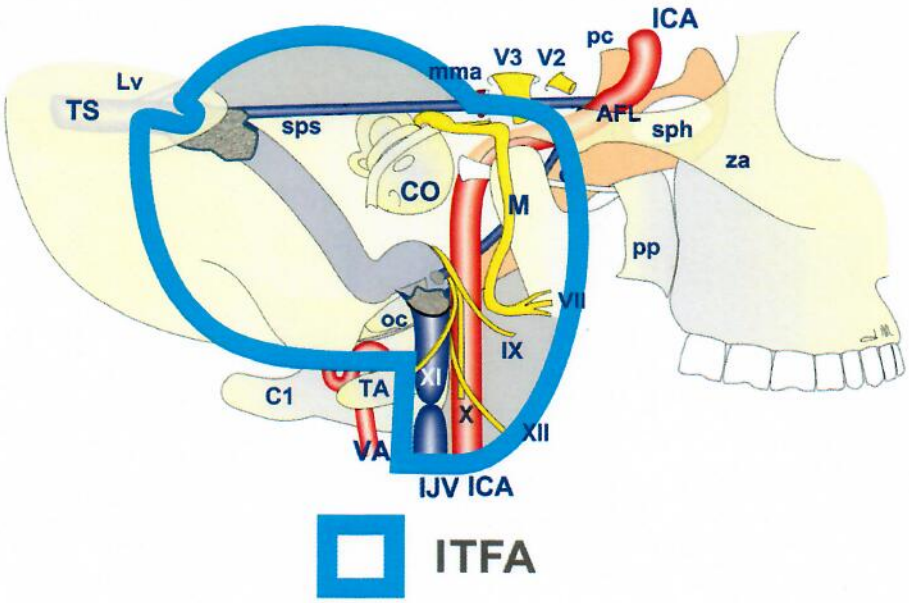


**Figure 2** Transcondylar, transtubercular extension improves postero-inferolateral and medial exposure.

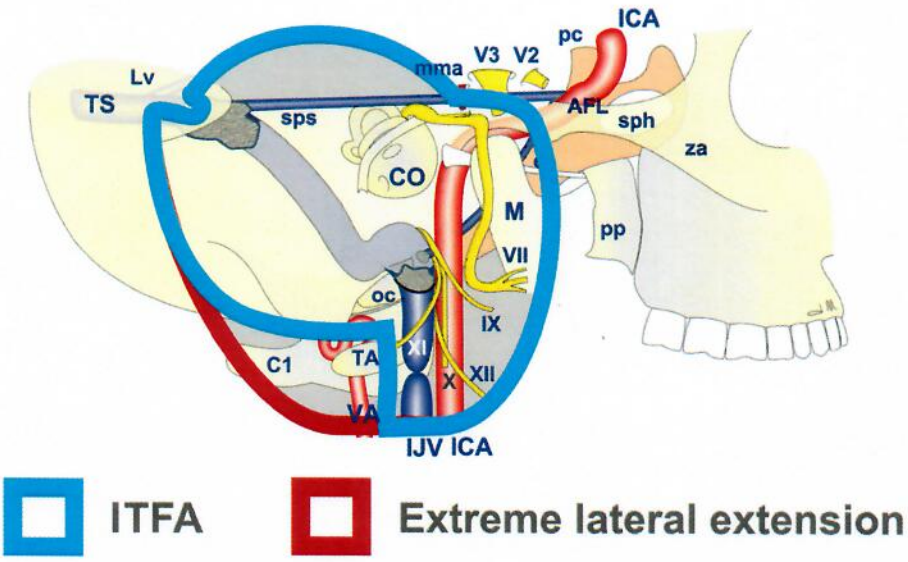


**Figure 3** Far lateral approach further extends postero-inferolateral exposure.

## STEPS OF ITFA-A WITH TRANSTUBERCULAR-TRANSCONDYLAR EXTENSION

As described in the previous sections, the ITFA-A 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 JB. The hypoglossal canal is then identified between the jugular tubercle and the occipital condyle above the vertebral artery, if indicated.

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 JB 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® packing. The tumor is then separated from the LCNs. 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 bone of the 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. Closure of the Eustachian tube, cavity obliteration, and watertight closure of the subcutaneous and cutaneous tissues are carried out as with conventional ITFA-A.

## CONSIDERATIONS IN THE MANAGEMENT OF COMPLEX TJPS

Complex TJPs, which include multiple tumors or tumors that have been previously dealt with by surgery or radiotherapy, pose unique challenges to even the most experienced skull base surgeon. The following issues need to be taken into consideration while managing such complex cases.

### Large tumors

Large TJPs extend along the internal carotid artery and into the petrous apex or intradurally destroying the medial wall of the JB involving the LCNs along the way. C3 and C4 tumors are generally considered large tumors. C2 tumors can be managed using the ITFA-A, while C3 or C4 tumors can be dealt with using the ITFA-A alone or in combination with ITFA type B. If the tumor if found to involve the clivus, the occipital condyle, or the foramen magnum, the modified transcochlear approach can be used.

### Large intradural extension

A large intradural extension can be managed either by a single-stage or by a two-stage surgery (24). Our experience has shown that a planned second-stage resection may be preferable in case of extensive dural involvement. The advantage of two-stage surgery is that a clear plane of dissection can be established between the tumor and the brain stem due to the devascularization of the tumor after the first-stage surgery and subsequent shrinkage of the intradural mass (Figure 4A–D). Another reason for staging the surgery is the argument that LCNs involved with tumor would need to be sacrificed, resulting in severe cough. This would lead to an increase in intracranial pressure facilitating cerebrospinal fluid leaks (40). We prefer to stage surgery when tumors have over 2 cm of intradural extension. For the second stage, a petro-occipital-trans-sigmoid (POTS) approach is preferred, but a modified transcochlear approach or an enlarged translabyrinthine approach may also be used.

### Extension to the foramen magnum, clivus, or cavernous sinus

Tumors extending to the foramen magnum, clivus, or cavernous sinus are considered complex cases. These areas can be reached by a modified transcochlear approach or an enlarged translabyrinthine approach (37). Drilling of the clival bone until healthy bone is reached is important to ensure total disease clearance.

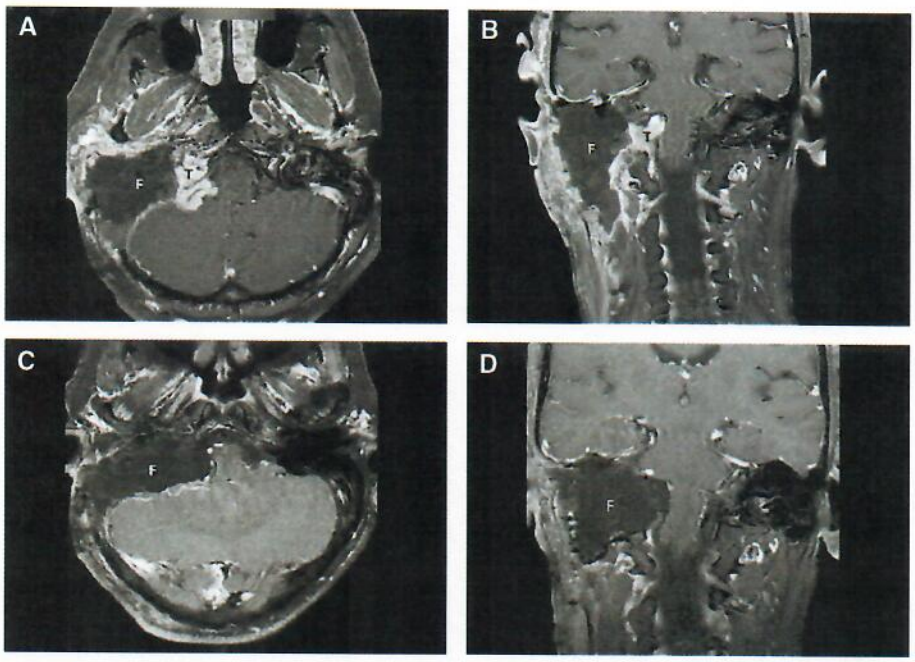


**Figure 4 Imaging.** (A and B) MRI, axial, and coronal views after the first-stage surgery. The residual intradural tumor is noted. The surgical defect is filled with abdominal fat. (C and D), MRI, axial, and coronal views after the second-stage surgery. After the surgery, there is no residual tumor. F, fat; T, intradural tumor.

## Involvement of the ICA

By classification, TJPs involve the ICA due to their close anatomical proximity (8). Dissection from the ICA can be achieved by subperiosteal dissection in the carotid canal or sub-adventitial dissection in the vertical portion (41). However, when the artery is stenosed or surrounded to a great extent by tumor (>270 degrees), manipulation without endovascular intervention may be risky (42). Permanent balloon occlusion (PBO) can be performed when the ICA is infiltrated by tumor, if there is evidence of adequate collateral blood flow. In case of insufficient collateral flow, it is suitable to perform an intraluminal stenting of the artery (Figures 5A–D and 6). We have introduced stenting of the cervical and petrous segments of ICA since early 2003 as a method to avoid pre-operative closure of the ICA or high-risk bypass procedures and to protect the artery during surgery (43–46). Stenting of the ICA reinforces the artery and allows more aggressive carotid dissection and mobilization of the artery when necessary (24)

## Single ICA on the lesion side

In the case of a single carotid artery on the side of the lesion, the possible management options include "wait and scan," partial resection, followed by radiotherapy

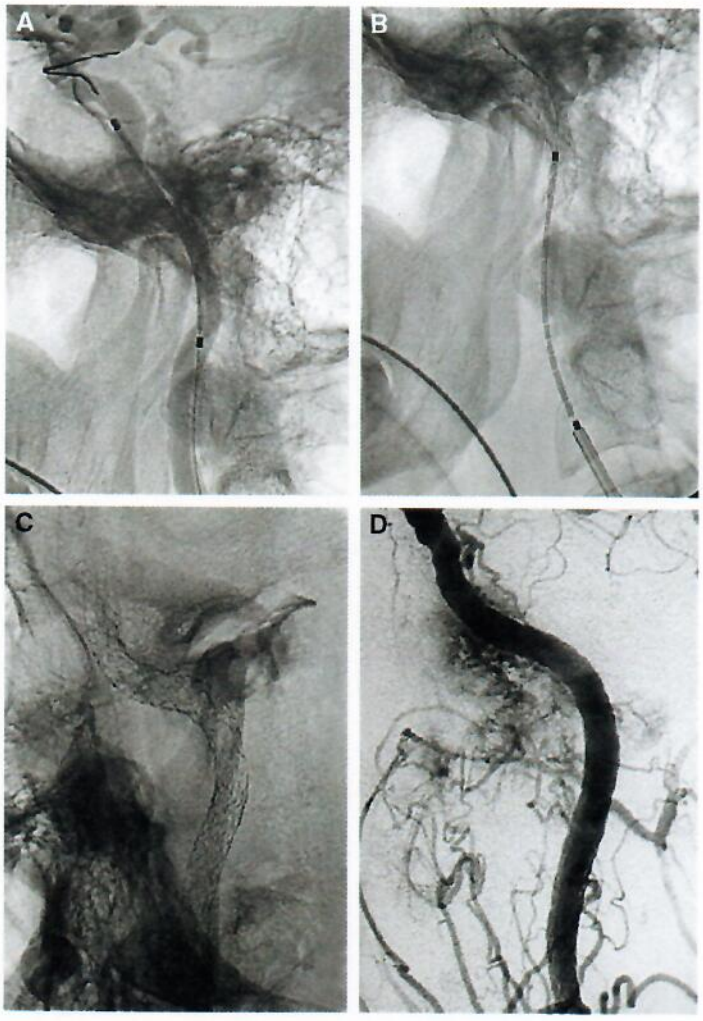


**Figure 5 Stent insertion.** (A and B) Insertion of the stents in the petrous and cervical portions of the internal carotid artery (ICA). (C) Digital x-ray in oblique projection showing the stents fully deployed into the petrous and cervical segments of the ICA. (D) Digital subtraction angiography of the ICA after stenting showing resolution of the stenosis.

or total removal after preoperative reinforcement with stents (44, 47). Bypass surgery in such patients can lead to cerebral ischemic damage; hence, stenting is considered the best option.

## Vertebral artery involvement

TJPs involving the VA are extremely uncommon. Only 11 cases were reported worldwide, of which eight belong to our series. We emphasized the importance of

**Figure 6 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.

vertebral artery involvement in paragangliomas by introducing a "V" Class to the Fisch classification (2). Therefore, the vertebrobasilar system must always be included in the angiographic assessment of TJPs planned for surgery. Apart from the assessment of the VA directly, this is also useful for detecting anastomotic connections between the external carotid and the VA, which are potentially dangerous during embolization (48). The involvement of the V3 segment of the VA requires the employment of an extreme lateral extension to standard ITFA-A. As mentioned above, we prefer two-stage surgery in the case of large intradural extension (Figure 7A–F).

## Dominant or unilateral sigmoid sinus on the lesion side

Obliteration of the sigmoid sinus and closure of the jugular vein are almost an integral step in surgery for TJPs. However, ligation of the sigmoid sinus cannot be performed when it is the dominant or only sigmoid sinus. In fact, ligation may lead to intracranial hypertension, venous congestion, and brain edema (37). Under such circumstances, the ipsilateral mastoid emissary vein or the condylar vein has to be preserved whenever possible. When the collateral venous drainage cannot be preserved, 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 HNPs

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 post-operatively. According to our management protocol, in patients presenting with LCN deficits on the side of the larger tumor, surgery is recommended on that side first, following which the smaller tumor is either followed up or irradiated. On the contrary, if the patients present with LCN deficits on the side of the smaller tumor, surgery is performed on the smaller tumor, following which the larger tumor is followed up with MRI.

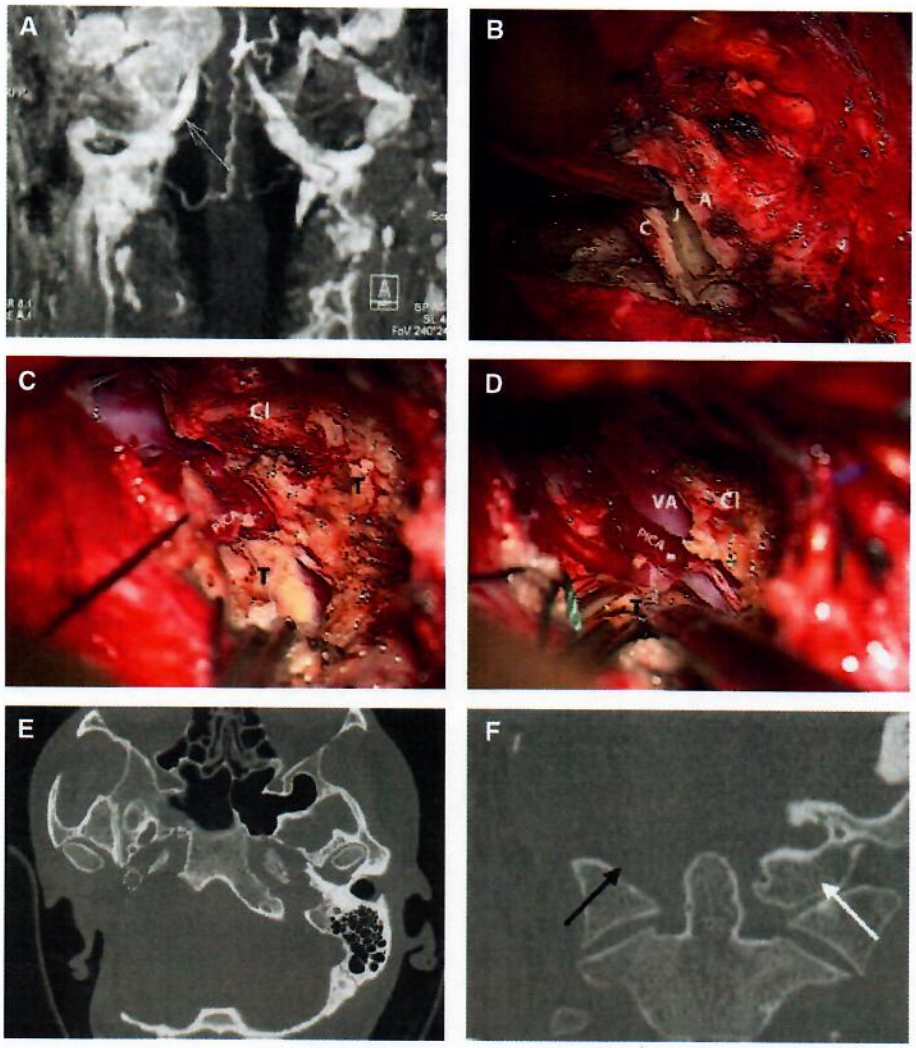


**Figure 7** (A) A class C4Di2Vi tumor. MRI coronal image showing the tumor attached to the VA. (B–F) Surgical sequences of extreme lateral transcondylar approach. (B) The transverse process of the atlas (A) is drilled out and the atlanto-occipital joint (J) is removed. C = Condyle. (C) The tumor (T) is attached to the vertebral and posteroinferior 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 the absence of the surgically removed occipital condyle (black arrow) compared to non-operated side (white arrow).

During follow-up, if the larger tumor shows evidence of growth, a subtotal resection may be performed with the preservation of LCN function or the patient may be irradiated. In patients with no presenting LCN deficit, a "wait and scan" approach is first applied. However, if the tumor shows growth, radiotherapy or subtotal removal of the tumor with LCN preservation is performed first.

Subsequently, if the tumor continues to grow despite radiotherapy or surgical removal, the other remaining treatment 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 cerebrospinal fluid leak and the risk of damage to the LCNs and FN (37, 42). 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 PBO or stenting is especially important. An ITFA-A with FN rerouting is recommended in all cases.

## GENETICS OF TJP

Paragangliomas have a strong genetic basis, being frequently (≈40% of the cases) associated with predisposing germline mutations in one of at least 15 nuclear genes, most relevantly *SDHA/B/C/D*, that encode the four subunits of succinate dehydrogenase (SDH), a nuclear-encoded mitochondrial enzyme participating in both oxidative phosphorylation and the Krebs cycle, and *SDHAF2*, whose product is required for SDHA protein flavination (collectively the *SDHx* genes) (49). Head and neck paragangliomas are most frequently associated with mutations in *SDHC* and *SDHD* and, to a lesser extent, *SDHB* (50, 51). Patients with multifocal tumors often carry *SDHD* mutations, but in any case the metastatic potential is low (50, 51). Few genetic data are available for TJPs. The 41 TJP cases reported in our recent study (52) were analyzed for *SDHA/B/C/D/AF2* mutations at the Veneto Institute of Oncology, Padua, Italy. The median age at surgery for this series was 47 years (15–76 years): 21 patients were males and 20 were females. Overall, germline *SDHx* mutations were detected in 15/41 cases (36.6%). A germline *SDHx* mutation was found in 14 cases, respectively, mutated in *SDHA*, 1 case; *SDHB*, 5 cases; *SDHC*, 6 cases; *SDHD*, 2 cases; *SDHAF2*, 1 case. Thus, the *SDHx* mutation frequency in our TJP subset is comparable to that of paragangliomas in general and suggests a preference for mutations in *SDHC* and *SDHB*. This may be relevant, given that *SDHB* mutation carriers are at higher risk of malignant paraganglioma.

## DEVELOPMENTAL ORIGIN

As indicated by ultrastructural analysis, paragangliomas incorporate dysmorphic variants of the vascular (i.e., endothelial), perivascular (i.e., pericytic), glial (i.e., sustentacular), and neuroepithelial (i.e., chief) cells found in normal paraganglia (Figure 8) and may therefore provide a classic example of multipotent organoid tumorigenesis (52). In fact, our recent data, based on unique patient-derived *in vitro* and *in vivo* models, indicate that head and neck paragangliomas

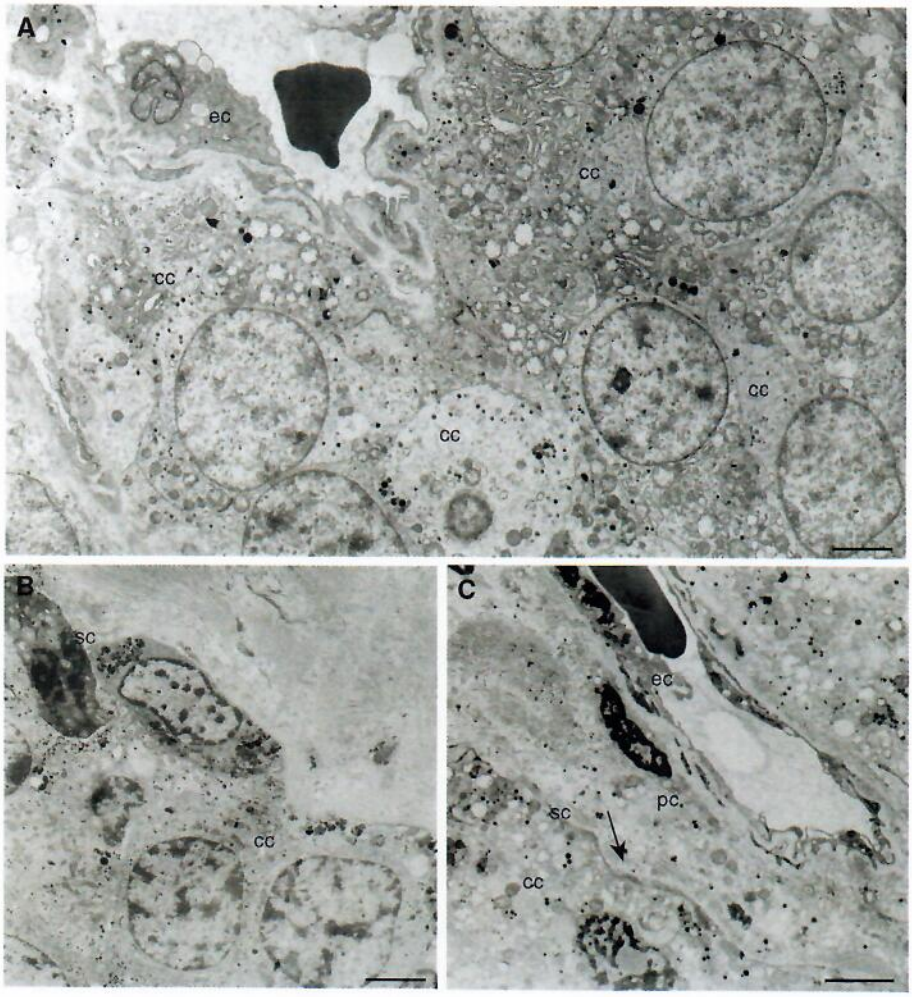


**Figure 8 Ultrastructural relationships among the main paraganglioma cell types, as exemplified in jugulotympanic tumors.** (A) Chief cells (cc), characterized by ovoid nuclei with focally condensed heterochromatin clumps and "salt and pepper" nucleoplasm, abundant cytoplasm with vacuolizations and swollen mitochondria, are situated close to a capillary lined by atypical endothelial cells (ec). (B) Sustentacular cells (sc), characterized by elongated nuclei and thin cytoplasm with abundant lipofuscin granules, indicative of oxidative stress, lie at the periphery of a nest of cc. (C) Ultrastructural relationships between the major paraganglioma cell types, which include cc, sc (only thin cytoplasmic projections along a cc are visible here), perycytes (pc), and ec. Bars: A, 10 µm; B–C, 6 µm.

are sustained by tumorigenic stem-like cells that engage in dysregulated histo/organogenetic processes (52, 53). We found that head and neck paragangliomas, including TJPs, contain stem-like cells with hybrid mesenchymal/vasculoneural phenotype that are stabilized and expanded in culture. The paraganglioma cultures depended on the downregulation of the miR-200 and miR-34 families, which we found responsible for the control of NOTCH1, PDGFRA, and ZEB1

protein expression levels (52, 53). High levels of these proteins, which are implicated in the promotion of the epithelial to mesenchymal transition, appear to sustain paraganglioma tumorigenesis. Both paraganglioma- and cell culture-derived xenografts recapitulated the typical vasculoneural paraganglioma structure. In our models, the histogenesis of the tumor tissue followed a hierarchy that originated from primitive mesenchymal-like neoplastic cells (52). Vasculoangiogenesis appeared to be the earliest developmental phase, and neurogenesis depended on the creation of a perivascular niche. Neuroepithelial differentiation was associated with severe mitochondrial dysfunction, not present in cultured paraganglioma cells, but acquired *in vivo* during xenograft formation. Importantly, it may provide a therapeutic target, possibly exploitable in the clinical setting to prevent tumor recurrence after surgery. In fact, imatinib, which interferes with endothelial-mural signaling, blocked paraganglioma xenograft formation. These results were unaffected by the *SDHx* gene carrier status of the patient, pointing to a common mechanism of tumor origin, regardless of the heterogeneity of the paraganglioma predisposing genes (52). Importantly, ZEB1 expression and the epithelial to mesenchymal transition, which appear to support paraganglioma development, are known to confer resistance to chemotherapy and radiotherapy, which may agree with scattered clinical evidence indicating that paragangliomas resist to these therapeutic approaches (52).

## HISTOPATHOLOGY

The data presented here are based on the literature and on the personal experience, derived from the diagnostic analysis of 94 TJP cases who underwent surgery at the Otology and Skull Base Unit, Gruppo Otologico, Piacenza, from 2002 to 2016. TJPs are usually smaller than carotid and vagal paragangliomas, and TJPs of the *cassa tympani* are in turn smaller (<1 cm) than those growing in the foramen jugular, at the cranial base or in the petrous bone. However, it must be said that only few TJP cases come to pathologists as sizeable tumor masses. In fact, the use of preoperative embolization and electrosurgery to reduce intraoperative bleeding and the piecemeal excision strategy necessary to remove tumor tissue growing within hard bone and along vessels and nerves make fragmentation and surgical artifacts unavoidable. The size of these fragments typically varies from a few millimeters to over 2 cm, exceptionally up to 5 cm in the major axis. The consistency is typically rubbery, but bone particles may be present and, if so, decalcification treatment may be mandatory. The very fact that most pathology specimens consist of irregular and partially necrotic fragments, crushed and altered by thermal injury, makes intraoperative diagnosis challenging, which explains why it is generally not requested. On the other hand, the pathologist is often asked only to confirm a diagnosis already proposed with a high degree of probability by the surgeon. Intraoperative diagnostic questions which impact on the surgical strategy arise only rarely, and mostly in cases with peculiar presentation (e.g., abnormal extension into the petrous part of the temporal bone, into and/or along the dura mater, or in the middle and external ear).

As other paragangliomas, TJPs generally show a well-defined organoid structure (54). The distinctive morphological units are classically defined as "zellballens," due

to their appearance in histological sections, where they present as nests or ribbons of relatively homogeneous, tightly compacted nests of epithelioid cells (chief cells) separated by a lace of vessels and/or fibrous tissue (Figure 9A). As highlighted using transmission electron microscopy (Figure 8), the zellballens are peripherally delimited by a thin rim of elongated glia-like nurse (sustentacular) cells, not easily recognizable by morphology but readily identifiable with an IHC reaction for S100 (Figure 9B–C). These cells surround the zellballens with their thin cytoplasmic extensions that may also insinuate within, sustaining and supporting the chief cells (53). Some peculiar features appear to be more frequent in TJPs than in other Paragangliomas. These include the following: (i) the zellballens tend to be less uniform in size and are frequently smaller, (ii) the chief cells tend to be smaller (55), (iii) there is frequent evidence of bone infiltration, and (iv) the tumor tissue tends to be more vascular (54).

With regard to 3D structure, it is evident that the zellballens are not isolated, but form a continuous reticulum where single tracts are of variable thicknesses. This can be easily appreciated with immunostaining reactions for chief cells (e.g., chromogranin A, synaptophysin), for sustentacular cells (e.g., S100), and for endothelial cells (e.g., CD34).

Fibrosis or sclerosis, a common feature in TJPs (54), usually occupies 5–25% of the tumor section area, although it may occasionally extend up to 80% and may distort the zellballens, simulating invasive carcinoma (53). Thus far, a sclerosing paraganglioma variant has been described mainly in mediastinal locations (57). Some TJPs mimic vascular lesions (hemangioma or hemangiopericytoma) (56) in that they present ectatic vessels, apparently devoid of blood due to surgical manipulations but prominently relative to the zellballens (54).

We never observed in our TJP series the peculiar small cell variant with "neuroblast-like" cells and fibrillar matrix, interpreted as a composite neoplasm, that is, paraganglioma with a neuroblastic component (54). Using light microscopy, we also never found evidence of the pigmented variety, characterized by lipofuscin or melanin accumulation. This variant was reported in various paraganglioma locations, including the vagal one, but not in the tympano-jugular area (58). However, using electron microscopy, we always detected in our TJP series evidence of lipofuscin generation in the form of oxidized lipid droplets, particularly in sustentacular cells (Figure 8).

As mentioned above, histological evidence of bone infiltration is nearly constant (70% of the cases in our series) and may not point to particularly aggressive tumor potential. On the other hand, massive necrosis and hemorrhage are rare (4% in our series) and may correlate with infiltration of large vessels and/or preoperative embolization. In fact, common iatrogenic features include focal or extensive necrosis, granulomatous reactions, and/or crushing and burning artifacts, which, when massive, make morphological diagnosis difficult or impossible.

Chief cells are homogeneous, round or oval, with a round nucleus, inconspicuous nucleolus, and granular cytoplasm, variably staining from amphophilic to pink. On histological sections, their diameter varies from 7 to 30 µm, being most frequently in the 12–15 µm range. Sometimes, probably due to iatrogenic artifacts, the chief cells appear even smaller, with dark nucleus and poorly evident, shrunken cytoplasm on an empty background. Chief cells may also exhibit extensive cytoplasmic vacuolization (clear cell change) (56). Very large isolated

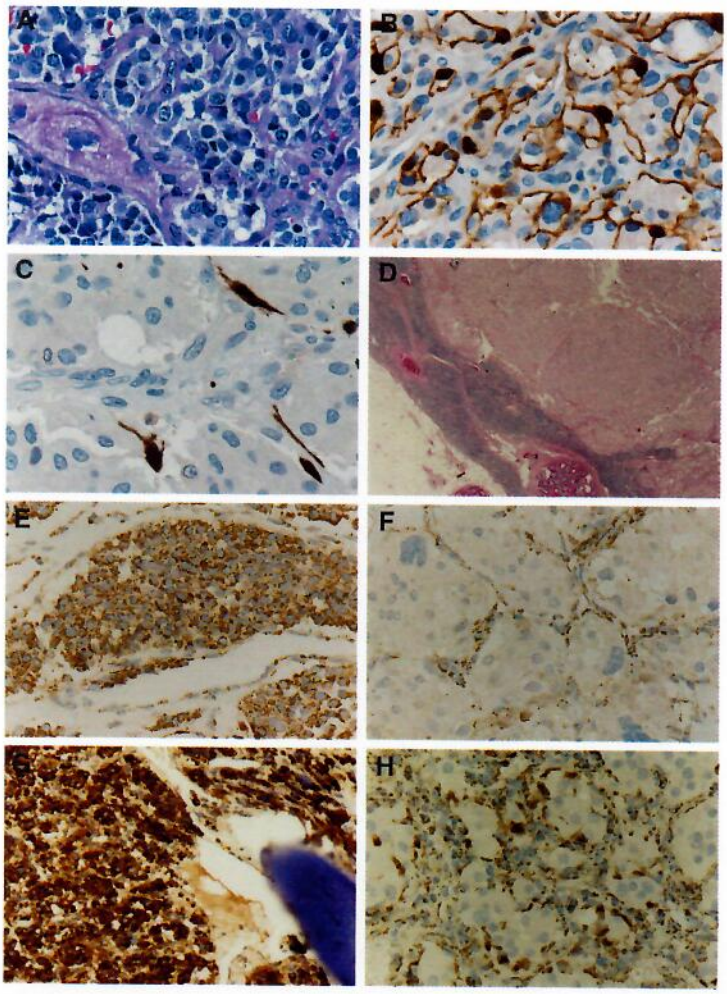


**Figure 9 Typical histopathological and immunohistochemical features in jugulotympanic paragangliomas.** (A) Classic morphology, characterized by tightly packaged nests ("zellballens") of rather uniform chief (neurosecretory) cells. (B) Variant morphology in another jugulotympanic paraganglioma, where "zellballens" of small diameter are highlighted by the dark brown immunohistochemical stain for the S100 protein, a marker of the sustentacular cells, which encircle the chief cells. Notably, the sustentacular cells display both nuclear and cytoplasmic S100 positivity. (C) Distinct morphological variant, where the sustentacular cells, highlighted by dark brown S100 immunostaining, are less abundant, while the zellballens are better organized and composed of larger chief cells. (D) Massive lymph node metastasis from a jugulotympanic paraganglioma showing focal iatrogenic embolization. (E) Intense SDHB positivity in all the cellular components (chief, sustentacular, and vascular cells) of a jugulotympanic paraganglioma not mutated in the *SDHx* genes. (F) Selective loss of SDHB immunostaining in chief cells and SDHB positivity of the other cell types (vascular and sustentacular) in a case mutated in SDHB. (G) Strong SDHA immunopositivity in all cell types, including chief cells, in a case infiltrating the temporal bone. This case did not carry mutations in SDHA. (H) Selective loss of SDHA immunostaining in chief cells and SDHA positivity of the other cell types in a case carrying an SDHA mutation. (A, D: H & E) Original magnifications 400x (A) and 20x (D); (B, C, E, F, G, H, G) Avidin-biotin complex immunoperoxidase, counterstained with H&E, original magnifications 400x (B, C, E, F, H) and 200x (G).

cells ("atypical cells") with vesicular, hyperchromatic, or even vacuolated nuclei are seen in a significant fraction of cases (18% in our experience) and their relevance is debated, although they are clearly not reliable as indicators of potential malignant behavior (54, 56, 59, 60). Mitoses are generally rare (<1 in 10 high-power microscopic fields) (56) and in our experience are practically absent.

Chief cells constantly show strong and diffuse immunoreactivity for synaptophysin, even in the presence of extensive artifacts. Chromogranin and vimentin staining are also characteristic, even if variable in different fields, which is also the case for other neuroendocrine markers, such as CD56 and NSE. The occurrence of paragangliomas negative for both chromogranin A and B has been reported (59). In a few cases, chief cells are stained with S100, as sustentacular cells. As other paragangliomas, TJPs are always negative for cytokeratins (60).

In our experience, the number of sustentacular cells is highly variable (from 0 to 60/HPF) (Figure 9B–C), with an average of 25 cells/HPF. Cases with abundant sustentacular cells tend to show very small zellballen diameters, down to microsheets of a single chief cell encircled by a single sustentacular cell. These patterns are difficult to interpret in terms of clinical significance. In fact, in a single case of lymph node metastasis, we found that the number of sustentacular cells ranged from 0 to 21 per high magnification field (400x).

The proliferative index, as determined with Ki67 immunostaining, is usually low, varying from 1 to 2%; only rare cases have higher proliferative indexes, ranging from 3 to 7%.

According to the literature (56, 59, 61, 62), there are no established clinical, histological, or immunohistochemical criteria that predict the biological behavior of TJPs. In fact, nuclear pleomorphism, mitotic activity, necrosis, or vascular or perineural invasion can be found in the so-called "benign" forms, as in the rare cases that metastasize to distant sites (60). Even immunohistochemistry for the proliferation marker Ki67, useful and applied in many neoplasms, is of no help, as it can result very low even in metastatic cases and there is no standardized cutoff value for its interpretation. Therefore, malignancy can be established only by the occurrence of lymph node and/or distant metastases (Figure 9D). The overall reported frequency of metastases in head and neck paragangliomas is less than 5% (59), but in TJPs it seems to be lower, possibly 2–4% (63). In a review of 53 metastatic cases, metastases involved, in order of frequency, bone, lungs, lymph nodes, liver, and other locations, and they presented up to 30 years after initial treatment (64)

However, recent studies have clearly indicated that head and neck paragangliomas that harbor *SDHB* gene mutations are more prone to develop metastases (61). Thus, immunostaining for the *SDHB* protein has become a fundamental screening tool. The high sensitivity (84–100%) and specificity (74–85%) of *SDHB* immunohistochemistry has been confirmed in various important studies (65–67). In cases not mutated for any of the *SDH* genes, the immune reaction for the SDHB protein stains with high intensity all the paraganglioma tissue components, including chief, sustentacular, and vascular cells (Figure 9E), while SDHB immunostaining results negative in the chief cells of the cases harboring mutations not only in *SDHB* but, with less consistency, also in *SDHA*, *SDHAF2*, *SDHC*, and *SDHD* (65) (Figure 9F). Similarly, in non *SDHA* mutated cases, SDHA immunostaining marks all cell types, including chief cells (Figure 9G), while the rare cases harboring an

*SDHA* mutation show loss of SDHA immunostaining in chief cells (Figure 9H) (59). In the subset of our TJP series thus far analyzed for SDHB immunohistochemistry, we found *SDH* gene family mutations, concordant with SDHB loss, in nearly 40% of the cases (27/69) and of SDHA mutations in only 2.8% (2/69) of cases. So far, only 1 of the 27 cases positive for *SDHB* mutation has metastasized.

Histopathologically, the differential diagnosis of TJP includes the tumors more frequently encountered in the specific TJP location: in the jugular and intracranial region meningioma (68), schwannoma (23), and even the rare meningeal hemangiopericytoma; in the acoustic channel middle ear adenoma (54), which often shows endocrine differentiation. Unusual neoplasms that should also be considered include endolymphatic sac tumor and metastatic lesions, particularly from renal cell carcinoma (54), melanoma, and salivary gland carcinomas. Finally, given that paragangliomas can occur even in intra/parasellar locations (69), hypophyseal adenoma might have to be considered in differential diagnosis. Apart from morphology, combined immunohistochemistry for synaptophysin, S-100 and cytokeratin usually resolves diagnostic doubts.

## CONCLUSION

Paragangliomas are sluggish, generally slow-growing tumors that rarely metastasize and are thus considered of benign nature. However, they steadily grow along the regional neurovascular bundles, are highly infiltrating, and appear to be resistant to radiotherapy/chemotherapy (52). Therefore, surgery remains the mainstay of treatment. This is particularly challenging for TJPs, which arise at the skull base and necessitate particular surgical skills, available only at few highly specialized centers. We covered in this chapter the technical developments and the novel approaches that, in the last two decades, made curative surgery of TJPs possible. Nonetheless, there is a need to develop new paradigms of treatment for inoperable, recurring, or metastatic TJPs. This requires a thorough understanding of the etiology of paraganglioma, where factors, both genetic and environmental, that impact mitochondrial metabolism and cellular differentiation appear to be implicated (52). Importantly, preclinical evidence suggests that treatments that interfere with vasculogenesis may prevent paraganglioma formation in a murine xenograft model (52). This might open the way for the development of postsurgical therapies aiming at the prevention of disease recurrence (52). Further research is needed to build up knowledge and tools that could allow further and hopefully decisive improvements in the prevention and therapy of TJPs and of paragangliomas in general.

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# FOREWORD

Paragangliomas and pheochromocytomas are rare tumors of the autonomic nervous system that pose important clinical questions. Their presentation may be extremely variable. Classic sites of origin, such as the adrenal medulla and the autonomic branches of the lower cranial nerves, are the most frequent locations, but other sites may also be involved. Paragangliomas may indeed arise in connection with autonomic neural branches almost anywhere in the thoracic, abdominal, and head and neck regions. Some of these locations are accessible only by surgeons with special skills, not easy to acquire, given the rarity of the disease in general and of the specific locations, in particular.

Early diagnosis may be problematic, particularly when patients are seen by physicians that do not have specific experience. This may have relevant consequences, as surgical resection, which must be radical, is still the mainstay therapy, and late diagnosis may complicate surgery. In fact, paragangliomas, despite their slow growth, in most cases not more than few millimiters in diameter per year, tend to relentlessly infiltrate adjacent anatomical stuctures, most often extending along regional neurovascular bundles. With time, this behavior makes their resection difficult and, in some instances, even impossible. Such is often the case for those paragangliomas that, arising at the skull base, extend within the skull, either through neurovascular foramina or by direct bone erosion. Another challenge is represented by the possible secretion of catecholamines, more frequent in pheochromocytomas and sympathetic thoraco-abdominal paragangliomas. This may *per se* entail life-threatening cardiovascular complications. Such tumors require cautious surgical approaches and well-trained multidisciplinary surgical teams.

A critical, but still poorly understood, characteristic of paragangliomas seems to be their resistance to radio- and chemotherapy. In this regard, the search for effective non-surgical therapeutic approaches is made even more difficult by the rarity of the patients, which makes comparative evaluation of treatment modalities challenging or impossible. This is compounded by marked differences in tumor location, size, and type among treated cases. Slow growth complicates the assessment of therapeutic results, as, dealing with tumors that may naturally grow at most few millimeters per year, it is difficult to distinguish the effect of therapies. It cannot be excluded that inappropriate therapeutic interventions, particularly with radiotherapy, could contribute to aggressive evolution and/or increased difficulties in case of later surgery. Timely surgery is indeed the safer option, considering also that metastatic spread, even if extremely rare, can never be completely excluded, even for well-differentiated paragangliomas.

The above-mentioned surgical and clinicopathological issues are not the only factors that contribute to the important place that paragangliomas and pheochromocytomas occupy in oncology. In fact, these are the tumor types in which the impact of genetic predisposition factors is highest. Germline or somatic mutations in at least 20 different genes have been implicated in the pathogenesis of paragangliomas and pheochromocytomas, and as much as 40% of the patients carry germline predisposing mutations, most notably in the 5 genes that encode the protein components of complex 2 of the mitochondrial respiratory chain. In this

regard, paragangliomas and pheochromocytomas have been hailed as "Warburg's tumors", *i.e.*, prototypic tumors that fulfill Warburg's concept on the role of deficient mitochondrial respiration in cancer. Beyond the scientific relevance, this impacts on patient management, as some mutations are linked to more aggressive and even metastatic tumor behaviour. Furthermore, constitutional predisposition means that a patient with paraganglioma may develop, throughout life, multiple independent tumors. Such event heavily impacts on the quality of life, and may pose specific surgical challenges, for example when distinct paragangliomas involve bilaterally the carotid arteries. Additionally, despite the unpredictable penetrance of the mutations, an increased risk for relatives can never be ruled out.

All these issues highlight the importance of paragangliomas and pheochromocytomas. In front of this, even today, there is a relative scarcity of comprehensive therapies available for these tumors. This book, although small, intends to contribute to fill the gap of knowledge if these diseases, making a series of chapters readily available, which address several critical questions that concern the genetics, pathology and treatment of paragangliomas and pheochromocytomas. With enhanced knowledge, hope emerges that the development of new therapies is within reach for these patients.

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# PREFACE

Paraganglioma and pheochromocytoma are highly interesting tumors that still represent a diagnostic and therapeutic challenge. Their organization follows to a remarkable extent that of the normal tissues of origin, *i.e.*, the paraganglia and the adrenal medulla. In fact, in some cases, their pathological effects are mediated by the uncontrolled release of physiological products of the paragangliar system, *i.e.*, catecholamines, Thus, paragangliomas and pheochromocytomas may present clinically with hypertension, tachycardia, hyperglycemia, and gastrointestinal effects. Prevention of the potentially life-threatening complications of excessive cathecolamine release is therefore of primary relevance. An additional challenge of paragangliomas, and of some pheochromocytomas, is their unpredictable behaviour. Mostly, these are slow-growing tumors that remain confined to the site of origin, however, they tend to slow and relentless infiltration of the adjacent tissues, a process that may complicate surgical resection, particularly for those paragangliomas that infiltrate the anatomically complex region of the skull base. Furthermore, for poorly understood reasons, an unpredictable minority of paragangliomas and pheochromocytomas exhibits metastatic capacity. The problem with these metastatic tumors, and with those that cannot be radically removed with surgery, is that systemic therapies are largely ineffective, while the efficacy of radiotherapy is still debated.

In the last two decades, exciting research progresses have been made in the field of paraganglioma and pheochromocytoma genetics. Several hereditary paraganglioma syndromes have been defined, and, although no new therapies were developed based on these new data, it is now possible to identify, with some degree of reliability, subsets of patients that are at risk of more aggressive tumor behavior. In any case, paraganglioma and pheochromocytoma treatment requires specialized knowledge and solid experience, which, given the rarity of these diseases, is available only in the context of highly specialized centers.

This new book includes specific chapters written by experts from several countries that deal with relevant aspects of paraganglioma and pheochromocytoma diagnosis and therapy. Chapter 1 addresses the genetic findings that are most relevant to diagnosis and management, chapter 2 deals with the biochemical diagnosis, chapter 3 with imaging, chapter 4 with the surgical and pharmacological management, mainly of trunk paraganglioma and pheochromocytoma, chapters 5 and 6 with the histopathological, genetic and clinical characteristics of carotid body, vagal and tympano-jugular paragangliomas.

We hope that these chapters will provide the reader with useful insight into important aspects of state-of-the-art diagnosis, management and treatment of paragangliomas and pheochromocytomas.

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