12

Skull Base Tumors

MIKHAIL CHERNOV AND FRANCO DEMONTE

Skull base tumors arise from the cranial base or reach it, either from an intracranial or extracranial origin. A diverse group, these tumors present unique management challenges because of their relative rarity, typically deep location, close proximity to critical neurovascular structures, and extension beyond classically taught anatomic and specialty boundaries. Management outcomes for skull base tumors are maximized when their treatment is approached in a multidisciplinary fashion, utilizing the knowledge base of varied medical, surgical, and radiotherapeutic specialists.

CLASSIFICATION

Skull base tumors may originate from the neurovascular structures of the base of the brain and the basal meninges (e.g., meningioma, pituitary adenoma, schwannoma, paraganglioma), the cranial base itself (e.g., chordoma, chondrosarcoma), or the subcranial structures of the head and neck (e.g., paranasal sinus carcinomas). A unified classification system does not exist for the plethora of pathologies, some quite rare, that may affect this area of the brain (Table 12–1).

Classifications based on location are useful for clinicopathologic correlation due to the relatively constant constellation of signs and symptoms produced by tumors located in specific regions of the skull base and due to the propensity for certain tumor pathologies to have a regional specificity (Table 12–2). Tumor location is also the prime determinant of the surgical approach that is selected.

Whereas location is the most important consideration for surgical planning, the tumor's biologic behavior dictates the need for, and order of, the various available therapies needed to optimize patient outcome. Some tumors, such as meningiomas and schwannomas, may require complete surgical excision only to optimize patient outcome. Pathologies such as paranasal sinus carcinomas may, however, require induction chemotherapy, surgical excision, and radiation therapy (RT) to achieve local control and possibly cure (Table 12–3).

In general, the outcome of surgery for basal tumors depends on the type, size, and location of the neoplasm, patient's age and general medical status, and extent of preoperative neurologic disability (Lang et al., 1999). Large tumor size, encasement of major cerebral arteries, invasion of the cavernous sinus and severe brain stem compression can necessitate incomplete tumor resection, whereas older age and low preoperative Karnofsky score have been associated with increased risk of stroke and longer hospital stay (Holmes et al., 1995).

MENINGIOMA

Meningiomas (see Chapter 11) occur with an incidence of 2.6 per 100,000 persons per year and account for 20% of all intracranial tumors. Forty percent of all meningiomas arise from the base of the anterior, middle, or posterior fossa and are the most common skull base tumors. Sphenoid wing meningiomas make up almost half of these tumors; tuber-

Table 12–1. Tumors of the Skull Base

Site of Tumor Origin	*Tumor Pathology*
Basal neurovascular structures and meninges	Meningioma Schwannoma Pituitary adenoma Craniopharyngioma Paraganglioma Hemangiopericytoma
Cranial base	Chordoma Chondrosarcoma Osteosarcoma Plasmacytoma Metastasis
Subcranial with upward extension	Sinonasal carcinomas Olfactory neuroblastoma Juvenile angiofibroma Nasopharyngeal carcinoma Adenoid cystic carcinoma Primary sarcomas

Table 12–2. Classification of Skull-Base Tumors Based on Location

Location	*Clinical Features*	*Common Pathologies*
Anterior skull base	Anosmia, frontal lobe dysfunction, increased intracranial pressure, nasal obstruction, epistaxis, visual changes	Meningioma, olfactory neuroblastoma, sinonasal malignancies
Middle skull base		
Central	Pituitary hypo- or hyperfunction, optic neuropathy (nerve and chiasm)	Pituitary adenoma, meningioma, craniopharyngioma, sphenoid sinus carcinoma
Paracentral	Optic neuropathy, sphenocavernous syndrome	Meningioma, schwannoma, adenoid cystic carcinoma, nasopharyngeal carcinoma
Lateral	Proptosis, facial dysesthesia and pain, trismus, epistaxis	Meningioma, schwannoma, juvenile nasal angiofibroma, adenoid cystic carcinoma, sarcoma
Posterior skull base		
Cerebellopontine angle	Hearing loss, facial numbness or weakness, dysmetria, ataxia, lower cranial nerve dysfunction, brain stem signs, increased intracranial pressure	Acoustic neuroma, meningioma, epidermoid, trigeminal neuroma, cholesterol granuloma
Clival	Abducens palsy, bilateral cranial neuropathies, brain stem signs	Chordoma, meningioma, paraganglioma, nasopharyngeal carcinoma, schwannoma, chondrosarcoma
Jugular foramen	Palsies of cranial nerves 9,10,11 (Vernet's syndrome), 9,10,11,12 (Collet-Sicard syndrome), 9,10,11,12, and sympathetics (Villaret's syndrome)	Paraganglioma, schwannoma, meningioma, metastasis
Foramen magnum	Suboccipital neck pain (C2 dermatome), ipsilateral dysesthesias, contralateral dissociated sensory loss, progressive weakness, wasting of intrinsic hand muscles	Meningioma, schwannoma, chordoma, intramedullary tumor

Table 12–3. Classification of Skull-Base Tumors by Biologic Behavior

Benign	Meningioma, schwannoma, paraganglioma, pituitary adenoma, dermoid, epidermoid, juvenile angiofibroma, cholesterol granuloma, osteoma
Low-grade malignancy	Chordoma, chondrosarcoma, adenoid cystic carcinoma, desmoid, low-grade fibrosarcoma, olfactory neuroblastoma, low-grade sarcomas, hemangiopericytoma
High-grade malignancy	Carcinomas, high-grade sarcomas (e.g., rhabdomyosarcoma, Ewing's sarcoma, osteogenic), lymphoma, metastases

culum sella tumors and olfactory groove tumors comprise the other half. Meningiomas of the posterior and middle fossa are less common, with incidences of 8% and 4%, respectively.

PITUITARY ADENOMA

In 2.6% to 15% of cases pituitary adenomas (see Chapter 8) may attain giant size (more than 4 to 5 cm in any direction) and exhibit extensive invasion of the skull base and paranasal sinuses (Pia et al., 1985; Majos et al., 1998). These are mainly endocrinologically inactive tumors in the elderly and prolactinomas in the young. Clinical and imaging features of giant pituitary adenomas differ from tumors that are smaller in size.

SCHWANNOMA

Intracranial nerve sheath tumors represent only 4% to 8% of intracranial neoplasms with the most common being vestibular schwannomas, followed by trigeminal nerve tumors. These neoplasms can arise, although infrequently, from other cranial nerves, both intra- and extracranially. Although schwannomas can develop as an isolated disease process, most intracranial nonvestibular tumors and 5% of vestibular schwannomas are associated with neurofibromatosis type 2 (NF2).

Pathology and Pathogenesis

Schwannomas are typically globoid, ovoid, or dumbbell-shaped, well-circumscribed tumors. They arise from Schwann cells, which form the myelin sheaths surrounding peripheral nerves. Tumors may have small or large cystic components and can be moderately vascular. The cellular components of schwannomas are typically organized into densely packed hypercellular areas of spindly cells ("Antoni type A") with intervening hypocellular zones composed of loosely organized stellate cells ("Antoni type B"). The compact Antoni type A tissue often, but not invariably, exhibits prominent nuclear palisading (Verocay bodies). Cytologically, no differences are found between spontaneous and familial tumors; however, on histologic examination approximately 40% of the NF2 neoplasms appear to have grapelike clusters that can infiltrate the fibers of the individual nerves. Growth fraction varies from 0.36% to 3.15% (Lesser et al., 1991).

Diagnosis and Treatment

Vestibular Schwannomas

Vestibular schwannomas represent nearly 6% of all intracranial tumors. The tumors arise at the transitional zone between the central and peripheral myelin sheaths of the nerve. The majority of neoplasms originate within the internal auditory canal; however, more medially located tumors constitute 10% to 15% of cases. Whereas tumors in the more typical location compress the adjacent auditory nerve early in their growth, the medial tumors may grow to a significant size without causing hearing loss. Clinical features, as well as treatment strategy and prognosis, are greatly influenced by the size and extension of the tumor.

Unilateral hearing loss occurs in more than 90% of patients and is often accompanied by tinnitus. Cochlear nerve dysfunction usually is the most long-

standing symptom followed by vestibular disturbances, which may have an intermittent course. Imbalance is encountered in 50% of cases and vertigo in 19%. Trigeminal nerve signs are the third most common symptom, with 50% of patients reporting facial numbness (Pitts et al., 1996). Larger tumors can cause facial weakness, signs of brain stem compression, and obstructive hydrocephalus. The average duration of symptoms is 3.7 years (Matthies and Samii, 1997). By the time of diagnosis 63% to 80% of vestibular schwannomas already fill the cerebellopontine cistern with or without compression of the brain stem (Matthies and Samii, 1997; Gormley et al., 1997) (Fig. 12–1).

Management alternatives include observation, microsurgical removal, and stereotactic radiosurgery. Currently, the ideal treatment for symptomatic patients with vestibular schwannoma is complete microsurgical excision of the tumor. Concomitant goals include preservation of facial nerve function, low morbidity and mortality, and, when possible, preservation of hearing.

The choice of surgical approach needs to take into account the size and the amount of extension of the tumor into the internal auditory canal (IAC) as well as the patient's hearing ability and experience of the surgical team. Every attempt should be made to preserve useful hearing, although it must be realized that when the tumor is greater than 2 cm in size or when it fills the fundus of the IAC this goal is not often realized. Total tumor removal can be accomplished in most patients, with less than a 1% mortality and excellent long-term tumor control. Hearing preservation is possible in 48% of small tumors, 25% of medium, and only occasionally in cases of large neoplasms. Similarly, facial nerve function can be preserved in 96% of small tumors, 74% of medium, and 38% of large tumors (Gormley et al., 1997).

Stereotactic radiosurgery is the principal alternative to microsurgical resection of vestibular schwan-

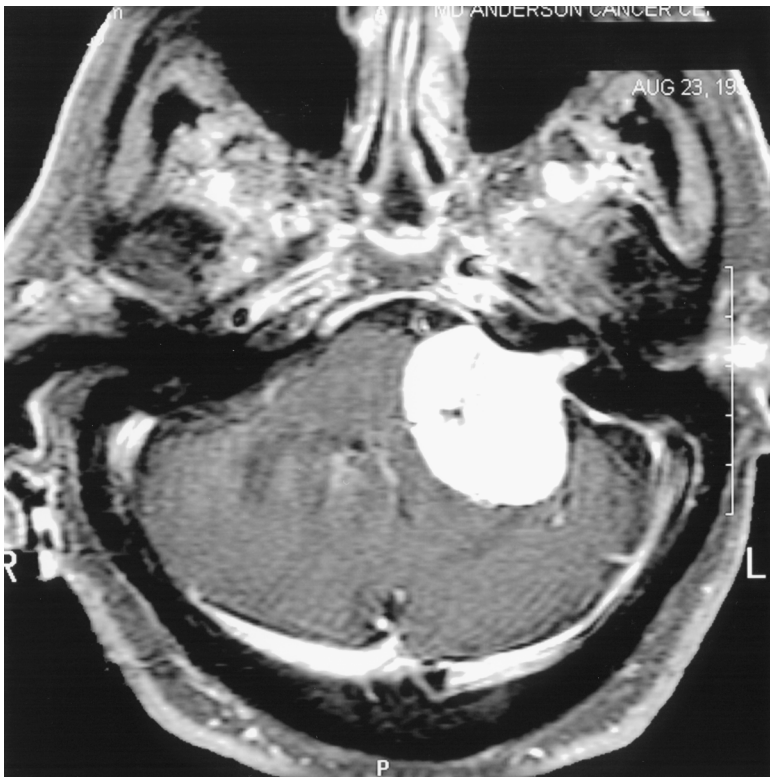

Figure 12–1. Axial post-contrast T_1-weighted MRI reveals a giant left-sided acoustic neuroma. Note the extension of the tumor to the lateral end of the internal auditory canal and the marked brain stem compression.

nomas. The goals of radiosurgical treatment are prevention of tumor growth, maintenance of neurologic function, and prevention of new neurologic deficits (Kondziolka et al., 1998). The rate of tumor control (shrinkage or stabilization of the neoplasm) is 96.9% at 3 and 5 years (Fig. 12–2). Ogunrinde et al. (1994) reported facial nerve function of grade I or II in 100% of patients post-treatment, dropping to 95% at 2 year follow up. Two years after radiosurgery 25% of patients still had mild residual trigeminal nerve sensory symptoms. The incidence of hearing preservation is typically 100% immediately following treatment but drops to 50% at 6 months and to 45% at both 1 and 2 years following treatment (Ogunrinde et al., 1994). A trend of improved rates of hearing preservation with smaller tumor diameters was noted.

During the first 4 years after radiosurgical treatment 2% to 3% of patients required microsurgical removal of tumors (Pollock et al., 1998; Sims et al., 1999; Shirato et al., 1999).

Trigeminal Nerve Schwannomas

Schwannomas of the trigeminal nerve account for 0.07% to 0.36% of intracranial tumors and 0.8% to 8% of intracranial Schwann cell tumors (McCormick et al., 1988; Pollack et al., 1989). One-half of these tumors are primarily located in the middle fossa arising from the ganglionic segment of the trigeminal nerve (Jefferson's type A tumors [Jefferson, 1955]).

Trigeminal schwannomas of the ganglionic segment result in facial numbness or pain and corneal hypesthesia in 80% to 90% of patients, which are the initial complaints in about 60% of these patients. A few patients (10% to 20%), however, never develop trigeminal dysfunction. Tumors of the ganglionic segment are more frequently associated with facial pain (52%) than those of the trigeminal root (28%) (McCormick et al., 1988). Diplopia is the initial symptom in about 15% of patients, but is present in 50% by the time of diagnosis and is usually due to an abducens palsy. Facial weakness and hearing loss are rare symptoms of this lesion. When they occur the presumptive mechanisms are through involvement of the greater superficial petrosal nerve, facial nerve, and eustachian tube or cochlea in the temporal bone.

Tumors of the trigeminal root account for 20% to 30% of trigeminal schwannomas and are usually confined to the posterior fossa (Jefferson's type B tumors). The clinical presentation is usually a combination of hearing loss, tinnitus, and facial nerve and cerebellar dysfunction. Early trigeminal symptomatology may imply the diagnosis, but as many as 10% of patients with vestibular schwannomas initially present with trigeminal nerve dysfunction. As a corollary, 6% of patients with trigeminal schwannomas initially complain of hearing loss.

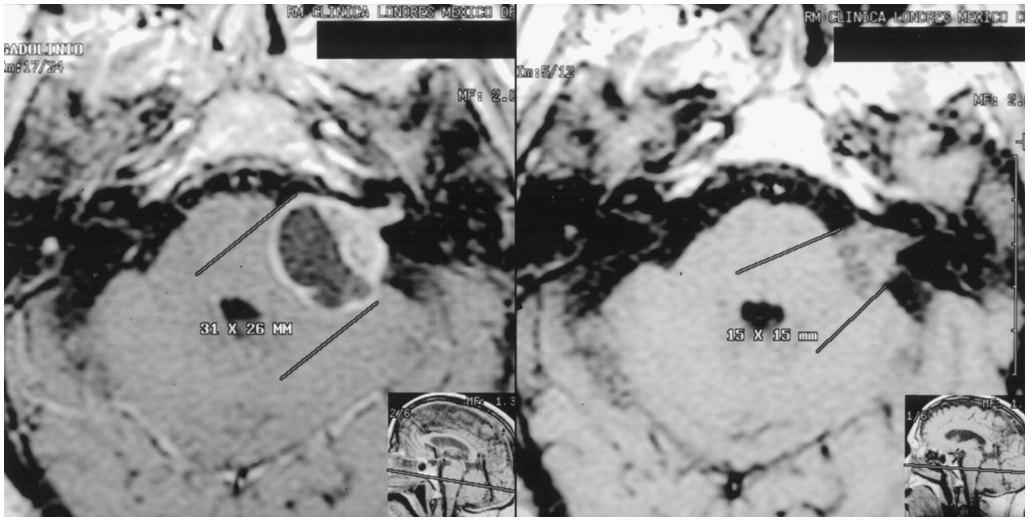

Figure 12–2. Pretreatment (left) and post-treatment (right) axial T_1-weighted MRIs demonstrate a marked reduction in size of a cystic acoustic neuroma treated by gamma knife radiosurgery. The post-treatment scan was performed without contrast.

Impairment of lower cranial nerve function and long tract signs are noted at diagnosis in 30% to 50% of patients.

Dumbbell-shaped tumors, which occupy both the middle and posterior fossae, make up 15% to 25% of all trigeminal schwannomas (Jefferson's type C tumors). Their clinical presentation is a composite of the symptoms and signs of tumors occurring in the ganglionic segment and in the posterior fossa (Fig. 12–3).

Complete excision, as for vestibular schwannomas, nearly always results in cure and is the goal of each surgical procedure. When results from five recent surgical reports were combined, 72 of 93 patients had a gross total tumor excision (GTR), 9 of 93 had a near total excision (NTR), and 12 of 93 had a subtotal or partial resection (STR). One recurrence was noted following GTR. Tumor progression occurred in 6 of 9 of near-total resections and in 5 of 12 subtotal resections (Bordi et al., 1989; Dolenc, 1994; McCormick et al., 1988; Pollack et al., 1989; Samii et al., 1995a). Tumors of the trigeminal root were generally approached through a retrosigmoid craniectomy, whereas a variety of approaches were necessary for the middle fossa or dumbbell-shaped tumors. These approaches included the standard subtemporal approach (Bordi et al., 1989; McCormick et al., 1988), the frontotemporal epidural approach (Dolenc, 1994), and combined approaches such as the petrosal (Samii et al., 1995b), supra- and infratentorial approach (McCormick et al., 1988), or subtemporal and infratemporal approaches (Pollack et al., 1989).

Before 1970, a mortality rate of 25% had been reported for patients with these tumors. In the recent surgical series noted above there was only one instance of operative mortality reported. Morbidity consisted mainly of new or worsened trigeminal deficits in 43 of 93 patients (46%), although instances of improvement occurred. Other morbidity included ab-

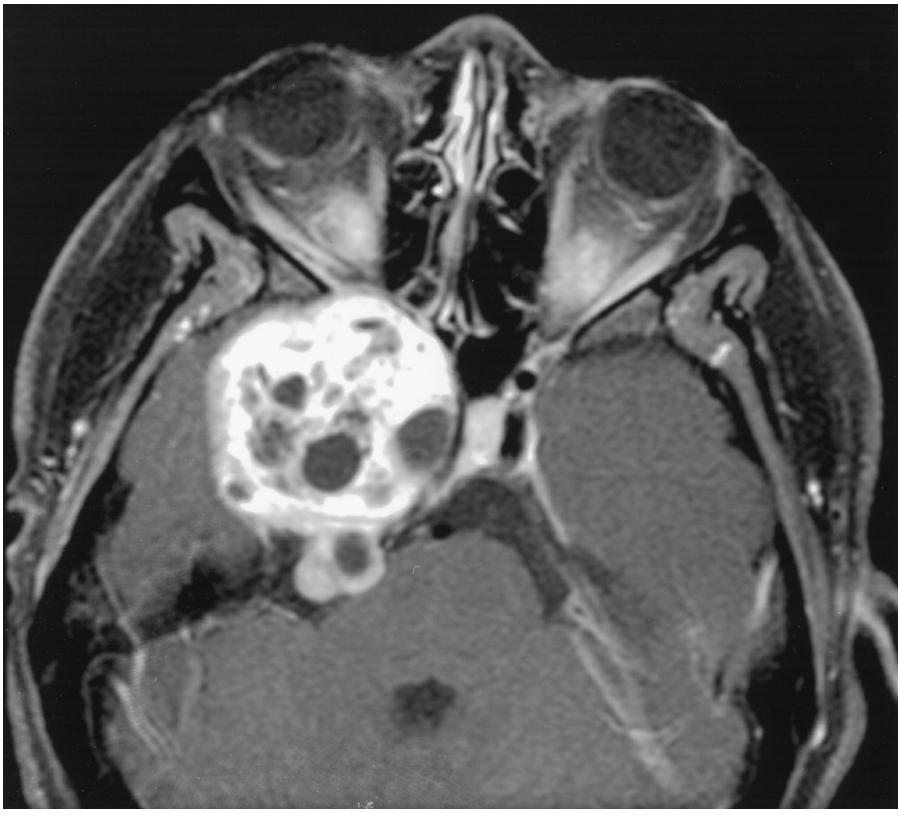

Figure 12–3. Axial post-contrast T_1-weighted MRI reveals a dumbbell-shaped trigeminal schwannoma predominately involving the right middle fossa with extension through Meckel's cave into the posterior fossa.

ducens nerve palsies in two, facial palsy in two, and hearing loss in three patients.

Radiosurgical treatment of a group of 16 patients with trigeminal schwannomas achieved a tumor control rate of 100%, improvement of neurologic symptoms in 5 patients, and absence of any new neurologic deficits during the evaluation period (follow-up, 44 months; Huang et al., 1999).

Facial Nerve Schwannomas

Slowly progressive facial weakness is the typical clinical presentation of a facial nerve schwannoma. Although sudden facial weakness occurs in approximately 11% of cases, 27% of patients with facial nerve schwannomas never manifest facial weakness. Facial spasm has been reported in as many as 17% of patients. Hearing loss of a conductive, sensorineural, or mixed nature occurs in approximately 50% of patients. Facial schwannomas located in the middle ear may cause conductive hearing loss, whereas tumors in the labyrinth and internal auditory channel usually result in cochlear or retrocochlear hearing dysfunction, respectively. Tinnitus and vertigo, or dizziness, occur in 13% and 10%, respectively. External manifestations of the tumor such as a mass, pain, or otorrhea occur in 30% or more of patients (Lipkin et al., 1987).

These tumors are rare, accounting for only 1.5% of cerebellopontine angle tumors (Baker and Ojemann, 1993). Schwannomas of the facial nerve involve the tympanic or vertical segments in most patients (58% and 48%, respectively) and multiple segments are almost always affected.

Facial schwannomas may appear as a soft tissue mass in the tympanomastoid compartment, cerebellopontine angle, or middle fossa, accompanied by destruction of the fallopian canal and/or widening of the IAC, in which case differentiation from vestibular schwannomas may be a challenge (O'Donoghue et al., 1989). Imaging features specific for facial neuromas include enlargement of the labyrinthine segment of the fallopian canal associated with a middle fossa mass; erosion of the anterosuperior aspect of the internal auditory canal; and contrast enhancement of the geniculate ganglion and distal facial nerve in the case of cerebellopontine angle tumor (Inoue et al., 1987; Parnes et al., 1991).

Rarely, the tumor, if small, may be separable from the nerve, but in most cases resection and facial nerve grafting are required (Dort and Fisch, 1991; King and Morrison, 1990; O'Donoghue et al., 1989). At best, a House grade 3 facial weakness can be expected following facial nerve grafting. Complete excision is curative.

Schwannomas of the Jugular Foramen (Nerves IX, X, XI)

Although it is difficult, if not impossible, to identify the specific nerve of origin (Pluchino et al., 1975), the clinical presentation and surgical management of jugular foramen schwannomas are more a function of anatomic location than specific nerve origin (Franklin et al., 1989; Horn et al., 1985; Kaye et al., 1984; Samii et al., 1995a; Tan et al., 1990). Jugular foramen tumors comprise 2.9%–4% of intracranial schwannomas. Marked cystic degeneration is not rare. Kaye et al. (1984) classified these tumors into three types (A, B, C) based on their location. Type A tumors are primarily intracranial masses with only minor extension into the foramen. Tumors within the bony foramen with or without an intracranial component are classified as type B (Fig. 12–4). Type C tumors are primarily extracranial with only minor extension into the bony foramen or the posterior fossa.

Patients with type B and C tumors present with various forms of the jugular foramen syndrome (Table 12–2), but hoarseness is usually the initial symptom. Type A tumors may not cause dysfunction of the lower cranial nerves and may cause a clinical syndrome indistinguishable from that of a vestibular schwannoma.

Type A tumors are generally removed through a standard retrosigmoid suboccipital craniectomy, whereas type B and C tumors usually require combined approaches, such as the combined posterior fossa–infratemporal fossa approach or the infratemporal approaches of Fisch (Franklin et al., 1989). Postoperative cranial nerve morbidity rates of 38% have been reported (Samii et al., 1995a).

Radiosurgery can be a good alternative for the treatment of small jugular foramen schwannomas. Pollock et al. (1993) reported five patients with jugular foramen schwannomas treated with the gamma knife. With a mean follow-up period of 10 months, tumor control was attained in three patients without an increase of cranial nerve deficits.

The management of lower cranial nerve dysfunction is by far the most important aspect of the pa-

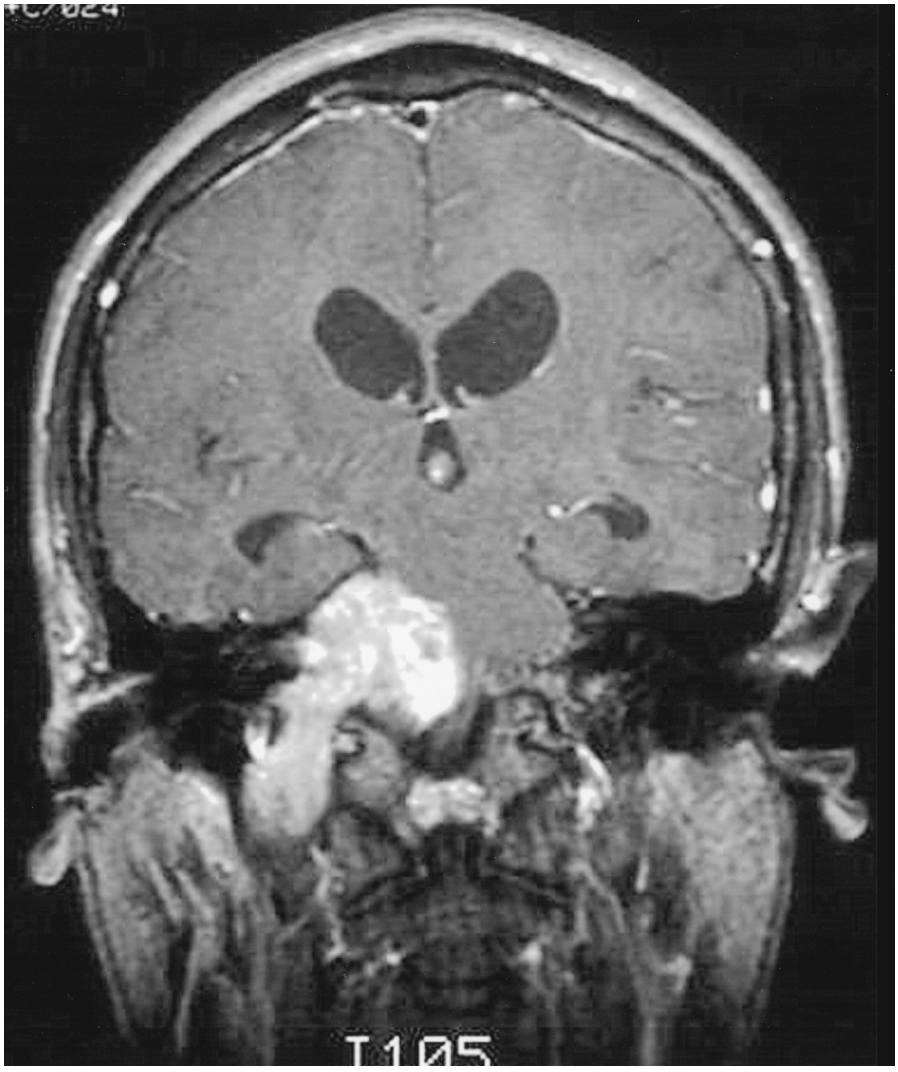

Figure 12–4. Coronal post-contrast T_1-weighted MRI identifies the jugular foramen component of this type B jugular foramen schwannoma.

tients' care. If extensive jugular foramen dissection is necessary, early tracheostomy may be warranted to avoid aspiration pneumonitis. Patients must be kept NPO until definite objective evidence of an adequate swallowing mechanism without aspiration is obtained.

A modified barium swallow, consultation with a speech pathologist, and laryngoscopy should be arranged. Pooling of secretions, a dysfunctional swallowing mechanism, or aspiration may be seen, thus identifying those patients who require further rehabilitative maneuvers.

Schwannomas of Cranial Nerves III, IV, VI, and X

Schwannomas of the cranial nerves subserving extraocular muscle function are extremely rare. Clinical presentation usually involves diplopia due to dysfunction of the tumor's nerve of origin, but may include decreased visual acuity, hemiparesis, ataxia of gait, paresthesias, and symptoms of intracranial hypertension (Celli et al.,1992; Jackowski et al., 1994; Tung et al., 1991). Treatment is surgical resection, which may occasionally be associated with

functionally normal eye movements (Schultheiss et al., 1993).

Hypoglossal schwannomas, when they occur, are usually located entirely within the intracranial compartment or, less commonly, have a dumbbell-shaped appearance with both intra- and extracranial components (Odake, 1989). Purely extracranial tumors can also occur. Unilateral lingual atrophy, deviation, and fibrillation are nearly universal findings. Intracranial hypertension, long tract signs, ataxia, and dysfunction of the other lower cranial nerves may occur. Surgical removal is best accomplished via a transcondylar approach, either alone or in combination with an anterior transcervical approach. Purely extracranial tumors can be removed via an anterior transcervical approach alone.

Schwannomas of the Nasal Cavity and Paranasal Sinuses

Schwannomas of the nasal cavity and paranasal sinuses arise from the ophthalmic or maxillary branches of the trigeminal nerve and autonomic ganglia and constitute only 4% of schwannomas in the head and neck region. Identification of the nerve of origin is rarely possible. In the majority of cases multiple paranasal sinuses are involved.

The clinical presentation is typical for tumors of the nasal cavity and paranasal sinuses. Nasal obstruction, epistaxis, mucopurulent rhinorrhea, hyposmia, localized facial swelling, facial or orbital pain, and proptosis are usual manifestations. Deficits of the extraocular nerves can develop with sphenoidal tumors.

Surgical excision is the preferred treatment modality for schwannomas of the paranasal sinuses. En bloc excision should be performed in cases of malignancy.

NEUROFIBROMATOSIS

Treatment of tumors of patients with either form of NF usually consists of surgical removal of neoplasms, although irradiation may be helpful. Surgical management must have a clear goal, such as the relief of pain, prevention of compression, or decompression of critical nervous tissue, including brain, brain stem, or spinal cord (Pitts et al., 1996). Overall, the chances of anatomic and functional nerve preservation in NF2 patients are lower than in unilateral tumors (Samii et al., 1997).

A good outcome is best achieved when surgery is performed early and when there is good preoperative hearing function. Welling (1998) recommends early removal of small neoplasms if hearing is useable binaurally. The smallest tumor is removed first to maximize hearing preservation opportunity. If hearing is preserved and the second tumor is smaller than 1.5 cm, it is removed 3 to 6 months later. If hearing is not preserved, the second tumor is followed expectantly until either hearing is lost or brain stem encroachment requires removal.

Radiosurgical treatment can be effective in NF2 patients with vestibular schwannomas. Subach et al. (1999) reported a 98% tumor control rate over a median follow up of 3 years. Useful hearing was preserved in 43% of patients and normal facial nerve function in 81%.

CHONDROSARCOMA

Chondrosarcoma is a tumor of cartilaginous origin with nonuniform biologic behavior. It represents 0.15% of all cranial space-occupying lesions. Nearly one-half of these are located in the cranial base and constitute 6% of skull base neoplasms (Hassounah et al., 1985; Korten et al., 1998). The middle cranial fossa is affected in 64% of cases, middle and posterior fossae in 14%, anterior cranial fossa in 14%, and posterior cranial fossa in 7% (Kveton et al., 1986).

Chondrosarcomas may develop at any age with an average of 37 years (Evans et al., 1977). Overall there is no sex predominance. Tumor growth may be bulky, permeative, or mixed. Dural invasion is present in 30% of cases (Korten et al., 1998). The majority of tumors are nearly avascular; however, in about 30% the vascularity can be significant (Hassounah et al., 1985). Distant metastases from skull base chondrosarcomas are reported in 10% of cases (Hassounah et al., 1985).

Pathology

It is assumed that chondrosarcomas originate from remnants of embryonal cartilage or from metaplasia of meningeal fibroblasts. Typically, the tumor is composed of multiple, interconnecting lobules of varying size with chondroid or myxoid consistency, which can

contain central necrosis. Several tumor subtypes have been described: conventional (grades I to III), myxoid, clear cell, dedifferentiated, and mesenchymal (Barnes and Kapadia, 1994).

Conventional chondrosarcomas represent 62% of chondrosarcomas of the cranial base (Korten et al., 1998). Microscopically they are composed of hypercellular hyaline cartilage, which contains cytologically atypical chondrocytes within lacunae. On the basis of differences in nuclear size, cellularity, mitotic rate, and frequency of lacunae with multiple nuclei, these tumors are graded in a three-tier system. The exclusive presence or marked preponderance of small, densely staining nuclei is a typical sign of grade I (well-differentiated) neoplasms. Multiple nuclei within one lacuna are easily found. Dense cellularity, presence of significant numbers of moderately sized or larger nuclei, and rare mitotic figures are features of grade II (moderately differentiated) chondrosarcoma. The presence of 2 or more mitoses per 10 higher power fields indicates a grade III (poorly differentiated) neoplasm. Overall 5 year survival rates for grades I, II, and III chondrosarcomas are 90%, 81%, and 43%, respectively (Evans et al., 1977).

Mesenchymal chondrosarcomas constitute 30% of skull-base chondrosarcomas and represent a distinct clinicopathologic entity (Stapleton et al., 1993). This tumor arises from primitive multipotential mesenchymal cells, usually manifests at a young age (10 to 30 years), and is most typically seen in females (Hassounah et al., 1985). Microscopically, this tumor is characterized by a bimorphic pattern of small or large islands of relatively well-differentiated cartilage and sheets of primitive undifferentiated round or spindle-shaped cells (the presence of the latter is the most typical sign). The stroma is rich in collagen fibrils. Well-developed vascularity is typical. Mesenchymal chondrosarcoma has a high frequency of dural and cerebral invasion, local recurrence, and systemic metastases (Hassounah et al., 1985; Korten et al., 1998).

Diagnosis

The clinical manifestations of chondrosarcoma are mainly related to its preferred location at the skull base. The most common signs and symptoms are dysfunction of extraocular movement with diplopia (51%), headache (31%), hearing loss, dizziness and tinnitus (21%), and sensory disturbances of the face (21%). The median period between presentation and diagnosis is 15 months (Korten et al., 1998).

Computed tomography (CT) most commonly reveals bone destruction and tumoral calcification, the latter being encountered in 56% of tumors (Hassounah et al., 1985). On T_1-weighted magnetic resonance imaging (MRI), chondrosarcomas have a low to intermediate signal intensity and are isointense or hypointense to gray matter. On proton density and T_2-weighted images they have a high signal intensity and are hyperintense to gray matter (Korten et al., 1998). Contrast enhancement is typically heterogeneous. The radiologic distinction of chondrosarcoma and chordoma is usually not possible.

Treatment

If possible, gross total tumor removal in a one-stage operation is advocated for chondrosarcoma, as repeated surgical interventions risk tumor progression, development of scar tissue, and secondary spread of tumor cells (Hassounah et al., 1985; Korten et al., 1998) (Fig. 12–5). Macroscopically complete removal of intracranial chondrosarcomas has been accomplished in 5% to 47% of cases (Stapleton et al., 1993; Gay et al., 1995; Rosenberg et al., 1999). Sixty percent of patients have been reported to experience at least transient deterioration of function immediately after surgery. The most common postoperative complications are cerebrospinal fluid (CSF) leak (30%) with secondary meningitis (10%) and permanent cranial nerve palsy (Gay et al., 1995). Local recurrence after surgery is 53% with a mean recurrence-free period of 3 years. Risk of recurrence is greater among patients who were already operated on and in cases of partial resection. Recurrence-free survival rates at 2, 3, and 5 years are 67%, 56%, and 43%, respectively (Korten et al., 1998).

In general, chondrosarcomas are considered to be refractory to conventional radiation therapy (RT). Local control rates of 78% and survival rates of 83% have been reported 5 years following proton irradiation (Castro et al., 1994). Despite the high rates of local success of charged particle radiotherapy, complication rates have been considerable (27%). Tumor volume influences control rate. In one series all tumors with volumes of 25 cc or less remained locally controlled, whereas only a 56% control rate was found for larger neoplasms (Hug et al., 1999). Subtotal tumor resection with preservation of functionally

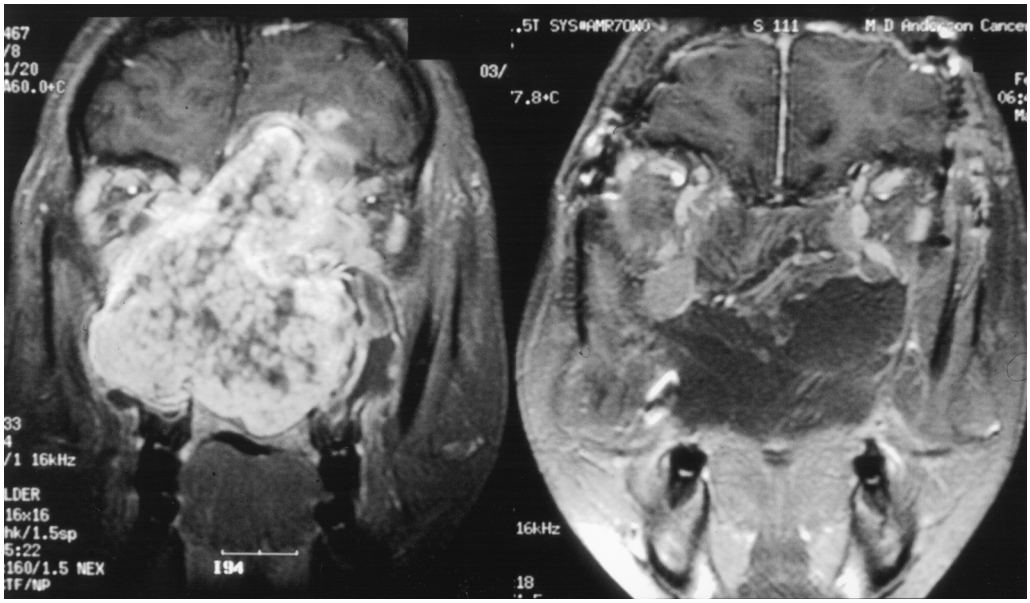

Figure 12–5. Coronal post-contrast T_1-weighted MRIs reveal complete removal of this massive midfacial, skull base chondrosarcoma. A one-stage en bloc resection with free tissue transfer reconstruction was performed.

important structures and improvement of the tumor–normal tissue configuration to allow better targeting geometry for postoperative proton beam irradiation has been advocated. Such an approach resulted in 99% 5 year local control and disease-specific survival rates for conventional chondrosarcoma (Rosenberg et al., 1999).

CHORDOMA

Chordomas are slowly growing, locally aggressive, malignant tumors derived from embryonic remnants of the notochord. Nearly 35% of these neoplasms arise from the skull base, and these constitute 0.1% to 0.2% of primary intracranial tumors. The male/female ratio in chordomas is 1.5:1, with a mean age of patients of 46 years (Forsyth et al., 1993).

In 79% of cases, chordomas are located in the posterior fossa with not uncommon extension into the sphenoid sinus, parapharyngeal space, nasopharynx, suprasellar cistern, and middle cranial fossa. Although typically considered as midline tumors of the clivus, nearly one-third of intracranial chordomas have eccentrically positioned extensions. Cavernous sinus involvement is encountered in 65% of cases, whereas encasement of the internal carotid or basilar artery occurs in 36%. By the time of surgery one-third of tumors exhibit dural erosion (Maira et al., 1996).

Pathology

Macroscopically chordoma is usually a lobulated, soft gelatinous mass that destroys bone. It commonly calcifies, may show areas of hemorrhage and necrosis, and usually grossly appears somewhat demarcated.

Three subtypes of chordomas have been identified pathologically (Barnes and Kapadia, 1994). The most common variant shows no evidence of cartilaginous or additional mesenchymal components. It is composed of cells arranged in cords with eosinophilic cytoplasm lying in a mucinous background. Cytoplasmic vacuolation is common. Lobules of tumor cells are separated by fibrovascular septa. Mitotic figures, nuclear pleomorphism, areas of necrosis, hemorrhage, and calcification may be present without prognostic significance. A defining feature of classic chordomas is their immunopositivity for markers of epithelial differentiation, specifically keratins. Reactivity for epithelial membrane antigen is common, whereas carcinoembryonic staining is less frequently seen (Mitchell et al., 1993). Chondroid chordoma contains both chordomatous and cartilaginous com-

ponents in a highly variable ratio. The cartilaginous component may appear either histologically benign or malignant. The vast majority of these tumors arise from the cranial base. Dedifferentiated chordomas are rare. They contain areas of conventional chordoma as well as malignant mesenchymal components. In these cases, prognosis is poor and most patients are dead of disease within 6–12 months.

Metastases can develop, with the most common sites of distant spread being the lungs, bones, lymph nodes, liver, and skin.

Diagnosis

Clinical presentation depends on the site of origin and direction of growth. The most typical symptoms are diplopia (49%), headache (24%), and ataxia (4%). Palsy of the sixth nerve is encountered in 57% of cases, lower cranial nerves in 36%, sensory fifth in 27%, third in 22%, and optic neuropathy in 12%. The median time from symptom onset to diagnosis has been reported as 10 months (Forsyth et al., 1993).

Radiographic assessment reveals a midline soft tissue mass associated with osteolytic bone destruction and occasional calcifications. The typical CT appearance of an intracranial chordoma is of a well-defined extra-axial mass, with both hyperdense and hypodense areas associated with bone destruction, foci of calcification, and varying degrees of encroachment of adjacent neural structures (Brown et al., 1990). On T_1-weighted MRI, chordomas exhibited low to intermediate signal intensity with a typically hyperintense signal on T_2-weighted images. Heterogeneous enhancement with gadolinium is seen (Meyers et al., 1992) (Fig. 12–6).

Treatment

Skull base chordomas are locally aggressive tumors, and surgery in conjunction with postoperative RT is the standard form of treatment. Staged surgeries using different approaches may be needed for removal of the tumor (Gay et al., 1995). Gross total resection of the tumor is the surgical goal. Even in the best of circumstances, however, this can be accomplished in only 67% of patients due to involvement of critical neurovascular structures (Maira et al., 1996). Because of the invasive nature of the tumor, local recurrences are the rule and most of these appear within 3 years of treatment with the mean interval to the first recurrence being 12.5 months. Despite various salvage treatments, stabilization of disease at the time of recurrence is uncommon (Hug et al., 1999).

For improvement of local control and survival in the cases of incomplete tumor resection a radiotherapeutic dose of at least 55 Gy of fractionated RT is necessary. This still achieves only a 39% to 51% 5 year survival and an 18% to 35% 10 year survival

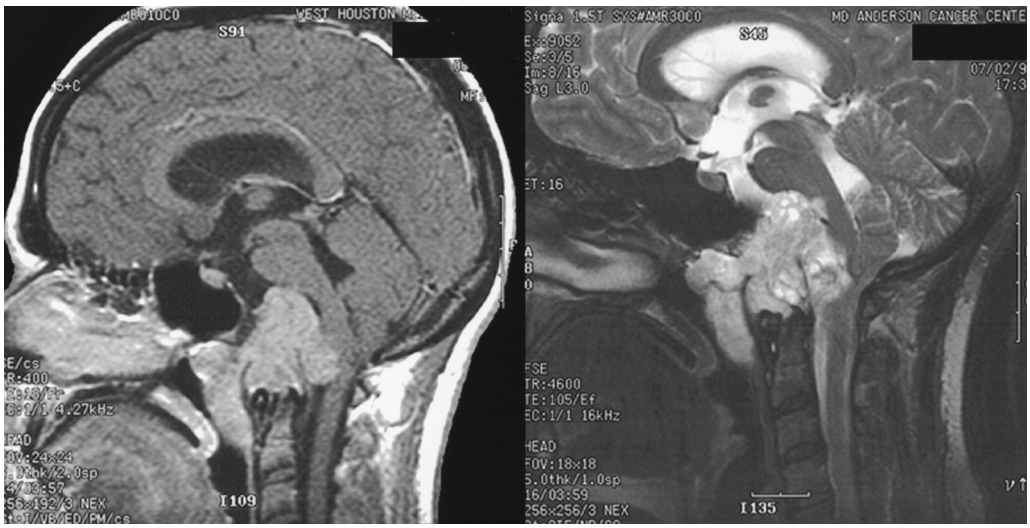

Figure 12–6. Sagittal post-contrast T_1-weighted (left) and T_2-weighted (right) MRI of a patient with a clival chordoma. Note the increased signal seen on the T_2-weighted images. The tumor extends from the posterior nasopharynx to compress the brain stem.

(Fuller and Bloom, 1988; Forsyth et al., 1993). The most common cause of death is uncontrolled local disease progression. Proton beam irradiation resulted in a 59% to 63% 5 year local control rate and a 72% to 79% 5 year survival (Castro et al., 1994; Hug et al., 1999). The 10 year survival rate for these patients is still only 45% (Rosenberg et al., 1999). Older age, female gender, high proliferative index, and large intracranial tumor volume are negative prognostic factors, and in these cases more aggressive management is warranted (Forsyth et al., 1993; Matsuno et al., 1997; Terahara et al., 1999). Several, mainly unsuccessful, chemotherapeutic attempts have been made to treat patients with chordoma. Use of vincristine alone or in combination with methotrexate resulted in a degree of symptomatic improvement (Harwick and Miller, 1979; Fuller and Bloom, 1988).

PARAGANGLIOMA

Paragangliomas are the most common tumors of the middle ear and, after acoustic neuromas, are the most common tumors of the temporal bone. These tumors have a distinct predilection for females, who make up more than 80% of patients in the series of tympanic, jugular, and vagal paragangliomas. Most of these tumors occur in the sixth decade of life.

Paragangliomas are slow-growing tumors that extend along anatomic planes of least resistance (along blood vessels and mastoid air-cell tracts and through cranial nerve foraminae). Malignancy occurs in 10% of cases, and catecholamine secretion is detected in another 5%.

Hearing loss occurs in 90% of patients with glomus tympanicum tumors and in 70% of patients with glomus jugulare tumors, but only rarely in patients with glomus vagale tumors. The hearing loss is more often conductive than sensorineural. Pulsatile tinnitus, an audible bruit, or spontaneous aural bleeding can be seen in 60% to 70% of patients with tympanicum or jugulare tumors and in 30% of those with vagale paragangliomas.

Involvement of the facial nerve occurs in approximately 20% of patients with tympanicum or jugulare tumors. The vertical mastoid segment is the usual site of compression, although compression in the soft tissue of the stylomastoid foramen may also occur.

Dysfunction of the lower cranial nerves occurs in 13% of patients with glomus jugulare tumors and in 70% of patients with glomus vagale tumors. A change in voice may precede other symptoms by 2 to 3 years in patients with glomus vagale tumors. Vocal cord paralysis is the usual finding on examination. If present, hypoglossal paresis denotes tumor extension into the hypoglossal canal or high in the neck.

Pathology

Macroscopically, paragangliomas have a beefy red brown to gray appearance, with hemorrhage or fibrosis. They may have a thin capsule and are composed of round or polygonal epithelioid cells. Histologically, the tumor is composed of two cell types: chief cells (type I) arranged in compact cell nests laden with neurosecretory granules; and sustentacular (type II) or modified Schwann cells found peripheral to the chief cells (Barnes and Kapadia, 1994). Nuclei are centrally located with finely clumped chromatin and a moderate amount of eosinophilic, granular cytoplasm. Immunohistochemical stains confirm the neuroendocrine nature of the chief cells, which are diffusely and strongly positive for neuron-specific enolase, synaptophysin, and chromogranin. In contrast, the sustentacular cells may show positivity for S-100 protein, glial fibrillary acidic protein, and nerve growth factor receptor. Nuclear pleomorphism, necrosis, mitoses, and even vascular or neural invasion, may be seen in benign tumors and are not sufficient criteria for the diagnosis of malignancy, which is encountered in 2% to 13% of cases.

Diagnosis

The tumor is usually isointense to muscle on T_1-weighted MRI and hyperintense on T_2-weighted images. Multiple punctuate and serpiginous areas of signal void due to high velocity flow in tumor vessels are frequently seen, resulting in the classic "salt-and-pepper" heterogeneity seen on T_2-weighted images (Olsen et al., 1987) (Fig. 12–7A). Angiography confirms the hypervascular nature of the tumor (Fig. 12–7B). "Bone window" CT is invaluable for the detection of bone erosion and can be helpful in the clinical staging of lateral skull-base paragangliomas (Table 12–4).

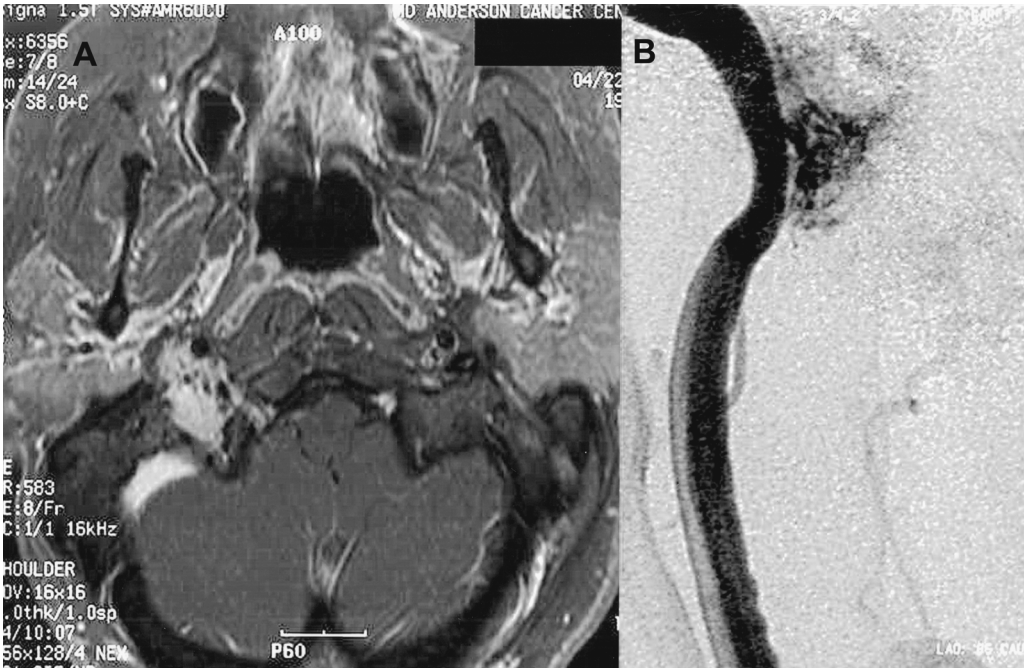

Figure 12–7. **(A)** Axial post-contrast T_1-weighted MRI reveals signal voids within the contrast-enhancing tumor in the right jugular foramen. **(B)** Right lateral internal carotid angiogram confirms the hypervascular nature of this paraganglioma.

Treatment

Surgical excision is generally considered the method of choice in the treatment of paragangliomas. Tumor control rates of 90% to 100% have been reported following gross total resection. Whereas surgical excision can be safely performed in small localized lesions, in extensive neoplasms it can be accompanied by serious morbidity. The risk of postoperative lower cranial nerve deficit is approximately 30% (Jackson, 1993). Upper aerodigestive tract procedures may be required in as many as 19% of patients (Anand et al., 1990; Green et al., 1994). Reported perioperative mortality varies from 0% to 5% (Green et al., 1994; Gjuric et al., 1996). Subtotal resection with preservation of functional cranial nerves with subsequent RT may be a valuable treatment alternative for selected patients. Gjuric et al. (1996) reported a 67% long-term tumor control rate with this approach

Radiation therapy is an accepted primary treatment modality for paragangliomas. It may be recommended when there is demonstrable involvement of

Table 12–4. Fisch Classification of Glomus Jugulare Tumors

Type A	Tumors confined to middle ear cleft (tympanicum)
Type B	Tumors limited to the tympanomastoid area with no bone destruction in the infralabyrinthine compartment of the temporal bone
Type C	Tumors involving the infralabyrinthine compartment with extension into the petrous apex
Type D	Tumors with intracranial extension less than 2 cm in diameter
Type E	Tumors with intracranial extension greater than 2 cm in diameter

Source: Fisch U, Fagan P, Valavanis A. 1984. The infratemporal fossa approach for the lateral skull base. Otolaryngol Clin North Am 17:513–552.

the internal carotid artery in patients who fail a balloon occlusion test; in bilateral tumors with contralateral deficits of the lower cranial nerves or concerns of venous return; in patients with poor medical condition or refusal of surgery; and in cases with contralateral sensorineural hearing loss (Anand et al., 1993). With a mean follow up of 10.5 years, Konefal et al. (1987) achieved long-term control in all patients with localized paragangliomas treated with radiation (minimum dose 46 Gy). In seven patients with massive disease, radiation was able to control tumor in five. Carrasco and Rosenman (1993) reviewed 24 series of patients treated with RT and found an overall 90% rate of survival, with only 5% of patients dying of their disease. Sims et al. (1999) reported good results in four patients with skull-base paragangliomas treated by linac-based radiosurgery with a single marginal doses of 15 to 17.5 Gy. Despite a possible decrease in blood and urine norepinephrine levels, radiation may not completely control the secretory activity of the tumor (Pluta et al., 1994).

OLFACTORY NEUROBLASTOMA

Olfactory neuroblastoma, also known as esthesioneuroblastoma, is an uncommon malignant neoplasm of neuroectodermal origin, arising from the olfactory neuroepithelium of the superior third of the nasal septum, cribriform plate, and superior turbinates. The mean age of patients is 45 years, with a nearly equal distribution between males and females (Levine et al., 1999). Orbital invasion is encountered in 17% of cases, whereas intracranial extension is identified in 25%.

Pathology

On gross examination, the tumor is polyploid, soft, pink to red brown, and hemorrhagic. Microscopically it is composed of discrete nests or lobules of small round cells with hyperchromatic nuclei and sparse cytoplasm. The stroma is pink, delicate, neurofibrillary, or edematous and well vascularized. Mitoses are rare. Homer-Wright pseudorosettes are seen in 30% to 50% of olfactory neuroblastomas. Flexner true rosettes are infrequent. Necrosis, dystrophic calcification, and vascular or lymphatic invasion are not uncommon. According to Hyams, four grades of olfactory neuroblastomas can be delineated (Table 12–5).

Immunohistochemistry can reveal staining of the tumor cells for neuron-specific enolase (100%), synaptophysin (65%), and chromogranin.

Diagnosis

Unilateral nasal obstruction and epistaxis are typical manifestations of olfactory neuroblastoma. In 20% of patients, rhinoscopy can disclose a red–gray mass, located high in the nasal cavity. Other symptoms include headache, periorbital swelling, hyposmia, and visual disturbances. Nearly 6% of patients present with cervical metastases.

Radiographs usually reveal an intranasal soft tissue density sometimes with bone erosion, septal deviation away from the involved side, occasional calcifications, and pacification of the paranasal sinuses. The imaging appearance of olfactory neuroblastoma does not allow differentiation from other sinonasal malignancies, but is invaluable in tumor staging. On CT, olfactory neuroblastoma is usually seen as a homogeneous iso- or slightly hyperdense lesion, with homogeneous and moderate contrast enhancement.

Table 12–5. Hyams' Grading System of Olfactory Neuroblastomas

Feature	*Grade I*	*Grade II*	*Grade III*	*Grade IV*
Architecture	Lobular	Lobular	Nearly lobular	Nearly lobular
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary matrix	Prominent	Present	Minimal	Absent
Rosettes	Homer-Wright	Homer-Wright	Flexner	Absent
Necrosis	Absent	Absent	Present	Common

Source: Hyams VJ, Batsakis JG, Micheals L. 1988. Tumors of the Upper Respiratory Tract and Ear. Washington, DC: Armed Forces Institute of Pathology, p 343.

"Direct" coronal images can be useful for delineation of tumor extension into the orbits and through the cribriform plate (Eustace et al., 1995). On T_1-weighted MRI, olfactory neuroblastoma is usually hypointense. (Fig. 12–8)

Treatment

En bloc craniofacial resection of the tumor, cribriform plate, and overlying dura is the preferred treatment for olfactory neuroblastoma (Biller et al., 1990; Morita et al., 1993). Whereas localized tumors can be treated successfully with excellent long-term results, management of advanced disease is much more challenging. Preoperative RT (average dose, 51.1 Gy) with or without chemotherapy (cyclophosphamide, vincristine, adriamycin) can result in a 50% reduction in tumor volume in nearly one-half of patients, which can facilitate surgical removal (Polin et al., 1998). Platinum-based chemotherapy can be effective for advanced high-grade tumors (McElroy et al., 1998).

The estimated survival rates of patients with olfactory neuroblastoma are 97% at 1 year, 74% to 87% at 5 years, and 54% to 60% at 10 years (Dulguerov and Calcaterra, 1992; Polin et al., 1998). Recurrences following therapy are encountered in 30% to 70% of patients. In the series of Levine et al. (1999),

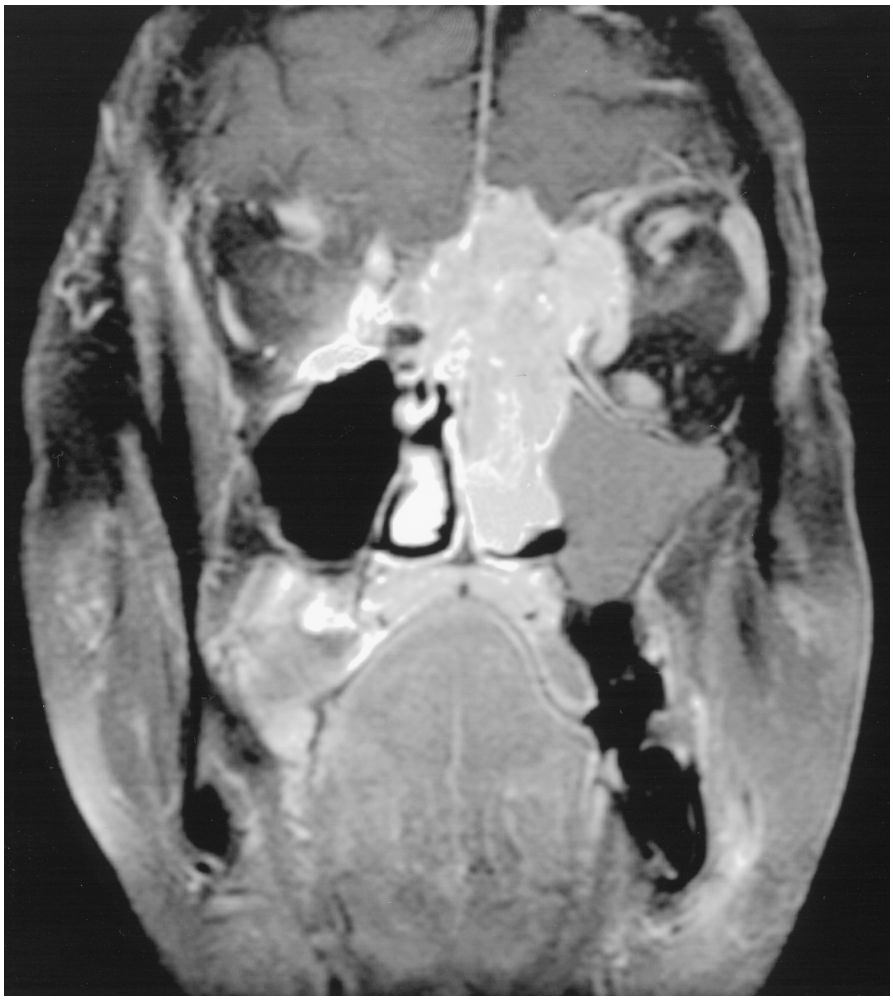

Figure 12–8. Coronal post-contrast T_1-weighted MRI of a patient with a large olfactory neuroblastoma. Note the extension of this tumor intracranially and into the left orbit.

the longest duration for the presentation of the first recurrence was 13.3 years. Cervical lymph node metastases may develop in 10% to 40% of cases. The lungs and bones are common sites of distant metastases. Salvage rates for olfactory neuroblastoma are far superior to those of other superior nasal vault malignancies, with a 82% 5 year survival rate after salvage treatment for local recurrence (Morita et al., 1993).

The histologic grade is an important prognostic indicator. In the series of McElroy et al. (1998) the mean survival from the time of initial diagnosis was 139.5 months for low-grade and 32.25 months for high-grade tumors. Advanced Kadish stage is associated with a higher rate of disease-related mortality and characterized by aggressive clinical behavior, independently of tumor grade (Polin et al., 1998; Levine et al., 1999). Three year disease-free survival is 100% for Kadish stage A patients, 80% for stage B, and 40% for stage C (Kadish et al., 1976). Involvement of the brain is a poor prognostic sign. Advanced aged is also predictive of a decreased probability of disease-free survival.

CARCINOMAS OF THE ANTERIOR SKULL BASE

Carcinomas of the anterior skull base may arise from the nasal cavity, paranasal sinuses, pharynx, or the major and minor salivary glands of the upper aerodigestive tract. The anterior skull base is most frequently affected due to direct extension of the neoplasm with erosion of the bone.

Diagnosis

Disease presentation is often nonspecific and depends on the site of origin of the tumor. Sinonasal tumors can grow to a large size before causing significant symptoms. The most frequently encountered signs and symptoms include nasal obstruction, loss of the sense of smell, epistaxis, rhinorrhea, serous otitis media, diplopia, exophthalmos, and facial hypoesthesia, swelling, or pain. Approximately 10% of patients do not have symptoms of tumor. Fewer than 10% of patients have cervical lymphadenopathy, and fewer than 7% have distant metastases. Second malignancies are discovered in 10% to 20% of patients.

Pathology

Squamous cell carcinoma is the most common tumor of the paranasal sinuses, accounting for 50% of most surgical series. The maxillary sinus is the most common site of origin. Adenocarcinoma most frequently occurs in the upper nasal cavity or in the ethmoid sinuses. The grade of this tumor is highly correlated with prognosis. Adenoid cystic carcinomas arise from the major and minor salivary glands and characteristically infiltrate diffusely, especially along perineural pathways, contributing to a high rate of recurrence and late metastasis. Neuroendocrine carcinomas are malignancies of the exocrine glands found in the normal nasal and paranasal mucosa. Differentiation from olfactory neuroblastoma is important as these tumors are exquisitely chemosensitive and are primarily treated without need for extensive surgery (Table 12–6) (Perez-Ordonez et al., 1998).

Table 12–6. Criteria for Differential Diagnosis Between High-Grade Olfactory Neuroblastoma and Small Cell Neuroendocrine Carcinoma

Criteria	*High-Grade Olfactory Neuroblastoma*	*Neuroendocrine Carcinoma*
Lobular architecture	+/−	−
Neurofibrillary stroma	+/−	−
Rosette formation	+/−	−
Cell sizes	Large	Small
Nucleoli	Conspicuous	Not found
Immunohistochemistry		
S-100	Slightly positive	Negative
NF	Positive	Negative
Keratin	Uncommon	Diffuse
Mean proliferative index	7.4%	67%

Data are from Perez-Ordonez et al. (1998).

Sinonasal undifferentiated carcinoma is an extremely aggressive tumor with a high rate of early metastatic spread. Affected patients rarely live beyond 2 years. Other less common tumors of the nasal cavity and paranasal sinuses include mucoepidermoid carcinoma, melanoma, plasmacytoma, lymphoma, and various sarcomas.

Treatment

Tumor pathology and extent, the availability and potential success rates of adjuvant therapies, as well as the potential for functional impairment and esthetic deformity are all important parameters to consider when planning the best management options for a patient with anterior skull base malignancy. In most cases, surgery and radiation are employed as a combined treatment modality, but other adjuvant therapies such as radiosurgery, brachytherapy, and chemotherapy may be indicated.

Patient outcome is variable and depends on the tumor pathology, primary site and any extensions, and completeness of surgical excision. Several recent surgical series have reported survival rates of 47% to 70% at 5 years and 41% to 48% at 10 years for all types of malignancies. McCutcheon et al. (1996) reported median survival times of 20 months for squamous cell carcinoma, 26 months for adenocarcinoma, and 40 months for olfactory neuroblastoma.

REFERENCES

Al-Mefty O. Management of glomus jugulare tumors. 1988. Contemp Neurosurg 10:1–6.

Anand VK, Leonetti JP, Al-Mefty O. 1993. Neurovascular considerations in surgery of glomus tumors with intracranial extensions. Laryngoscope 103:722–728.

Baker FG, Ojemann RG. 1993. Surgical approaches to tumors of the posterior fossa cranial nerves (excluding acoustic neuromas). In: Barrow DL (ed), Surgery of the Cranial Nerves of the Posterior Fossa. AANS Publications Committee. Park Ridge, NJ: American Association of Neurological Surgeons, 322 pp.

Barnes L, Kapadia SB. 1994. The biology and pathology of selected skull base tumors. J Neurooncol 20:213–240.

Berger MS, Edwards MS, Bingham WG. 1982. Hypoglossal neurilemmoma: case report and review of the literature. Neurosurgery 10: 617–620.

Biller HF, Lawson W, Sachdev VP, Som P. 1990. Esthesioneuroblastoma: surgical treatment without radiation. Laryngoscope 100:1199–1201.

Bordi L, Compton J, Symon L. 1989. Trigeminal neuroma. A report of eleven cases. Surg Neurol 31:272–276.

Brown RV, Sage MR, Brophy BP. 1990. CT and MR findings in patients with chordomas of the petrous apex. Am J Neuroradiol 11:121–124.

Cantu G, Solero CL, Mariani L, et al. 1999. Anterior craniofacial resection for malignant ethmoid tumors—a series of 91 patients. Head Neck 21:185–191.

Carrasco V, Rosenman J. 1993. Radiation therapy of glomus jugulare tumors. Laryngoscope 103(suppl 60):23–27.

Castro JR, Linstadt DE, Bahary JP, et al. 1994. Experience in charged particle irradiation of tumors of the skull base: 1977–92. Int J Radiat Oncol Biol Phys 29:647–655.

Celli P, Ferrante L, Acqui M, Mastronardi L, Fortuna A, Palma L. 1992. Neurinoma of the third, fourth, and sixth cranial nerves: a survey and report of a new fourth nerve case. Surg Neurol 38:216–224.

Day JD, Fukushima T. 1998. The surgical management of trigeminal neuromas. Neurosurgery 42:233–241.

Dolenc VV. 1994. Frontotemporal epidural approach to trigeminal neurinomas. Acta Neurochir (Wien) 130:55–65.

Dort JC, Fisch U. 1991. Facial-nerve schwannomas. Skull Base Surg 1:51–56.

Dulguerov P, Calcaterra T. 1992. Esthesioneuroblastoma: the UCLA experience 1970–1990. Laryngoscope 102:843–849.

Eustace S, Suojanen J, Buff B, McEniff N, Janvario J, Norris C. 1995. Preoperative imaging of esthesioneuroblastoma. Clin Radiol 50:639–643.

Evans HL, Ayala AG, Romsdahl MM. 1977. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer 40:818–831.

Farrior JB 3rd, Hyams VJ, Benke RH, Farrior JB. 1980. Carcinoid apudoma arising in a glomus jugulare tumor: review of endocrine activity in glomus jugulare tumors. Laryngoscope 90:110–119.

Franklin DJ, Moore GF, Fisch U. 1989. Jugular foramen peripheral nerve sheath tumors. Laryngoscope 99: 1081–1087.

Forsyth PA, Cascino TL, Shaw EG, et al. 1993. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. J Neurosurg 78:741–747.

Fuller DB, Bloom JG. 1988. Radiotherapy for chordoma. Int J Radiat Oncol Biol Phys 15:331–339.

Gay E, Sekhar LN, Rubinstein E, et al. 1995. Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. Neurosurgery 36:887–897.

Gjuric M, Rudiger Wolf S, Wigand ME, Weidenbecher M. 1996. Cranial nerve and hearing function after combined-approach surgery for glomus jugulare tumors. Ann Otol Rhinol Laryngol 105:949–954.

Gormley WB, Sekhar LN, Wright DC, Kamerer D, Schessel D. 1997. Acoustic neuromas: results of current surgical management. Neurosurgery 41:50–60.

Green JD Jr, Brackmann DE, Nguyen CD, Arriaga MA, Telischi FF, De la Cruz. 1994. Surgical management of previously untreated glomus jugulare tumors. Laryngoscope 104: 917–921.

Harwick RD, Miller AS. 1979. Craniocervical chordomas. Am J Surg 138:512–516.

Hassounah M, Al-Mefty O, Akhtar M, Jinkins JR, Fox JL. 1985. Primary cranial and intracranial chondrosarcoma: a survey. Acta Neurochir (Wien) 78:123–132.

Holmes B, Sekhar L, Sofaer S, Holmes KL, Wright DC. 1995. Outcomes analysis in cranial base surgery—preliminary results. Acta Neurochir (Wien) 134:136–138.

Horn KL, House WF, Hitselberger WE. 1985. Schwannomas of the jugular foramen. Laryngoscope 95:761–765.

Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. 1999. Stereotactic radiosurgery for trigeminal schwannomas. Neurosurgery 45:11–16.

Hug EB, Loredo LN, Slater JD, et al. 1999. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg 91:432–439.

Inoue Y, Tabuchi T, Hakuba A, et al. 1987. Facial nerve neuromas: CT findings. J Comput Assist Tomogr 11:942–947.

Jackowski A, Weiner G, O'Reilly G. 1994. Trochlear nerve schwannomas: a case report and literature review. Br J Neurosurg 8:219–223.

Jackson CG, Cueva RA, Thedinger BA, Glassock ME 3rd. 1991. Cranial nerve preservation in lesions of the jugular fossa. Otolaryngol Head Neck Surg 105:687–693.

Jefferson G. 1955. The trigeminal neurinomas with some remarks on malignant invasion of the gasserian ganglion. Clin Neurosurg 1:11–54.

Kamerer DB, Hirsch BE. 1987. Paragangliomas ("glomus tumors") of the temporal bone. In: Sekar LN, Schramm VL Jr (eds), Tumors of the Cranial Base. Diagnosis and Treatment. Mount Kisco, NY: Futura Press, pp 641–654.

Kadish S, Goodman M, Wang CC. 1976. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer 37:1571–1576.

Kaye AH, Hahn JF, Kinney SE, Hardy RW Jr, Bay JW. 1984. Jugular foramen schwannomas. J Neurosurg 60:1045–1053.

King TT, Morrison AW. 1990. Primary facial nerve tumors within the skull. J Neurosurg 72:1–8.

Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. 1998. Long-term outcomes after radiosurgery for acoustic neuromas. N Engl J Med 339:1426–1433.

Konefal JB, Pilepich MV, Spector GJ, Perez CA. 1987. Radiation therapy in the treatment of chemodectomas. Laryngoscope 97:1331–1335.

Korten AG, ter Berg HJ, Spincemaille GH, van der Laan RT, Van de Wel AM. 1998. Intracranial chondrosarcoma: review of the literature and report of 15 cases. J Neurol Neurosurg Psychiatry 65:88–92.

Kveton JF, Brackmann DE, Glasscock ME 3rd, House WF, Hitselberger WE. 1986. Chondrosarcoma of the skull base. Otolaryngol Head Neck Surg 94:23–32.

Lang DA, Neil-Dwyer G, Garfield J. 1999. Outcome after complex neurosurgery: the caregiver's burden is forgotten. J Neurosurg 91:359–363.

Lesser THJ, Janzer RC, Kleihues P, Fisch U. 1991. Clinical growth rate of acoustic schwannomas: correlation with the growth fraction as defined by the monoclonal antibody Ki-67. Skull Base Surg 1:11–15.

Levine PA, Gallagher R, Cantrell RW. 1999. Esthesioneuroblastoma: reflections of a 21-year experience. Laryngoscope 109:1539–1543.

Lipkin AF, Coker NJ, Jenkins HA, Alford BR. 1987. Intracranial and intratemporal facial neuroma. Otolaryngol Head Neck Surg 96:71–79.

Lund VJ, Howard DJ, Wei WI, Cheesman AD. 1998. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses—a 17-year experience. Head Neck 20:97–105.

Majos C, Coll S, Aguilera C, Acebes JJ, Pons LC. 1998. Imaging of giant pituitary adenomas. Neuroradiology 40:651–655.

Maira G, Pallini R, Anile C, et al. 1996. Surgical treatment of clival chordomas: The transsphenoidal approach revisited. J Neurosurg 85:784–792.

Mariniello G, Horvat A, Dolenc VV. 1999. En bloc resection of an intracavernous oculomotor nerve schwannoma and grafting of the oculomotor nerve with sural nerve. Case report and review of the literature. J Neurosurg 91: 1045–1049.

Matthies C, Samii M. 1997. Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation. Neurosurgery 40:1–10.

McCormick PC, Bello JA, Post KD. 1988. Trigeminal schwannoma: surgical series of 14 cases with review of the literature. J. Neurosurg 69:850–860.

McCutcheon IE, Blacklock JB, Weber RS, et al. 1996. Anterior transcranial (craniofacial) resection of tumors of the paranasal sinuses: surgical techniques and results. Neurosurgery 38:471–479.

McElroy EA Jr, Buckner JC, Lewis JE. 1998. Chemotherapy for advanced esthesioneuroblastoma: the Mayo Clinic experience. Neurosurgery 42:1023–1028.

Meyers SP, Hirsch WL Jr, Curtin HD, Barnes L, Sekhar LN, Sen C. 1992. Chordomas of the skull base: MR features. Am J Neuroradiol 13:1627–1636.

Mitchell A, Scheithauer BW, Unni KK, Forsyth PJ, Wold LE, McGivney DJ. 1993. Chordoma and chondroid neoplasms of the spheno-occiput. An immunohistochemical study of 41 cases with prognostic and nosologic implications. Cancer 72:2943–2949.

Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. 1993. Esthesioneuroblastoma: prognosis and management. Neurosurgery 32:706–715.

Odake G. 1989. Intracranial hypoglossal neurinoma with extracranial extension: review and case report. Neurosurgery 24:583–587.

O'Donoghue GM, Brackmann DE, House JW, Jackler RK. 1989. Neuromas of the facial nerve. Am J Otol 10:49–54.

Ogunrinde OK, Lunsford LD, Flickinger JC, Kondziolka D. 1994. Stereotactic radiosurgery for acoustic nerve tumors in patients with useful preoperative hearing: results at 2-year follow-up examination. J Neurosurg 80:1011–1017.

Olsen WL, Dillon WP, Kelly WM, Norman D, Brant-Zawadzki M, Newton JH. 1987. MR Imaging of paragangliomas. AJR Am J Roentgenol 148:201–204.

Parnes LS, Lee DH, Peerless SJ. 1991. Magnetic resonance imaging of facial nerve neuromas. Laryngoscope 101: 31–35.

Perez-Ordonez B, Caruana SM, Huvos AG, Shah JP. 1998. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. Hum Pathol 29:826–832.

Pia HW, Grote E, Hildebrandt G. 1985. Giant pituitary adenomas. Neurosurg Rev 8:207–220.

Pitts LH, Jackler RK, Fuller GN. 1996. Intracranial nerve sheath tumors. In: Levin VA (ed), Cancer in the Nervous System, 1st ed. New York: Churchill Livingstone, pp 199–210.

Pluchino F, Crivelli G, Vaghi MA. 1975. Intracranial neurinomas of the nerves of the jugular foramen. Report of 12 cases. Acta Neurochir (Wien) 31:201–221.

Pluta RM, Ram Z, Patronas NJ, Keiser H. 1994. Long-term effects of radiation therapy for a catecholamine-producing glomus jugular tumor. Case report. J Neurosurg 80:1091–1094.

Polin RS, Sheehan JP, Chenelle AG, et al. 1998. The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: the University of Virginia experience. Neurosurgery 42:1029–1037.

Pollock BE, Lunsford LD, Kondziolka D, et al. 1998. Vestibular schwannoma management. Part II. Failed radiosurgery and the role of delayed microsurgery. J Neurosurg 89:949–955.

Pollock IF, Sekhar LN, Jannetta PJ, Janecka IP. 1989. Neurilemomas of the trigeminal nerve. J Neurosurg 70:737–745.

Pollock BE, Kondziolka D, Flickinger JC, Maitz A, Lunsford LD. 1993. Preservation of cranial nerve function after radiosurgery for nonacoustic schwannomas. Neurosurgry 33 :597–601.

Rosenberg AE, Nielsen GP, Keel SB, et al. 1999. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. Am J Surg Pathol 23:1370–1378.

Samii M, Babu RP, Tatagiba M, Sepehrnia A. 1995a. Surgical treatment of jugular foramen scwannomas. J Neurosurg 82:924–932.

Samii M, Migliori MM, Tatagiba M, Babu R. 1995b. Surgical treatment of trigeminal schwannomas. J Neurosurg 82: 711–718.

Samii M, Matthies C, Tatagiba M. 1997. Management of vestibular scwannomas (acoustic neuromas): auditory and facial nerve function after resection of 120 vestibular scwannomas in patients with neurofibromatosis 2. Neurosurgery 40:696–706.

Schultheiss R, Kristof R, Schramm J. 1993. Complete removal of an oculomotor nerve neurinoma without permanent functional deficit. German J Ophthalmol 2:228–233.

Sen CN, Sekhar LN. 1993. Complications of cranial base surgery. In: Post KD, Friedman ED, McCormick P (eds), Postoperative Complications in Intracranial Neurosurgery. New York: Thieme Medical Publishers, pp 111–131.

Shah JP, Kraus DH, Bilsky MH, Gutin PH, Harrison LH, Strong EW. 1997. Craniofacial resection for malignant tumors involving the anterior skull base. Arch Otolaryngol Head Neck Surg 123:1312–1317.

Shirato H, Sakamoto T, Sawamura Y, et al. 1999. Comparison between observation policy and fractionated stereotactic radiotherapy (SRT) as an initial management for vestibular schwannoma. Int J Radiation Oncol Biol Phys 44:545–550.

Sims E, Doughty D, Macaulay E, et al. 1999. Stereotactically delivered cranial radiation therapy: a ten-year experience of linac-based radiosurgery in the UK. Clin Oncol (R Coll Radiol) 11:303–320.

Spector GJ, Druck NS, Gado M. 1976. Neurologic manifestations of glomus tumors in head and neck. Arch Neurol 33:270–274.

Stapleton SR, Wilkins PR, Archer DJ, et al. 1993. Chondrosarcoma of the skull base: a series of eight cases. Neurosurgery 32:348–356.

Subach BR, Kondziolka D, Lunsford LD, Bissonette DJ, Flickinger JC, Maitz AH. 1999. Stereotactic radiosurgery in the management of acoustic neuromas associated with neurofibromatosis type 2. J Neurosurg 90:815–822.

Tan LC, Bordi L, Symon L, Cheesman AD. 1990. Jugular foramen neuromas: a review of 14 cases. Surg Neurol 34:205–211.

Terahara A, Niemierko A, Goitein M, et al. 1999. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. Int J Radiat Oncol Biol Phys 45:351–358.

Tung H, Chen T, Weiss MH. 1991. Sixth nerve schwannomas. Report of two cases. J Neurosurg 75:638–641.

Welling DB. 1998. Clinical manifestations of mutations in the neurofibromatosis type 2 gene in vestibular schwannomas (acoustic neuromas). Laryngoscope 108:178–189.

Woods CI, Strasnick B, Jackson CG. 1993. Surgery for glomus tumors: The Otology Group experience. Laryngoscope 103(Suppl 2):65–70.